DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING:

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE AND

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE

Tuesday, January 24, 2006

8:05 a.m.

Holiday Inn Select
The Ballrooms
8120 Wisconsin Avenue
Bethesda, Maryland

PARTICIPANTS

Alastair Wood, M.D., Ph.D., Chair, NDAC
LT Darrell Lyons, BSN, Executive Secretary

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE

Neal L. Benowitz, M.D.
Terrence F. Blaschke, M.D.
Ernest B. Clyburn, M.D.
Ruth M. Parker, M.D.
Wayne R. Snodgrass, M.D., Ph.D.
Robert E. Taylor, M.D., Ph.D., FACP, FCP
Mary E. Tinetti, M.D.

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE

Erik R. Swenson, M.D., Chair
Mark L. Brantly, M.D.
Steven E. Gay, M.D., M.S.
Carolyn M. Kercsmar, M.D.
Michael Schatz, M.D.
David A. Schoenfeld, Ph.D. (By Telephone)

CONSULTANTS (VOTING)

Marie R. Griffin, M.D., NDAC
Sonia Patten, Ph.D., NDAC (Consumer Representative)
Karen Schell, RRT, PADAC (Consumer Representative)
Nancy Sander, PADAC (Patient Representative)

CONSULTANTS (NON-VOTING)

Theodore Reiss, M.D., PADAC (Industry Representative)
George S. Goldstein, M.D., NDAC (Industry Representative)

FDA

Charles Ganley, M.D.
Robert Meyer, M.D.
Badrul Chowdhury, M.D., Ph.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. WOOD: I am Alastair Wood. Let's begin by introducing all the members of the committees.

Ted, do you want to start?

Introductions

DR. REISS: I am Ted Reiss from Merck Research Labs. I am on the Pulmonary Advisory Committee. I am the industry representative.

DR. GOLDSTEIN: I am George Goldstein. I am an independent consultant who serves as industry liaison representative to the Nonprescription Drug Advisory Committee.

DR. GAY: I am Steven Gay, Medical Director of Critical Care Support Services, Assistant Professor of Medicine, University of Michigan.

DR. BENOWITZ: Neal Benowitz. I am at the University of California, San Francisco. I am an internist, clinical pharmacologist, medical toxicologist, and member of the NDAC Committee.

DR. BRANTLY: Mark Brantly, Professor of Medicine at University of Florida. I am a pulmonary physician. I am on the Pulmonary Drug Advisory Committee.

DR. BLASCHKE: Terry Blaschke, clinical pharmacologist, internist, Stanford, NDAC.

DR. SNODGRASS: Wayne Snodgrass, Clinical Pharmacology, Medical Toxicology, Pediatrics, at the University of Texas.

DR. CLYBURN: I am Ben Clyburn. I am in Internal Medicine at Medical University of South Carolina, on NDAC.

DR. PARKER: Ruth Parker, Internal Medicine, Emory University School of Medicine, NDAC.

DR. SCHATZ: I am Michael Schatz, Department of Allergy, Kaiser Permanente, San Diego, and on the Pulmonary and Allergy Advisory Committee.

DR. TAYLOR: Robert Taylor. I am an internist, clinical pharmacologist, with Howard

University College of Medicine, NDAC.
DR. WOOD: I am Alastair Wood. I am an internist and clinical pharmacologist from Vanderbilt.

LT LYONS: Darrell Lyons, Executive Secretary for the NDAC meeting.
DR. SWENSON: I am Erik Swenson at the University of Washington, on the Pulmonary and Drugs Advisory Committee.

MS. SCHELL: I am Karen Schell. I am a respiratory therapist. I represent the consumer on the Pulmonary-Allergy Drugs Committee.
DR. TINETTI: Mary Tinetti, Internal Medicine, Geriatrics, and I am on the NDAC

Committee, at Yale University.
DR. KERCSMAR: Carolyn Kercsmar, pediatric pulmonologist, Case School of Medicine, Pulmonary-Allergy Advisory Committee.
DR. PATTEN: I am Sonia Patten. I am an

anthropologist on the faculty at Macalester College in St. Paul, Minnesota. I am the consumer representative, consultant to NDAC.

MS. SANDER: I am Nancy Sander, president and founder of Allergy and Asthma Network Mothers of Asthmatics. I am here as Patient Advisor to the PADAC Committee.

DR. GRIFFIN: Marie Griffin, internist and pharmacoepidemiologist, Vanderbilt, on NDAC.

DR. CHOWDHURY: I am Badrul Chowdhury, Director, Division of Pulmonary and Allergy Products, FDA.

DR. MEYER: Bob Meyer. I am the Director of the Office of Drug Evaluation II at FDA.

DR. GANLEY: Charley Ganley. I am the Director of Office of Nonprescription Products at FDA.

DR. WOOD: Darrell, do you want to read the Conflict of Interest?

Conflict of Interest Statement

LT LYONS: The following announcement addresses the issue of conflict of interest and is made 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 committees' 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 at this meeting with the following exceptions.

In accordance with 18 U.S.C. Section 208(b)(3), the following participants have been granted waivers. Please note that all interests are in firms that could potentially be affected by the committee's decisions.

Dr. Terrence Blaschke for consulting on an unrelated matter for an affected firm. He receives less than $10,001 per year.

Dr. David Schoenfeld, co-founder and part owner of the Clinical Research Organization, has unrelated contracts with two affected firms for which he receives less than $10,001 per year from one firm, and from $10,001 to $50,000 per year from another firm, and for consulting for an affected firm on an unrelated matter for which he receives less than $10,001 per year.

Ms. Nancy Sander for owning stock in an affected firm valued from $25,001 to $50,000, and for serving on an advisory board for an affected firm on an unrelated matter for which she receives less than $10,001 per year.

Dr. Steven Gay for serving on a speakers bureau for three affected firms. He received less than $10,001 per year from two firms and between $10,001 to $50,000 per year from the other.

A copy of the waiver statement may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would also like to note that Dr. Theodore Reiss and Dr. George Goldstein have been invited to participate as industry representatives acting on behalf of regulated industry. Dr. Reiss and Dr. Goldstein's role on this committee is to represent industry interests in general, and not any one particular company. Dr. Reiss is employed by Merck. Dr. Goldstein is a retired employee of Sterling Drugs.

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

Thank you.

DR. WOOD: Dr. Schoenfeld will be calling in, so I guess once he gets on, why don't we ask him to introduce himself between somebody's talk.

Charley.

Welcome and Introductory Comments

DR. GANLEY: I just wanted to make some brief introductory comments. I wanted to thank members of the Pulmonary and Allergy Committee and the Nonprescription Drugs Committee for participating in this meeting.

I also want to acknowledge the efforts by

the advisors and consultant staff and project management staff who put this meeting together. It's a very huge workload for them and they do an outstanding job all the time, so thanks.

Before Dr. Meyer introduces the topic, the purpose of today's meeting is to make a determination of essential use status of CFC-based epinephrine MDIs for nonprescription treatment of asthma.

[Slide.]

The products affected by today's discussion are NDA 16-126, the sponsor is Wyeth, and they market epinephrine metered dose inhalers, 0.22 milligrams per inhalation. I am not sure if

they market the 0.3 mg per inhalation, they can discuss that. The other is a generic application aNDA 87-907, which the sponsor is Armstrong, and they have a similar inhaler to the Wyeth inhaler.

[Slide.]

There are several types of products marketed as nonprescription drugs, and I am not going to go into great detail about this. As I

just noted, the metered dose inhalers are marketed by Wyeth and Armstrong, and both of those sponsors are going to present today.

We contacted them in early October and told them about the meeting, so that they had ample time to prepare. There is another collection of products marketed under OTC Monographs. In your background packages, we gave you a little brief history, and it is not necessarily important that we go into that history in great detail unless you have specific questions regarding it.

There are oral ingredients available particularly the ephedrine ingredients. Those are marketed as single-ingredient agents. They are behind the counter because of DEA regulations. Because of issues related to conversion to methamphetamine, they were put behind the counter in the late nineties.

Also available are epinephrine solutions, and those are to be administered by a bulb nebulizer.

[Slide.]

When we published the notice in November for this meeting, there were several questions that we had asked particularly from the public, because FDA does not readily have access to this

information, and I am not going to go through them in detail here.

Many of the public comments that you have received on this are related to our specific questions that we asked for background for this

meeting.

So, I am going to end it right there and turn it over to Dr. Meyer. As he noted, he is the Director of Office of Drug Evaluation III, which oversees the Pulmonary Division, and has been

involved in this issue for longer than he cares to think, I think.

FDA Presentation

DR. MEYER: Good morning. I would like to echo Dr. Ganley's thanks to the committees for

being here today. This is a rather different topic for the NDAC from yesterday certainly, and for the Pulmonary Drugs Advisory Committee, this continues

a conversation that we began last summer looking at the remaining essential uses for CFC.

To the Pulmonary Committee, then, I beg your indulgence a little bit, because much of this

talk that I am about to give, you have already heard if you were here at that meeting, but I thought it would be important for those who may not have been here, most especially the Nonprescription Drugs Advisory Committee members, to hear it.

So, what I would like to do at this point is talk about the history of the Montreal Protocol itself, which is the international treaty which was started to protect the ozone layer, and then talk about the FDA and Federal regulations on CFCs and

do this by way of background to the meeting.

[Slide.]

Just to start this off, the picture that is shown here is actually from an ozone satellite, a European one, and we hear a lot about the ozone

hole over the South Pole, but this is actually a northern hemisphere drawing, or depiction I should say, and in this, there is--I am not sure if I have

a pointer--right in this area, there is actually, if you look down here, this is falling ozone levels, so there is actually a hole over or relative paucity of ozone over Greenland and other areas of Europe, particularly Scandinavia, if you look right here.

This is not just a matter for penguins or for Australians. This is a global issue of some importance.

[Slide.]

I am not an atmospheric scientist, but I would like to just briefly speak about what the ozone layer is and what it does for us as a way of introducing the topic.

The ozone layer, as it is referred to, is really an area of relative increase in the amount of ozone in the particular stratum of the atmosphere. This is occurring at about 23 to 24 kilometers above the earth, and in that region, about 90 percent of atmospheric ozone resides.

That layer is important in that it filters ultraviolet light, particularly the UV-B light, and

thereby protects the surface from the full amount of UV light that sunlight contains.

[Slide.]

Now, because of increasing loss of ozone in the middle to latter part of the last century, there was a noticeable rise in UV-B levels throughout the world, but particularly problematic in some areas, such as Australia, where, in fact, schoolchildren now have to go out to recess with hats on. It's a law.

The increased UV-B leads to increased skin cancers, both melanoma and non-melanoma type, cataracts, and impaired immunity in humans, but there is also other deleterious effects on the environment in terms of animal life, and, in fact, in terms of man-made substances, too, such as plastics on dashboards, and things like that.

[Slide.]

So, as far as the general background goes, I would like to get into the development of the U.S. laws and regulations with regard to the ozone protection and the Montreal Protocol, and because

these have happened in overlapping timeframes, the talk will go back and forth somewhat in terms of touching upon these.

[Slide.]

1974 was an important year in all this. That was the year that two scientists, Molina and Rowland, published an article that tied ozone depletion to stratospheric chlorine levels from degraded CFCs.

I have got the citation there. This later was Nobel prizewinning because of its importance.

At that time, the use of CFCs was really ubiquitous. They were used in refrigerators, in air conditioners, in coffee cup foam, you know,

that styrofoam of all sorts, and in many consumer and medical aerosol products because they are very inert and stable molecules. It is actually, in fact, the stability that was so problematic, because these freely released CFCs would find their

way up into the stratosphere and have half-lives in the stratosphere measured in decades to actually centuries.

[Slide.]

Surprisingly quickly, as somebody who knows how regulations go, surprisingly quickly, after that seminal work by Rowland and Molina, the United States actually took regulatory action to ban the use of CFCs in consumer spray cans and aerosols. This was done under the EPA regulations.

So, in other words, things like hair sprays and spray paint, other typical consumer aerosols have not had CFCs in them for several decades now.

In conjunction with that action, FDA published a rule under our Code of Federal Regulations, which is in Chapter 21. That citation is 2.125, which banned the use of CFCs in FDA-regulated product, but allowed for essential exemptions.

It is important to point out at the time that this rule was finalized, those exemptions were fairly broad. They were things, very broad categories like for the steroids, it would say the nasal steroids, and it actually didn't I believe

even say corticosteroids, the nasal steroids for human use.

So, it didn't go into the moieties and it didn't really break it down further. Beta agonists were all grouped under an adrenergic banner.

[Slide.]

Skipping to the Montreal Protocol, in 1987, so about 13 years after Rowland and Molina's work, 27 nations got together and one of those being the United States, and initiated a global treaty in Montreal, which later became known as the "Montreal Protocol on Substances that Deplete the Ozone Layer." Now, I am going to refer to it in the talk from hereon as the "MP."

The original protocol now has over 180 signatory countries, so it is a very broad protocol in terms of its participation, and it is also regarded as the model for successful global environmental treaties. It has had great success in terms of not only the number of countries participating, but the level at which they are participating and cooperating.

[Slide.]

Originally, under the protocol, the phaseout of CFCs was slated for 2000, and that was decided in London in 1990. However, over the next couple of years, there was increasing data from satellites and from other science that the actual destruction of the ozone layer was worse than anticipated, so in Copenhagen, in 1992, the decision was made to move the phaseout of CFCs up until the end of 1995.

The Montreal Protocol importantly, I should point out, although we are here to talk about chlorofluorocarbons in asthma inhalers because that is what is germane to these committees and to the FDA, the Montreal Protocol contains controls on many, many substances that are known to deplete ozone, so beyond CFCs, it includes things like halons, HCFCs, methyl bromide, which is very widespread in terms of its use in agriculture, and carbon tetrachloride, as well as other substances.

[Slide.]

So, under the Montreal Protocol, as of

January 1st, 1996, all uses of CFCs were banned in industrialized countries, and the rest of the world was to meet this ban or is to meet this ban by the year 2010.

MDIs for asthma and COPD currently are exempted under essential use processes, and I underline "currently" because although there is no set date at which these products could no longer be considered essential, it is clearly envisioned

under the protocol that that will eventually happen that all uses of CFCs including in asthma inhalers will, in fact, cease at some point.

Now, the nomination process has gone on yearly. It generally occurs two years before the

need, so, in other words, the 2007 nomination was recently reviewed and actually approved in Dakar in 2005.

This year actually, because as things get towards the latter parts of the phaseout, there is

more complications. It is harder to predict two years hence. There was actually a re-review of the 2006 nominations in Dakar this year.

[Slide.]

I wanted to go over a few of the provisions of the Montreal Protocol that are important in terms of the discussion today for you to understand these to take to consideration.

Decision IV/25, this is just for interest sake. This generally means it is with the fourth meeting of the party, and it was the 25th decision, so at any meeting of the parties, they make a number of decisions that don't actually change the fundamental protocol, but are accepted by the parties and are adopted generally in a unanimous fashion or consensus fashion.

So, at the fourth meeting of the parties, they decided that all essential uses of CFCs was based on the products being necessary for public health without adequate alternatives, and those alternatives could either not be there because of technical reasons, or not be there because of global economic reasons, global meaning large, macroscopic economically, not so much can an individual patient afford it.

These determinations were, at that time, also very broad, so the determination was that CFCs in MDIs for asthma and COPD were considered essential under Decision IV/25, not each individual brand or type of inhaler, but that general use of CFCs in MDIs was considered essential.

[Slide.]

Now, at the twelfth meeting of the parties, it was decided that any product approved after December 2000 must individually meet the criteria under IV/25, so in other words, they were going from global to saying that any new product had to individually meet that standard of being necessary for public health and that there were no technical or economically feasible alternatives.

So, this was product-centered and, in essence, what it did is it precluded any further new CFC generic products, and I should point out, although it is not the topic of today's discussion, there are only two inhalers that are subject to generic competition at this point, that being albuterol, and actually, the second one is germane

today, and that being epinephrine.
So, no new types of inhalers would be subject to generics under this rule, and it also precluded new CFC products all together unless they

met the very high hurdles of Decision IV/25.
The thinking behind that I think was that in the off chance that, say, there was a cure for AIDS or bird flu, or something, that could only be formulated in CFCs, you didn't want to close the

door on that, but on the other hand, you didn't want a proliferation of new products that could be delivered reasonably by any other technology.
[Slide.]
At the fifteenth meeting of the party,

there were a couple of new decisions taken, and that was that the essential uses after this decision started being on an individual basis, so in the past, a country like the United States would go to the parties and say we need, for instance,

3,000 tons for the year 2004.
Those are made-up numbers, but it would just say that, and it would describe what was going

into that usage, but it wouldn't be explicit about it. Under this provision, we now have to explain how many tons are going for each individual use.

This one also said that no quantity of essential use of CFCs would be authorized for albuterol beginning with this year's meeting of the party, this past year's meeting of the party in Dakar, if a plan for albuterol phaseout had not been submitted to the open-ended working group.

That is a sort of planning meeting of the parties by the summer of 2005, and, in fact, the FDA published a final rule in March 2005 on albuterol, stating that in the United States, albuterol will no longer be considered an essential use of CFCs after the year 2008.

[Slide.]

Now, the U.S. is a signatory party to the Montreal Protocol, but we still have to make this a part of our laws and regulations, and a large part of that was affected by the Clean Air Act Amendments of 1990, and there are implementing EPA regulations for that Clear Air Act Amendment that

specifically refer to the Department of Health and Human Services and FDA's determinations of essentiality by referring specifically to our Regulation 2.125, which contains the essential

listings of medical essentiality.

Again, we originally published that Rule 2.125 back in 1978, long before the Montreal Protocol was envisioned or back before we had any inkling of how this may play out.

[Slide.]

Now, as published in 1978, our 21 CFR 2.125, our regulation on the CFCs, it was promulgated stating that the CFC containing products would be misbranded or adulterated, in

other words, they would be illegal under the Food, Drug, and Cosmetic Act unless deemed essential, and under our regulation, the essential uses were based on there being no technically feasible alternative, that it provides a substantial health, public, or

environmental benefit, and that the release of CFCs was either small or that it was justified given the benefit that the product provided.

[Slide.]

Importantly, though, when that rule was finalized, it had no mechanism to determine when uses would no longer be considered essential.

Again, it was published long before the Montreal Protocol process was even thought of. So, there was no way to delist them.

There was a mechanism to add new uses, and new uses were added over the year, but at the time

it was published, it had no way to remove them.

As I mentioned earlier, it listed the essential uses and broad classes, and I gave the example already of the adrenergic bronchodilators for human use, so any adrenergic bronchodilator,

epinephrine, bitoterol, albuterol, metaproterenol, and so on, was put under that general rubric.

So, FDA realized that we needed to change this regulation to make it more responsive to what was expected by the Clean Air Act and the Montreal

Protocol, so in 1996, FDA published an Advanced Notice of Proposed Rulemaking proposing to revise 2.125.

[Slide.]

That was quite controversial at the time. We got a lot of press and some public, I might even say disinformation campaigns that suggested we were about to rip asthma inhalers out of the hands of patients, which clearly wasn't true, particularly since this was an Advanced Notice of Proposed Rulemaking, and needed two cycles of public comment before it could become final.

Nonetheless, we got close to 10,000 comments, and that led to a substantial period of us revising, actually taking those comments into consideration, fully reviewing them, revising our proposed rule, and putting out the proposed rule, which was published in 1999.

That received much fewer substantive comments and had little controversy attached to it, and, in fact, we were able to finalize that with an amendment of 2.125, which was published in July of 2002.

By the Federal Register notice, when it was published, it went into effect that following

January.

[Slide.]

Let me just highlight a few of the revisions of that rule. We began to list individual moieties as essential uses rather than classes. So, for instance, albuterol was listed rather than under a rubric of adrenergic bronchodilators, it was separately listed as was epinephrine, as was bitoterol, as was metaproterenol, and so on.

The revisions to 2.125 also added a higher hurdle for the investigational new drug use of ozone depleting substances, and it raised the bar for new listings of essential uses, so it make it harder to use essential uses.

Again, we didn't want to close the door on it in case there was an important life-saving product that could only be formulated in CFCs, but it made it tougher.

It also listed--this was, in fact, a very important feature of it--it listed the criteria for determining individual uses, so when those

individually listed moieties could no longer be considered essential.

Let me just go through those quickly.

[Slide.]

A product could be considered no longer essential if there was at least one non-ozone-depleting substance, so, in other words, a product that does not contain an ozone- depleting substance, such as CFCs, that had the same active

moiety, the same drug, the same indication, the same route of administration, inhaled in this case, and about the same level of convenience.

So, it was acknowledged in the preamble to this that an alternatively propelled metered dose

inhaler would most easily meet this, but we didn't shut the door to things like dry powdered inhalers or hand-held nebulizers also being able to meet this, and that is part of the reason it has the provision about the same level of convenience

instead of demanding that it be exactly the same in terms of convenience.

The non-essentiality criteria called for

at least one year of post-marketing data for the non-ODS products. It importantly called for production capabilities and supplies to be adequate, so that we knew that the population that

depended on these products would be adequately served by the production capacity, and finally, there was a provision that patients who require the CFC product are served by the alternatives.

[Slide.]

Now, these non-essentiality criteria were for products where there was only one product in the marketplace. For products where there was more than one product or strength available, the main difference here was that there would have to be at

least two non-ozone-depleting substances with the same active moiety, same indication, and so on, so it just meant for a product that was represented by multiple different NDAs or different strengths within the product. We didn't want to just

consider one strength available in one product an adequate alternative.

[Slide.]

Now, this brings us closer to today's meeting. We had originally in our Advanced Notice of Proposed Rulemaking back in '96, proposed perhaps considering a therapeutic class approach.

In other words, if you took inhaled corticosteroids, for instance, if there are five products on the market, five different moieties on the market, we suggested in there that maybe we should think about the fact that if you had two or three alternatives, that the entire class could be considered nonessential, and we got much public commentary and substantive commentary that this was not a good way to approach this, because there are certain patients who uniquely respond to one member of a class.

So, the revisions to 2.125, when they occurred, took what we call a moiety-by-moiety approach, in other words, it was assessing continued essentiality on a product-by-product basis, but the problem with this is that it doesn't effectively deal with a product not being reformulated.

If a product is never reformulated, if you don't have some other mechanism to revisit the essentiality, it will sort of default to being essential in perpetuity, which is not what we would want.

So, the FDA, in the revisions, stated that beginning in January 1st, 2005, for products where they remained on the marketplace, used CFCs, but were not being reformulated or had not been reformulated, that we could begin to convene public meetings to discuss the continuing essentiality of those products, and, hence, that is why you are here today.

[Slide.]

So, in July, we had a meeting with the PADAC alone to discuss the prescription products, had a very good session with them, but we specifically excluded the discussion of epinephrine from that meeting, because it is an over-the-counter product, and we felt it necessary and important to have the Non-Prescription Drug Advisory Committee participate in that. That is

the genesis of today's meeting.

So, we are now convening this public meeting to discuss whether epinephrine, being that it is still listed as an essential use, continues to be essential.

Under the revisions of 2.125, that essential use is based on there being no technically feasible alternatives, that it provides substantial health, public, or environmental benefit, and that the release of CFCs are small or justified given the benefit.

Now, given the expertise of this committee or these committees, this is the bullet that we really want you to focus on today, that the product provides a substantial health, public, or environmental benefit, but particularly the health benefit, and relating that to the use of epinephrine as an OTC metered dose inhaler.

[Slide.]

I just wanted to give you sort of an idea of how the transition has gone in the United States at this point. What you see here is the original

listing of the products that were considered essential.

All the products in red are already no longer considered essential uses, so the nasal steroids have gone in terms of the CFC MDIs. There are adequate alternatives in terms of the aqueous formulations, and, in fact, there are some approved HFA formulations. I am not sure whether they have reached the market yet.

Things like non-asthma type drugs, contraceptive foams, rectal corticosteroid foams, nitroglycerine, polymyxin have gone away, as well.

The thing in blue here is albuterol, which is slated for phaseout at the end of 2008, but we have obviously not reached that date yet.

All the things in yellow are perhaps subject to delisting soon, because they are either no longer marketed or there are alternatives available, so you have got a fairly broad list there - bitoterol, salmeterol is no longer marketed as MDI. Fluticasone, there is a fluticasone HFA approved. Beclomethasone is no longer marketed as

a CFC MDI. It does have an HFA alternative.

Dexamethasone is no longer marketed. Ipratropium, there is now a HFA product, and we are assured that this will be withdrawn from the market

in the not too distant future, aerosolized talc for pleurodesis, ergotamine MDIs, and anesthetic drugs. So, you can see here that we are really paring down this list, and there are just a few products remaining.

As I said, in July, we discussed all the things in white here except for epinephrine, and we are here today to discuss that.

[Slide.]

So, these are the moieties where there has

been no current reformulation or direct alternative, and as I said, the important one for today is epinephrine. We already went over that point, I won't belabor it.

[Slide.]

Just to show you where all this has led worldwide, in 1996, at the start of the CFC ban, the essential use process actually exempted nearly

14,000 metric tons of CFCs, and we are down close to 2,000 for the year 2006, so there has been a substantial decline in all the parameters here, the amounts exempted by the parties, the amounts

actually used by the countries participating, and the stockpiles, as well.

So, we are getting to the latter parts of the phaseout, and it has been successful.

[Slide.]

So, a few slides as conclusions. The U.S. Government moved proactively to address the issue of ozone depletion and has had a key role in the success of the Montreal Protocol.

As I stated, that treaty is regarded as a

very model of a successful environmental treaty, and it has led to important reductions, not only the in the admissions of CFCs, but in many other ozone-depleting substances, as well.

[Slide.]

I believe this is my next to the next slide. This is the amount of chlorofluorocarbon or actually the equivalent amount of chlorine from

chlorofluorocarbons in the stratosphere, and the Y scale here is rather limited, but nonetheless, since the Montreal Protocol went into effect, there has been a decline in the amount of emissions of

CFCs or the amount of chlorine in the stratosphere as a result of there being fewer CFCs emitted and making their way into the stratosphere.

The ozone layer is expected to recover by the middle part of this century. There is some

unfortunate news that this may be a little bit later than 2050, recovery meaning to the 1980 levels, so not perhaps at the historical high, but back to the 1980 levels.

[Slide.]

So, the U.S. is progressing in the CFC transition. There are a lot of non-CFC products available at this point, and many CFC products have been withdrawn from the market without regulatory action, I might add.

Epinephrine MDIs arguably are unique in their therapeutic niche. They are the sole OTC bronchodilator available as a metered dose inhaler.

As Charley mentioned, there are provisions for bulb nebulizers, but as a metered dose inhaler, epinephrine is the sole OTC product.

So, the question really to the committee is do these OTC epinephrine MDI products remain an essential use in the year 2006.

[Slide.]

Again, the criteria that you need to consider are whether it provides a substantial health, public, or environmental benefit, again focusing on the health and perhaps the public benefit.

We would welcome your opinions on these other matters, but I don't believe any of you are atmospheric scientists, and I certainly am not, and I would also point out that under the Montreal Protocol and, in fact, under the U.S. laws, we don't really get into de minimis arguments, in other words, it is accepted that these CFCs will be phased out in total, and we don't look at individual uses as being small, for the most part because of the fact that we have accepted that all

CFCs should go away, and if you look at any individual use, if you parse down any kind of broad use into its individual components, you can start to argue that a particular use is small.

So, with that, I would be happy to take some clarifying questions.

DR. WOOD: Let's go back to your last slide. Our job is to essentially determine whether this provides substantial health benefit.

DR. MEYER: Right.

DR. WOOD: That is a higher hurdle than we usually apply actually.

DR. MEYER: You could certainly regard it that way.

DR. WOOD: I mean it is certainly higher than the regulations for approval of a new drug, for example.

DR. MEYER: Right.

DR. WOOD: Okay. Got it. Any questions?

[No response.]

DR. WOOD: Let's go straight on. The next speaker has canceled, so we are going to go

straight on to Dr. Berlin's talk.

Wyeth Consumer Healthcare Products

DR. BERLIN: Thank you, Professor Wood. I am Roger Berlin, President of Global Scientific Affairs for Wyeth Consumer Healthcare. We market Primatene Mist. It's the leading over-the-counter epinephrine metered dose inhaler, a product that consumers have relied on for about 40 years.

I want to thank both committees, the Nonprescription Drugs Advisory Committee and the Pulmonary and Allergy Drugs Advisory Committee for giving us this opportunity to come before you and defend the continued essential use exemption for epinephrine metered dose inhalers, which currently do contain CFCs as propellants.

[Slide.]

Our purpose today is to demonstrate that epinephrine metered dose inhalers, which I will refer to as epi-MDIs, meet all three elements required for essential use exemption: specifically, number one, the product provides a

significant public health benefit; number two, the release of CFCs from the product is small and justified given the benefit to consumers; number three, there is no technically feasible alternative currently.

We will provide data to support all three criteria as each is important to your overall consideration of this issue.

[Slide.]

We will also answer the specific FDA questions posed in the Federal Register notice announcing this meeting and shown earlier by Dr. Ganley, and we have recapped the questions here, and I will read through them.

1. Who currently uses OTC epinephrine metered dose inhalers?
2. How many of these MDIs are used annually?
3. What are the alternatives if these products are no longer available?
4. From literature sources, what is the value of the use of these products to the users,

and why do they use them?

5. What established treatment guidelines recommend the use of the product?

6. How many people with asthma do not have ready access to prescription medication through health care professionals?

We will use the available data to do our best to answer each of these questions for you.

[Slide.]

Before we get into the substance of our presentation, I want to make some general remarks in three important areas, and the first concerns available data.

We acknowledge that there is a limited amount of data on the product. The clinical studies, although well designed, have been done with small numbers of patients, and some of the data are from consumer survey research, some that we have conducted, and some from academic centers, but we think these data are of value in your deliberations.

We will show you what is available and

hope that you will concur that the body of evidence tells a consistent story of a product that is safe, effective, and needed by a substantial number of consumers.

We apologize for providing additional material to you this morning with your slide packet. This packet contains two additional publications, a colored copy of the label being implemented, and an update on specific data in your background package based on our ongoing quality review, and, of course, today's slides.

My second point concerns the role of an OTC asthma treatment. We recognize and respect the position some committee members may have that in the ideal world, all asthmatics would be cared for by experts, and their recommendations would be fully consistent with the National Asthma Education Prevention Program guidelines, and furthermore, that all patients would be 100 percent compliant in following those recommendations.

In the real world, however, we often fail to reach perfection, thus, the best choice may be

imperfect, but better than the alternative. We would ask that you keep an open mind in regard to the data we present, which we hope will convince you that the risk of removing this product is

significant and the current use is providing a benefit.

[Slide.]

My final introductory point concerns Wyeth's corporate responsibility with regard to

product and CFC emissions. I want to strongly emphasize that we are actively developing a CFC alternative. We intend to work with the FDA and our partner to bring this product to market as rapidly as possible.

All we ask is the ability to keep the product available over the counter to consumers until an acceptable alternative can be developed and approved.

[Slide.]

With these points in mind, here is our agenda. I will discuss the essential use criteria and respond to the FDA's questions, and I will

begin by describing the product and how it fits with the accepted guidelines for the treatment of asthma.

I will present the data that defines the public health need for the product. Then, I will discuss the amount of CFC emissions from the product, and talk about the technical barriers to reformulation, but importantly, the progress we are making in that effort. I will then proceed to a summary and conclusions.

[Slide.]

With us today is Stephen Campbell, Senior Vice President of Regulatory Affairs from our HFA development partner, Amphastar, and he is here to answer any questions you may have on the process of developing an alternative technology that does not harm the environment.

Also available is Dr. Kenneth Dretchen, Professor and Chairman, Department of Pharmacology, Georgetown University Medical Center, to address any questions you may have in his area of focus, autonomic pharmacology, in particular, epinephrine.

We would ask that, if possible, that you hold your questions until the conclusion of our presentation.

[Slide.]

Asthma, as you well know, is a chronic disease which is characterized by acute attacks, and pharmacotherapy for asthma thus falls into two general categories.

Controller medications are administered to prevent symptoms either by treating underlying inflammation or by provide long-lasting bronchodilatation, but asthma episodes cannot always be predicted or prevented.

Reliever medications, short-acting bronchodilators, such as epinephrine, are necessary to treat acute symptomatic episodes, the hallmark of the disease, and these episodes can come on suddenly with no warning, sometimes in the middle of the night, which is why reliever or rescue medicines, such as this product, are such a critical part of the patient's armamentarium and access is such a critical issue.

[Slide.]

We will begin with a brief review of the pharmacology. Epinephrine is a non-selective beta-adrenergic agonist with rapid onset, short duration of action, and alpha-agonist activity.

Specifically, the onset is approximately 15 seconds, and the duration of action, about 20 to 30 minutes. It is rapidly metabolized by catechol-O-methyltransferase and monoamine oxidase, and the alpha-agonist effect, which constricts the blood vessels, decreases systemic absorption of the drug, which improves tolerability.

[Slide.]

Let's consider how the product is labeled. The complete label is in your supplemental packet, as well as Appendix 7 of the backgrounder.

[Slide.]

This slide shows an excerpt regarding the uses. The product is labeled for temporary relief of occasional symptoms of mild asthma, wheezing, tightness of the chest, and shortness of breath, and thus, fits into the reliever category.

[Slide.]
The product is indicated for people who have been diagnosed with asthma by a doctor.
[Slide.]

The label also includes a warning to see a doctor if the consumer has more than two asthma episodes in a week.
[Slide.]
Although the product is labeled for use in children, data suggests that very little of the product is actually sold for use in this population.
[Slide.]
This picture shows what consumers receive when they open the product. The metered dose inhaler is shown on the top, and the insert, which repeats the label and also provides instructions on how to use the inhaler, is shown below.
[Slide.]

There is also a Primatene website. On the website, you can also find detailed information on how to use the product including graphic depictions

of how to administer the metered dose inhaler.
[Slide.]
The website also provides a learning center where consumers can get general information

on asthma. The website emphasizes that asthma is a serious disease that affects the way you breathe and should be diagnosed by a physician.
[Slide.]
Consumers can also learn what can trigger

or exacerbate asthma and other information, such as warning signs regarding their condition, and the full text of the website is also included in your background package in Appendix 7.
The package label, the package insert, the

website, and the 1-800 number all direct consumers to an emergency room or doctor if not responding to the medication or using it too frequently.
[Slide.]
The labeled use for the product is

consistent with the National Asthma Education and Prevention Program severity category of mild, intermittent asthma, as shown on the top panel.

The use is also consistent with the recommendations for quick relief of an asthmatic episode, which includes patients of all severity, and specifies treatment with a short-acting bronchodilator, as seen in the lower panel.

As noted previously by the FDA presentations, epinephrine metered dose inhaler is the only FDA-approved and proven effective short-acting bronchodilator in a metered dose form that is available without a prescription.

[Slide.]

I would like to emphasize that the product has a long history of safe and effective use in this country, with the first NDA being approved in 1956. Through the marketing history, we estimate that 183 million canisters have been sold, which translates to approximately 25 billion dosing episodes.

Between 2 and 3 million asthmatics currently rely on the product either in addition to their existing prescription asthma medication, or to a lesser extent, as their sole asthma relief

product. So, 15 to 20 percent of all U.S. asthmatics use this product each year.

[Slide.]

I will now sequentially address the three criteria necessary for essential use exemption beginning with a discussion of how epinephrine metered dose inhalers provide an otherwise unavailable public health benefit.

[Slide.]

In this section, I will demonstrate that there is a need for a reliever medication that consumers can easily--

DR. WOOD: You keep quoting that. Just let me interrupt you.

DR. BERLIN: Yes.

DR. WOOD: You keep quoting that. That is not actually what the regulation says, is it?

DR. BERLIN: I am sorry?

DR. WOOD: Otherwise unavailable important public health benefit. I thought it was a substantial public health benefit.

DR. BERLIN: Well, I believe this is the

correct language, but we will provide evidence during the talk, which does demonstrate that this provides a substantial and otherwise unavailable public health benefit, and if I am in error

slightly in the verbiage, I do apologize, but I think the evidence that we are presenting--

DR. SCHOENFELD: Is now joining.

DR. BERLIN: However the question is phrased, we will, in fact, answer that question.

DR. SCHOENFELD: Is now exiting.

DR. WOOD: Is that Dr. Schoenfeld? Okay. Go ahead.

DR. BERLIN: Thank you.

I will demonstrate that there is a need

for reliever medication that consumers can easily access OTC, that there are no other proven and safe effective FDA-approved reliever medications available as MDIs OTC, that without this product, consumers may turn to alternatives that are

unproven, possibly unsafe or ineffective, or would put a greater burden on our already overburdened emergency health care system, and that consumers

are generally using the product in accordance with the label and consistent with the NAEPP guidelines.

The data come from different sources and while each alone may not be definitive, they do

provide directionally consistent answers over time and across methodologies. I will also demonstrate that the product is effective and generally well tolerated, and I will begin by profiling the users of the product.

[Slide.]

Data show that there are two populations of people who use the product, the first being individuals who use this as their sole asthma medication, in many cases because of a lack of

insurance or financial resources to access prescription medication.

The second and larger group are dual users who utilize an OTC MDI as a stopgap when they run out of their prescription or don't have it handy.

Two independent, peer-reviewed academic studies provide further insight on these populations.

[Slide.]

Data from Kuschner, et al., shown here, suggest that, in general, both populations tend to have mild, intermittent asthma, and what they did is they recruited 50 asthmatic adults by

advertising and collected data via questionnaire and measures of lung function.

[Slide.]

On this slide, sole OTC users are shown in the green column on the left, dual OTC and Rx users

in the middle, and sole prescription users on the right, and this is a format you will see repeated in several following slides.

Ninety-three percent of the sole OTC users and 92 percent of the dual users had been diagnosed

by a physician in compliance with the instructions on our label. Sole users had been hospitalized for asthma less frequently and a smaller percentage had visited an emergency room, probably reflecting milder disease.

They also did pulmonary function tests, and I will highlight those on the next slide.

In sole users, the mean FEV1 was

approximately 90 percent and the peak flow variability approximately 10 percent. As you can see indicated by the callout box on this slide, these results fit comfortably into the NAEPP

pulmonary function definition of mild, intermittent disease.

[Slide.]

An intriguing study by Blanc, et al., looked at the use of OTC medications in asthmatic

adults who were being treated by pulmonary and allergy specialists.

They recruited 601 asthmatic adults from a random sample of specialist doctors, and they used a validated questionnaire to obtain information,

and the study specifically looked at the 12-month prevalence of reported use of OTC products and the potential association with two or more emergency room visits or any hospitalization for asthma, and the results are shown on this slide.

[Slide.]

What they found was that the frequency of use of OTC self-medication over 12 months was 6

percent even in this population seen by specialists, and given that these are asthma patients being treated by pulmonologists or allergists, these patients are all probably dual

OTC and prescription users.

Self-treatment with nonprescription products was not associated with a risk of two or more emergency room visits, as shown by the odds ratio of risk of 0.5, nor with hospitalization,

with an odds ratio of risk of 0.8, both less than 1.

[Slide.]

The study also look at the use of herbal teas and medications, and coffee and black tea.

The use rates were between 6 and 8 percent, similar to the rates seen with OTC asthma medications shown on the previous slide, as opposed to the lack of association seen with the FDA-approved OTC drugs, herbal teas and medications in coffee or black tea

did increase the odds ratio of risk for ER visits and/or hospitalizations, and the differences that are statistically significant are shown in green,

for example, the 2.5-fold increase in hospitalization associated with the use of herbal teas and medications.

It is important to keep these results in mind as we seek to answer the FDA's question about available alternatives if the product would be taken off the market.

We will now turn our attention to the Wyeth consumer survey data, which appeared to confirm what we have learned from these academic studies about who uses the product.

[Slide.]

This slide summarizes the five consumer survey research studies that have been conducted in order to understand more about the epinephrine metered dose inhaler user. Two of these were Nielsen studies, and the remaining three studies were sponsored by Wyeth.

We obtained data from a total of 4,332 asthmatics, of whom almost half or 1,944 used OTC asthma medications. These studies were conducted utilization standardized methodologies well

accepted in this area of investigation, and the samples were designed so that the results would be representative of the entire U.S. population.

I am going to walk through these studies briefly just to provide some perspective about how they were conducted and the questions that they asked.

[Slide.]

The first, the 1993 Nielsen Health Study, was a mail questionnaire of 61,000 adults, which yielded a sample of 2,713 past year asthmatics, and it looked at ailments, how they were treated, and the reasons for treatment choices of the respondents.

The second was a 1994 Nielsen Household Panel Study, which examined purchase incidence and frequency of purchase among 575 households that had purchased OTC medications, OTC asthma medications over the past 12 months.

[Slide.]

The third was a 1994 telephone survey, which looked at more than 800 asthma patients ever

treated with OTC drugs, more than 500 in the last year, and asked about their symptom profile, brands used, and physician involvement.

The fourth study was a Primatene Usage Study, which phoned 123 past year users to assess their symptoms and physician involvement.

Finally, the fifth was a 2005 Survey of Asthmatics conducted on the Internet, balanced to reflect the U.S. Census, which specifically looked at symptom profile, brands used, physician involvement, and insurance coverage among nearly 400 asthmatics.

[Slide.]

Shown here are the demographic characteristics of the survey population by study. The OTC user group, in general, resembles the total U.S. population on many demographic variables, the average age range from 39 to 45 years of age, 73 to 90 percent were Caucasian, and between 20 and 33 percent reported an income of less than approximately $20,000.

[Slide.]

In order to investigate how many people use epinephrine metered dose inhalers, how they used them, and how much they used, we have used data from the Centers for Disease Control combined with our own consumer survey data.

Now, the CDC estimates that there are 13.6 million current adult asthma patients, and based on our 1993 consumer survey, we estimate that 2 to 3 million, or 15 to 20 percent, of all of these U.S. adult asthmatics use an OTC asthma medication.

Our 2005 study indicates that about two-thirds are dual users of OTC and prescription products, while about a third use only an OTC product.

Finally, taking data on the number of canisters sold, which is derived from IRI, an organization with expertise in measuring sales of consumer products, and considering the number of purchasers, we can estimate that the average consumer use is 1.5 to 2.3 canisters per patient per year.

[Slide.]

This slide presents data about who uses the product and compares sole OTC users and dual OTC and Rx users to sole prescription users. More than 90 percent of both sole and dual OTC users had

been diagnosed by a doctor, which confirmed data that I showed you earlier from Kuschner.

Dual OTC/Rx and sole Rx users appear similar as expected given that both are under the care of a physician for their asthma, however, sole

users are much less likely to have visited a doctor for asthma treatment in the past year and less likely to have medical insurance or prescription drug coverage, and the statistically significant differences are highlighted in green.

[Slide.]

In a moment, I will talk about why consumers use the product, and you will see that there is a recurring theme, and that is access to medication and medical care.

Data show that this is a huge issue, and this is an issue that is not confined to this particular drug product. In 1999, Commonwealth

Fund Study found that 40 million Americans went without health care due to cost. Ninety-one percent of the uninsured, but importantly, 44 percent of the insured, who had delayed or did not obtain

health care, did so due to cost, and this was according to a report for the Center for Studying Health Care System change.

The U.S. Department of Labor says that there are 59 million working Americans who do not

have paid sick leave, which raises issues about the ability to take off work to go see a doctor. Even where people have prescription drug coverage, when there was a 2-fold increase of the co-pay, it resulted in asthmatics using 32 percent less

medicine as reported in a 2004 JAMA article.

So, it would appear from these data that both the insured, but more so the uninsured did without needed health care including filling prescriptions due to cost.

In the 2005 Internet study, sole OTC users cited access and cost as their most frequent reasons for using the product, and I will read

verbatim the three most frequent responses were: It is easier and quicker to obtain, it is more reasonably priced, and I don't have health insurance.

It was not clear from the survey whether the fourth reason, "I don't want to go to the doctor," may also have been related to cost. The last reason given was that, "OTC drugs work better for my asthma," and we believe this may be

attributable to the rapid onset of relief with this product, which I will discuss when I talk about efficacy.

[Slide.]

For people who use both prescription and

OTC medication, the so-called "dual users," access may be more related to the availability of the product for quick relief during an acute asthma episode when they don't have access to their prescription inhaler.

Lack of availability of a prescription inhaler is the most frequent reason cited with specific responses of "When I run out of my

prescription medication," or "When I have an asthma attack and don't have my prescription with me." The last reason, "When I feel an OTC medication will work better," may again reflect the extent to

which consumers value the product's rapid onset of relief during an acute asthma episode.

[Slide.]

We now turn to how consumers are using the product, and this slide looks first at the general

OTC use pattern, that is, both sole and dual users. It appears that the majority of product use is consistent with our label and is consistent with the NAEPP definitions of mild, intermittent asthma.

Specifically, 75 percent use the product

once per week or less frequently, 80 percent obtain relief with 1 or 2 inhalations, and 76 percent purchase one or two canisters per year.

The next slide which we will show focuses on the sole OTC users only.

[Slide.]

These data show that sole OTC users also use the product appropriately. They appear to have

milder asthma, as evidenced by fewer attacks and fewer visits to the emergency room, and they largely medicate for rescue.

Thus, sole OTC users are also using the product according to the label and consistent with the guidelines. Before turning to the data on safety and efficacy of the product, I would like to conclude this section by emphasizing that the product is the only asthma reliever MDI that is available without a prescription. Other products, such as herbals, have not been shown to be effective and data from Blanc, et al., suggests a 2.5 fold increased risk of hospitalization with herbal use.

[Slide.]

To summarize this section of our presentation, we believe that the product is needed because 2 to 3 million asthmatics rely on it either as their sole asthma medication or to back up their prescription medications during an acute asthmatic episode. It is the only asthma reliever MDI medication that has safety and efficacy data behind

it, which I will present in the next section.
[Slide.]
We believe that the data are sufficient to support the safety and efficacy of the product.

The studies we will review show that the product is an effective bronchodilator, and the pharmacology of inhaled epinephrine provides an explanation for the favorable safety profile seen in extensive marketed use. The few reported deaths, we believe

seem predominantly not related to the use of this product.
So, now, I will walk you through three studies that examine the efficacy of the product. The first two are in your background package, and

the third, which was recently published, has been provided to you in this morning's packet, and that is the study by Hendeles.
[Slide.]
These studies showed that the product is

effective in improving FEV1 in asthmatic patients, and the inclusion of a well-characterized beta agonist comparator in two of the three prospective

clinical trials increases our confidence in these results.

The first study by Pinnas and colleagues was published in 1991. In this study, all patients had moderate to severe asthma as defined by an FEV1 of between 30 and 80 percent of predicted with a mean FEV1 on entry of 55 percent.

Patients received either two inhalations of epinephrine, metaproterenol, or placebo given one minute apart in a full crossover design study, and I am going to focus on the effects seen during the initial 15 minutes prior to the administration of an oral bronchodilator.

[Slide.]

Although this product is indicated for mild asthma, this study demonstrated efficacy in moderate to severe asthma, and to orient you to this slide and the subsequent graphs, epinephrine is shown in red, active comparator in yellow, and placebo in green, and we have indicated the drug administration and the number of inhalations by the arrows. Time is on the horizontal and a measure of

FEV1 on the vertical.

The results expressed here are percent change in FEV1 on this particular graph.

The change in FEV1 exceeded 15 percent in all epinephrine treated subjects within 15 seconds of the second inhalation. Improvement in FEV1 with inhaled epinephrine was significantly better than placebo beginning 40 seconds after the first inhalation of the product, and as a point of comparison, onset of effect with epinephrine was statistically faster than with metaproterenol.

The last data point at 15 minutes shows comparability in therapeutic effect of both actives, and although the data are not shown here, inhaled epinephrine had no significant effect on heart rate.

[Slide.]

The second study by Dauphinee and colleagues in 1994 demonstrated efficacy in mild to moderate asthma. This was a randomized, double-blind, placebo-controlled crossover study in 24 patients who had mild to moderate asthma with an

average FEV1 on entry about 65 percent of predicted.

The dose of inhaled epinephrine was one inhalation followed by another inhalation one minute later.

[Slide.]

As this graph shows, this study demonstrated efficacy of the product in relieving mild to moderate asthma. The graph illustrates the response in percent improvement in FEV1 with success being predefined as an increase of 15 percent or more over baseline, 46 percent of epinephrine versus 4 percent of placebo after one inhalation, and 88 percent of epinephrine versus 16 percent of placebo after two inhalations met the predefined criteria for success.

The mean time to peak improvement was 7.5 minutes. The duration of response for the epinephrine group, that is, the time that the improvement in FEV1 exceeded 15 percent, was 23 minutes. The data again are not shown here, but it is important to note that there were no clinically

or statistically significant effects seen on heart rate or blood pressure with epinephrine.

[Slide.]

The third study by Hendeles was a randomized crossover study conducted in 8 inpatients with nocturnal asthma. These patients had a daytime FEV1 which exceeded 60 percent and a 20 percent or greater decrease in peak expiratory flow on at least 4 of 7 nights.

They had a mean FEV1 prior to treatment of about 45 percent, and the dose of epinephrine or albuterol was two, four, and eight inhalations given at 17-minute intervals.

[Slide.]

This slide shows that the product was effective in nocturnal asthma, and once again, drug administration is depicted by the arrowheads with the number of inhalations show inside those arrowheads.

We have shaded the left side of the graph in dark blue, because these are the results with the recommended dose of each agent. The lighter

area to the right shows the effects with exaggerated doses.

At the onset of the symptoms, FEV1 was similar in the two groups and significantly reduced from baseline, and either epinephrine or albuterol was given at the time patients awoke due to symptoms. So, that brings us finally to the results.

Two actuations of both epinephrine and albuterol, the recommended dose of each produced comparable improvements in FEV1, as shown at the 17-minute time point. The similarity of responses seen over the entire range of doses, even though there are two time points, were albuterol is statistically better than epinephrine with differences of 9 and 11 percent at 34 and 68 minutes respectively.

The maximum FEV1 achieve was 86 percent after epinephrine and 93 percent after albuterol, and again the difference was statistically significant.

This study importantly demonstrates that

epinephrine and albuterol were similarly efficacious in improving FEV1, especially when each was administered according to the label.

As I will show you in a few minutes, even the exaggerated doses did not result in an increased heart rate in the epinephrine group.

[Slide.]

Let's now focus on the safety profile of epinephrine metered dose inhalers, and given that epinephrine is a non-selective beta agonist, it is useful to consider the pharmacologic features that explain the favorable safety profile of the product, and there are several.

First, only 5 to 10 percent of the dose is absorbed systemically.

Second, epinephrine is rapidly metabolized by COMT in the lungs and by COMT and MAO in the blood.

Third, plasma levels are only elevated with exaggerated dosing, and even then, rapidly return to baseline in about 20 to 30 minutes. So, with limited systemic bioavailability, even at high

multiples of the recommended dose, it is not surprising that systemic effects are modest.

[Slide.]

On this slide, the red horizontal dashed line shows peak plasma epinephrine levels seen during vigorous exercise. From the study by Warren, as shown by the bar on the extreme right, it takes about 45 puffs, more than 20 times the recommended 2-puff dose, to approach the epinephrine levels seen during strenuous exercise.

[Slide.]

So, due to the limited absorption and rapid metabolism of epinephrine, it is therefore understandable that even after 45 actuations, there was only a modest increase in heart rate of 9 beats per minute in the Warren study, and these data suggest a wide therapeutic window for epinephrine metered dose inhalers.

[Slide.]

We are now returning to data from Hendeles. Data from Hendeles show that at 4 times the recommended dose, epinephrine did not result in

an increased heart rate. Plotted here on the vertical is heart rate in beats per minute. As a reminder, the red line is epinephrine, and the yellow line is albuterol.

Albuterol did cause significant increases in heart rate as the dose was increased, and there was a significant difference with epinephrine, and although the data are not included here, there was no change in blood pressure or EKG tracing for

either epinephrine or albuterol.

[Slide.]

Let's now turn to adverse events, specifically, death. The data show that there have been relatively few deaths reported over the

40-year history that the product has been available to consumers despite the fact that 183 million canisters have been sold and there have been approximately 25 billion dosing episodes.

To gather the data for this section, we

reviewed all spontaneous reports submitted to Wyeth since 1964 when we assumed the NDA and began to market Primatene Mist. All cases reported to the

American Association of Poison Control Centers during the period 1983 to 2005 were also reviewed, and I should note that 1983 is the date the Poison Control Center started its surveillance system.

From Wyeth and poison control centers, there were a total of 35 fatalities over 40 years. Since the preparation of the background document, we have obtained preliminary data from two FDA databases, the SRS, which covers 1969 through 1997,

and the AERS, which covers 1997 to 2005, and there were 15 cases from the FDA's database, but there still may be some overlap with our cases and we don't have sufficient data from these cases at this time to assess causality.

As we examine Wyeth and poison control centers' fatality reports in the next slide, the true number appears smaller and few appear attributable to the drug.

[Slide.]

We have attempted to categorize the cases recognizing that given the limited data, the categories assigned are our best approximations.

Of the 35 cases, we categorized 21 as providing insufficient information to fully assess causality.

Seven of these cases were deemed probably not related, including one reported death of a model. In 5 cases, significant purposeful abuse of the product was noted. There were 2 cases that we classified as possibly related to the administration of the product.

The first was a coroner's report of an 18-year-old who used epinephrine metered dose inhaler prior to playing soccer, and during the game, she collapsed and died, and the probable cause assigned by the coroner was arrhythmia secondary to asthma.

The second case was a 29-year-old asthmatic who had used the product for 16 years and suffered a fatal myocardial infarction, but no further information is available.

I want to put both of these numbers in perspective. We are talking about a total of 50 deaths when you count the FDA and the Wyeth and AAPCC data, and that is based on this 40-year

marketing history with 25 billion estimated dosing episodes.

For further reference, I would just note that there are approximately 5,000 reported deaths a year in the United States which are believed to be due to asthma.

It is important to point out that over the years, the safety of the product has been evaluated and debated by experts outside of and within the FDA, and they have seen most of the data that I have shared with you, and despite initial skepticism, their conclusion has been that they cannot identify a signal that the OTC use of the product poses a significant safety risk.

[Slide.]

Similarly, after considering the benefits and the risks, the need for a product for over-the-counter use has also been acknowledged, and I quote from the report on the Council of Scientific Affairs of the American Medical Association, which was published in Chest in 2000, and it says, "The availability of at least one OTC

asthma quick relief medication also allows individuals with mild asthma and those who do not have access to the health care delivery system to self-medicate."

[Slide.]

Just this past July, the FDA reaffirmed its confidence in the public health need for the OTC bronchodilator drug products. Specifically, they said, "FDA continues to believe that people with mild asthma can properly use OTC bronchodilator drug products to self-treat occasional wheezing, shortness of breath, and tightness of chest after their asthma has been diagnosed by a physician."

[Slide.]

Let's consider the alternatives. If the product were to be removed from the market, the alternatives would be as follows. First, emergency department utilization, which is already strained, may increase. Many patients without physicians already use them for routine care, and many departments are closing due to a lack of finances.

Patients may be forced to wait or to travel a distance to obtain emergency care, and the factor of cost for emergency care should not be ignored.

Based on data from a 1996 study of

Williams, of six community emergency rooms in Michigan, he estimated that the average charge to the patient was $312 for semi-urgent care and $621 for urgent care, and treatment of an acute asthma exacerbation would fit in one or the other

category.

Secondly, if the product were not available, consumer may seek out other alternative therapies that have no proven efficacy or safety. In fact, data I presented earlier showed consumers

taking these products are more likely to end up in an emergency room or hospitalized.

For dual users, let's consider the situation when a patient discovers after office hours that he has run out of his prescription or

left it behind, and goes through what I will call "channels," to obtain a refill.

So, the patient with an acute attack calls

the service, and the on-call physician after some delay calls the patient, and after speaking with the patient, calls the pharmacist, who then has to fill the prescription, and obviously this is not a

time cycle attuned to relieving an acute asthma episode.

Two-thirds of those who use the product, the dual OTC and Rx users, are already under the care of a physician, and we have reviewed the

significant issues of access to care that some of the sole users may face, and I would also add that our data show that 28 percent of the sole users have seen a physician in the last year for asthma.

So, while some users could attempt to go

to the emergency room or through routine channels or physicians to get medication, it would appear that taking the product off the market might exacerbate the problems that the patients face.

[Slide.]

I will now briefly recap the points that support the first element of essential use that epinephrine meets an otherwise unavailable

important or substantial health benefit.
Studies showed that 15 to 20 percent of all U.S. asthmatics rely on the product either as a stopgap when their prescription medication is

unavailable or because they otherwise have limited access to reliever medication.
The product has been shown to be an effective bronchodilator with a favorable safety profile, and its use by consumers is consistent

with the NAEPP definitions of mild, intermittent asthma and the guidelines for bronchodilator use.
Continued OTC access to this medication is critical because there is no other FDA-approved safe and efficacious MDI asthma reliever available.

[Slide.]
We will now focus on Criteria No. 2, that the release of CFCs from the product is small and justified given the benefit to consumers.
As I mentioned at the beginning of this

presentation, we are committed to developing and marketing a CFC-free product, and we are currently making progress toward that goal.

In a moment, I will present our HFA reformulation plan, but I would like to begin by providing some perspective on the current status of the environmental problem that we are seeking to address, and I will build on the excellent foundation provided by Dr. Meyer.

[Slide.]

For a perspective on this issue, I will point out that recently published data are encouraging, and they suggest that the Montreal Protocol is having the desired effect on the earth's ozone layer due to its success in limiting CFC production and release, and data published in the Journal of Geophysical Research indicate that the ozone layer is stabilizing or showing signs of increase, and this conclusion agrees with the 2005 report of the Intergovernment Panel on Climate Change.

The IPCC notes that there are two factors involved in restoring the ozone to its original levels. One is the control of CFC production in the developing nations, and the second has to do

with the release of CFC from so-called banks or CFCs already in existing equipment, such as fixed cooling and refrigeration units in the developed countries.

[Slide.]

Now, let's turn to the data regarding the specifics of the amount of CFCs released from the product. The data show that the epinephrine metered dose inhaler releases minimal CFCs.

The pie chart on the left of this slide captures the current situation with regard to medical uses of CFCs. In relation to other medical products, epinephrine metered dose inhalers represent 4 percent or 74 tons of the nearly 1,800

tons of CFCs granted medical use exemption in 2005.

Now, we recognize that based on your prior recommendation and recent FDA action, prescription CFC-containing MDIs may no longer be available somewhere around 2008, so for a further

perspective, the pie chart on the right illustrates that of the overall release of CFCs--and now we are talking about not just medical, but also

non-medical uses--we account for 0.04 percent of the total.

So, even after other medical use exemptions cease, this product will still represent a very small portion of the total release of ozone-depleting substances, and importantly, we do have a plan to reformulate the product to obviate the release of even this small amount of CFC.

[Slide.]

The third and last criterion for essential use exemption is that there are significant technical hurdles to reformulation, and I will briefly summarize the status of our past and current efforts and provide an explanation of why reformulation is a lengthy and complex, albeit not impossible, process.

[Slide.]

Providing this HFA alternative involves addressing two hurdles. The first is it is necessary to develop a pharmaceutically acceptable non-CFC formulation that delivers the right amount of drug to the appropriate place in the lung, and

then this formulation must undergo an extensive clinical testing program to meet FDA requirements for equivalency with existing product.

[Slide.]

Illustrated here is a clinical development program per FDA requirements for an HFA alternative as specified in a 1994 guidance document. The numbers above the boxes indicate the approximate time it takes to complete that section of the process, so, for example, the pharmacokinetic study takes 6 months, and so forth.

After all the studies are complete, we obviously have NDA preparation and submission, and the FDA has to review and hopefully approve the application. So, the clinical development process, we estimate will take approximately 4 years, and wherever and whenever possible, we will work with our development partner and with the FDA to expedite the process.

[Slide.]

We will now discuss where we are in our HFA reformulation program. I want to emphasize to

you that we have been working to reformulate or source an OTC product that does not contain CFCs for more than a decade.

Initially, we faced two challenges.

First, quite frankly, this was not an area of expertise for us, and we met this challenge by hiring outside consultants who were experts, and the second challenge was more difficult, and that was the wide range of patents that GSK and 3M had

developed around HFA formulations.

Our prototypes came back unacceptably, had unacceptable characteristics in terms of elevated levels of alcohol and delivery pressure, and given the outcome of these efforts, we then decided our

best chance of success would be to work with a partner with more expertise in this specialized area.

Unfortunately, many potential partners we approached were not interested in working with us

given the limited commercial opportunity of the OTC versus the prescription market, but we are pleased to report that we have recently found a partner in

this effort, Amphastar.

[Slide.]

In addition to their expertise in this area of HFA formulation, Amphastar has been able to license university patents that provide freedom to operate outside of the GSK and 3M patents I just mentioned.

Development work on the HFA epinephrine metered dose inhaler was begun approximately one year ago, and progress has been made in that there are now two formulations. One is suspension and one, a solution, and they are both nearing six months of stability.

[Slide.]

I will now briefly summarize our responses to the FDA's questions. Two to three million, or 15 to 20 percent of all U.S. asthmatics, currently use epinephrine metered dose inhalers. 4.5 million canisters are used annually, which translates to approximately 1.5 to 2.3 canisters per individual per year.

As I mentioned, there are no other

FDA-approved OTC MDI asthma relievers.

[Slide.]

Literature and survey data suggest that consumers depend on the product due to a lack of access to prescription medication or medical care, and the use is consistent with the NAEPP guidelines.

[Slide.]

Sole users, those who use only OTC medication, are less likely to have medical and/or prescription coverage. One-third don't have medical coverage, and 40 percent don't have prescription drug coverage.

[Slide.]

So, to summarize, our data are supportive of providing evidence of a safe, effective product that is appropriately used by the consumer. There is no other safe and effective OTC MDI alternative, and availability of the product is a benefit to both the sole and the dual OTC user.

[Slide.]

If the essential use exemption is

maintained for the product, consumers will have access to an FDA-approved OTC reliever while we move forward with reformulation of the product.

[Slide.]

If the decision is made to deny essential use exemption, all OTC metered dose inhalers at some point will be unavailable, there will be no OTC reliever medication, and while we know that few physicians recommend the product, we believe that

it provides an important otherwise unavailable and important public health benefit, and is safe and effective.

Specifically, about 1 million sole OTC users may have no OTC alternative, and the

approximately 2 million dual OTC-Rx users may have no backup if they run out of or do not have access to their prescription inhaler.

In total, that would leave about 2 to 3 million asthmatics without an OTC asthma MDI

option, and that is about 15 to 20 percent of the entire U.S. asthma population.

[Slide.]

In conclusion, we believe we have provided sufficient data to support each of the three elements required under the Code of Federal Regulations to maintain essential use exemption.

We provide an otherwise unavailable important public health benefit.

The product releases a small amount of CFCs, and there are significant technical hurdles to reformulation.

[Slide.]

We are here today to ask you to maintain the essential use exemption while we are developing a non-CFC alternative. Ultimately, given the realities that asthmatic patients face in the real

world, unavailability of this product may pose a greater risk.

With that, I would like to conclude my presentation and thank you for your time and attention.

DR. WOOD: Thank you very much.

Questions for Dr. Berlin from the committee? Wayne.

Question and Answer Period

DR. SNODGRASS: Do you have an estimate of your timeline for availability of a non-CFC product?

DR. BERLIN: Yes. Can we go back to the core timeline slide? We still have yet to meet with the FDA and get concurrence with the final development plan, so I want to be very clear that there hasn't been a chance to have a discussion with the FDA about this.

So, what I have done on this slide is I have laid out what is recommended in the 1994 guidance. As I have said here, I think the clinical development portion of this program would take approximately four years, and we still have to finalize some of the formulation work, so that we would estimate that the clinical supplies would be available in about a year to 15 months, so we are talking somewhere around five-plus years.

DR. WOOD: Bob.

DR. MEYER: I just wanted to go back to a question you raised earlier, Dr. Wood, about the

actual wording of the essential use criteria. The next to the last slide that we just saw has the correct quote, which is "otherwise unavailable important public health benefit."

DR. WOOD: Anyone else have questions?

DR. BRANTLY: Is there anything that is marketed in other places around the world that does not have CFCs?

DR. BERLIN: I checked the various databases that list OTC product availability in other places in the world. The only place that I am aware of that has an OTC sale of bronchodilators is, in fact, in Australia and New Zealand. It's under a different category.

It is called S3, which means that it is restricted to being dispensed by the pharmacist, so it is not on the shelf in front, and there is a treatment guideline that the pharmacist can choose to follow, it depends on where in the country, in dispensing the product, and I can't tell you whether, in fact, that is a CFC-containing or HFA propellant product.

DR. BRANTLY: So, what you are saying is that there is no over-the-counter bronchodilators at all in Europe?

DR. BERLIN: To the best of my knowledge.

I checked the Trade Association for Nonprescription Drug Use in Europe, which is called AESGP, and when I looked through their database, there were, in fact, no listings of an OTC product, but that said, I need to point out what I am sure is apparent to

everyone sitting around the table, that the health care system and the provision of prescription medicine is extremely different in Europe where most people don't pay for either visiting the doctor and/or any prescription medication. Even

some OTC medicines in some countries are covered under the health plans.

DR. BRANTLY: But it seems if there is no availability anyplace else in the world, and asthma deaths and morbidity are certainly no worse there

than here, how can you argue that it is such a critical need?

DR. BERLIN: The use of the product as an

OTC in the United States, I think has to be considered within the context of what our health care system realities really are, which is why I shared some of those data with you about the

problems that people face in accessing health care, and the fact also, I think, that needs to be taken into account is that two-thirds of the people who use the product are actually under the care of the doctor, and about 90 percent of both the sole users

and the dual users have been diagnosed by a physician.

The other point that I think it is important to keep in mind as a context for the discussion is that the data on how these consumers

used the product indicates that the vast majority are, in fact, using the product appropriately, that the product fits into the guidelines in terms of a short-acting beta agonist, bronchodilator, that they tend to use the product infrequently, that

they tend to use one or two puffs, that they tend to buy relatively few canisters per year, and the overall safety record is really very favorable.

There is, I believe, a pharmacologic reason to believe why that would be the case, so I think that this product in the context of the United States is used safely, and it is also

important to these consumers, and I read you some of the responses about why and how they value the product.

DR. BENOWITZ: Just one further question. Why was this product not available by prescription?

If it is comparable to albuterol in terms of effect and safety, how come it is not available as a competitor by prescription?

DR. BERLIN: I will take an initial attempt to answer that question, and then I think

if I don't do a good job, I will ask the FDA to help me out on this.

This product was initially approved in 1956, and at the time, there was a review panel, and the review panel determined that this was

appropriate as an effective bronchodilator and effective for use without a prescription. By the way, that is an opinion that has been reaffirmed on

multiple occasions when this product has been reviewed, and that is sort of how it came to be.

The standards I think have changed in what is required in bringing a new drug to market, so I think that if you were to bring a new molecular entity to market now, it would be highly likely that it would be approved direct OTC, but I think the situation here is very different.

We have a product. It has 40 years of safety and efficacy data behind it, and based on that, and even during these recurrent reviews, these expert panels have continued to feel that it is appropriate to have this product OTC.

DR. BRANTLY: I am troubled by we keep using the word "efficacy," and basically, the only data is that epinephrine basically increases the FEV1, which really doesn't meet the--I mean that is expected from the pharmacology and doesn't have any clinical outcomes other than temporary relief.

Are you aware of any studies that demonstrate that inhaled epinephrine decreases the number of ER visits, or any other sort of clinical

outcome that would sort of really demonstrate efficacy, meaningful efficacy?

DR. BERLIN: There is data in the Hendeles paper, which suggests that in addition to FEV1, the product is effective in relieving symptoms.

Let me go back and show some of the data which I think might help to address some of the concerns you raised, and why don't we begin with the Kuschner data, and then we can go on from there.

Can we bring up the core talk, please? Sorry, it will take us just a moment to bring up the slide.

Okay. Again, I understand the limitations of the database that we are dealing with, but this group in northern California went out and identified these patients, and then they looked at outcomes.

Now, outcomes are not necessarily related to what drug you use, there are other things that are going on, but what they found, in fact, is that the sole users tend to be hospitalized less. They

had a lower percentage of visiting the emergency room.

Slide off.

DR. WOOD: Just before we put it off, do I understand the n on that slide, these are 13 people?

DR. BERLIN: Absolutely.

DR. WOOD: The percentages of 13 people and comparing that? Will you put the slide back on just so we can see it again?

DR. BERLIN: You are absolutely correct. I began the comment by trying to indicate that we have a limited amount of data. I am doing the best with what we have to try to at least directionally provide some information about what the data would indicate.

We also have some data from Australia, and I will show that data to you. That's the Camino data, please.

Again, we had discussed earlier that albuterol is available--as a matter of fact, I think we won't show that because the data are more

pertinent to albuterol. But the point of showing that was simply to make the point that people who bought their product OTC did not have a greater risk of hospitalization or ER visits.

So, the last piece of information I think that we have in terms of what are the outcomes, again, with a limited database, and, you know, I have tried to be very transparent about that even in the introduction to the talk is that if you look

at the data, for example, from Kuschner, they also looked at what the FEV was or the FEV measurements were at 7 a.m., after the treatments, when the patient awoke, and, in fact, they were comparable.

Now, one other way of looking at this, and

it is an indirect way of looking at this, I realize it may not fully satisfy the question that you asked, is, well, can we learn something from the way that consumers use the product.

I think what you see is that they tend to

use it episodically, and they use a small number of puffs, and when we actually asked consumers how they valued the product in terms of whether it

worked for them, over 90 percent said that they rated the benefit of the product as good, very good, or excellent.

DR. WOOD: Dr. Gay.

DR. GAY: I have two questions. I am hopeful you can clarify for me a little bit of the utilization characteristics of this drug. By your own data, you are saying that 75 percent of these patients or approximately 75 percent of these

patients use this about once a week, and that about 80 percent of the patients use one to two puffs to completely relieve their symptoms.

However, you speak about selling 4.5 million units of this drug, and at about 250 to 270

puffs per unit, that's an awful lot of medication that is going unaccounted for.

What do you propose is happening with this medication, is it simply not being used and patients are throwing inhalers away, or are we

significantly underestimating how much of the drug is actually being used by the population at risk?

DR. BERLIN: I believe that we have gotten

data from several sources that generally indicate that the use of the product is appropriate in terms of the number of puffs. You are right, there are about 270 puffs, which would mean that if you had

1.5 of these a year, you would be somewhere up around 500 puffs, and I think what happens is that not all of the medication is used although I can't prove that point.

I think the take away message from this,

though, is if you look at the data that we have gathered, it has been gathered over a fairly long period of time and using different methodologies, and generally, has been fairly consistent, and I am sure that some of the discrepancy between the

averages that we showed you is that unfortunately, as with the prescription medications, I am sure that a small percentage of people are using the product in an otherwise unintended fashion.

When you look at dual OTC and Rx users

versus sole users, what you find actually from our consumer data and also from the Kuschner data, is that they actually tend to use more of the

medication and tend to use it more for maintenance than the sole users who actually seem to be very good at using it as a reliever medication.

That is the same sort of phenomenon I think that has been noted when people have gone out and looked at what happens with the way people use prescription inhalers, where despite the NAEPP guidelines, a relatively substantial proportion of people who are under the care of physicians are not using their beta agonist in a limited fashion that would be optimal.

So, overall, I think that, in particular, the sole users are fairly highly compliant and use the product in an appropriate fashion.

DR. GAY: That brings up, however, my second question. Part of the definition of where this drug is supposed to be used and how it is supposed to be used is in mild, intermittent asthma.

Clearly, if patients are overusing the medication, they aren't mild, intermittent asthmatics. More appropriately and more

importantly, I think, is as we look at this definition of mild, intermittent asthma, that's a definition that is made by a physician, and it is made by a physician based, not only on pulmonary

function criteria, but criteria in terms of symptoms, things like that.

Even in probably one of the more significant papers that you had given us, a whole lot of those patients defining themselves as mild,

intermittent asthmatics have not seen a physician, and thus, are giving themselves the definition of mild, intermittent asthma.

Isn't this a concern as we begin to look at how we are utilizing the drug and whether or not

patients are appropriately using the medication?

DR. BERLIN: Sure, those are all legitimate concerns, and let me at least provide what data we have about that.

Many of these patients, two-thirds of them

are under the care of a physician, so they use the epinephrine metered dose inhaler as a stopgap, where they run out of their prescription or didn't

bring it with them, so it is not a question of these patients diagnosing what the severity of their asthma is. They are seeing a physician for asthma.

The second thing is that the sole users, more than 90 percent of them had been diagnosed by a physician, and, in fact, even in the sole users, I am sorry, I can't see when responding, but even the sole users, 28 percent of them had seen a

doctor for their asthma in the last year, and more than 90 percent had been diagnosed by a physician at some point.

So, we think that the message is pretty good, and when you look at how the sole user was

using it, which is really where I think we should focus our concern, because they are the ones who are not under care by a physician for their asthma, you see that more than 90 percent use the medication as a reliever, and their use pattern is

consistent, at least with what you would expect from symptoms produced by mild, intermittent asthma.

The last point that I would make, and it is an important one, it concerns our labeling. Over time, the label has changed, and the FDA, in July of last year, proposed what I think are some very important improvements in the label to try to encourage patients to use this product in a limited fashion.

Although the comment period has closed, no final regulation has been issued. However, we chose to implement those additional warnings, and by the way, that was before we knew of this advisory committee, we chose to implement those additional warnings because we think it further educates the asthma patient, particularly the sole asthma patient, about how to use this.

My last point concerns what we have on our labeling, what we provide on the insert, what we provide on the website, what we provide on the 1-800 number. We are sensitive to this issue. If someone calls and says, "I am not better in 20 minutes," they are directed to get health care immediately.

If they call and they say they are using the product at a frequency that is outside of the label, we suggest they go to the doctor. Every piece of material says asthma is a serious illness,

you should see your doctor, but we do provide an alternative, and we have to be cognizant of the fact that not everyone can or will take the option of going to see a doctor and getting the prescription, and therefore, there is a need for

this kind of product.

DR. WOOD: I have concerns that I want to give you the opportunity to answer. You probably weren't here yesterday, but the committee went through another application, and central to that

were really the issues as to what constitutes an OTC drug.

Let me just read them to you. Does the product have an acceptable safety profile, low potential for misuse and abuse, reasonable

therapeutic index of safety? Can the condition to be treated be self-recognized? Importantly, when used under non-Rx conditions, is the product safe

and effective? And then do the benefits outweigh the risk in the OTC setting?

As I go through each of these, and sort of taking the following into account, you know, the world has changed since the 1950s in asthma treatment. There is new guidelines, there is inhaled corticosteroids, and real safety concerns about long-acting beta agonists from very large studies that are not entirely clear.

We have essentially zero safety and efficacy data here in randomized, controlled studies that would fit any criteria. We have got significant concerns about whether this is an indication that even is OTC-able in 2006, and certainly one that is subject to debate. We have no data on long-term safety of these drugs in any usual fashion. So, persuade me why I am wrong.

Then, the final thing is we have absolutely zero evidence that any of the data from other beta agonists is extrapolatable to an inhaled mixed alpha and beta agonist, which, for lots of reasons, might have a very different toxicity

profile and a very different profile from any of the drugs that are out there.

So, it seems to me we have got a kind of dearth of data and the compelling argument, what seems to be your compelling argument, is that while some people are entitled to second-rate medicine in this country because they don't have health insurance, and that is an unacceptable answer. That is not an OTC-able indication, not having health insurance.

DR. BERLIN: Thank you. I was here yesterday and particularly enjoyed some of the issues that came up in terms of the underwear. I think you have asked a large number of very legitimate and important questions, and I will try to go through them. I am not sure I will be able to do it in sequence, but I hope I will be able to satisfy some of the concerns you have raised.

First, is this an indication that is appropriate for OTC, and I would point out that this is not a self-diagnosed condition. The label specifically says for physician-diagnosed asthma.

This isn't the only OTC product that has it diagnosed by a physician, and we take I think some comfort in the fact that no matter how you look at it, whether it's an academic study or whether it's

the surveys we have done ourselves, the vast preponderance of people who use the product actually have been diagnosed by a physician.

So, I think that we have tried to provide a reasonable answer that the people are following

the label, they are diagnosed by a physician.

You have indicated some concerns about the adequacy of the safety data and the long-term safety, and I think what we tried to marshal as an answer to that was to demonstrate to you that over

the 40 years, that this product has had a very favorable safety profile and that there is also a pharmacologic reason to believe--which I think is very important particularly in view of the questions you have raised about the pharmacology,

and let me be a little bit more specific.

Number one, it is very hard to purposefully abuse the product. You have to take

lots of puffs, and you have to do it over a short period of time. So, the Warren study, for example, where they took 45 inhalations over 9.5 minutes, is really kind of an extreme test case. I mean it is very difficult.

I don't propose that anyone try to do that, because it would be off label, but it is just hard to get that much medicine in, and despite that, the levels that were produced of plasma epinephrine were physiologic levels, and the response of an increase in heart rate of 7 to 9 beats per minute was minimal.

So, I think that although we don't have some of the formal randomized, double-blind, placebo-controlled safety studies, we do have the evidence from 40 years of use with 25 billion dosing occasions, a pharmacologic reason why one would consider that that is reasonable data. so we feel fairly comfortable about the safety.

The other issue that I think you raised, or at least raised indirectly, had to do with whether the consumers were in a position to use the

product appropriately, which is a very legitimate question, and our data seem to indicate to us that if you ask the patients how they are using the product, the vast majority of them seem to have

understood the instructions that were provided by us on the product, and use it as a reliever medication.

They use the right amount of medication, and they use it for the right indication. So,

again, I think that although these are data that are somewhat atypical in the way we have gathered the data, I don't think they can be dismissed out of hand, because I think they do provide a consistent story about the fact that consumers are

using this product in an appropriate fashion, which again further supports the issue that this is not an unreasonable product to have OTC.

The last point, which I hope I have gotten all of them, really concerns a philosophical issue

about what kinds of alternatives we should provide. There are a variety of studies that have looked at how the U.S. health care system works, and some of

them specifically looked at asthma.

There is, for example, a study that looked at patients, and this was pediatric patients who were in the Baltimore-Washington, D.C. inner city

area, and 90 percent of these kids had some sort of insurance, usually, Medicaid, but 53 percent of them found it difficult to access the health care system even, even when they had an acute asthma episode, and there were other data that suggests

that if a physician writes a prescription, that up to a third of those prescriptions are not filled during the 12-month period.

So, as I opened my talk, I said in the ideal world, we would have a health care system

that was more functional for folks, but that sending someone to an emergency room is not necessarily a better alternative, and forcing someone to call an office even if it's during the day, I don't know if you have had an occasion to

call a doctor's office and try to get through, for an emergency, let alone for a prescription renewal.

I think we need to keep in the back of our

minds, and actually, in the front of our minds, that we need to provide something as an aid for these patients.

Again, I would point out that two-thirds of them are under the care of a physician, and they are using this as a stopgap, and it is a beta agonist, and it does work, and it looks like it has a fairly acceptable safety profile.

So, I hope I have been able to address some of your concerns.

DR. WOOD: Wayne.

DR. SNODGRASS: My understanding is there are rubber bulb nebulizers on the market. Do you know the relative particle size delivery versus the MDIs, the 5- to 10 micrometer size, for example?

DR. BERLIN: As far as we are aware, these are products that are theoretically on the market. We accessed IRI, which as I referenced early in the talk, is this organization that measures consumer sales, and we can't find a record of sales, so that is one thing.

The second thing is that the bulb

nebulizer is not something that is necessarily convenient to carry with you. I checked the Internet to find the average price of a bulb nebulizer. It's about $40 give or take without

tax.

The other thing is--and I am not an expert in this area, so I offer this last piece of information up in abject fear that you will ask me to follow up on this, because I am not an

expert--there is a paper in the European Journal of Respiratory Diseases in 1990, and they actually did a study where they looked at particle size depending upon the pressure with which you actuated a bulb nebulizer, and they found that there was a

fairly marked variability in the respirable fraction depending upon how hard you squeezed the bulb nebulizer.

DR. WOOD: Ms. Sander.

MS. SANDER: I have a number of questions.

The first is, do you have asthma?

DR. BERLIN: Actually, the answer to your question is I did have asthma when I was younger.

MS. SANDER: And did your mom take you to the doctor?

DR. BERLIN: I think the question is I was fortunate enough to have a mother who could take time off to take me to the doctor. That is part of the issue that I think we are talking about.

MS. SANDER: Of all the moms that contact our organization or that we interview, and focus groups across the country, no matter what their socioeconomic levels are, they seem to prioritize the fact that asthma is not an OTC disease, it's a very serious disease, potentially life-threatening.

A third of those people who die of asthma have a diagnosis of mild asthma, a third of them who die have a diagnosis of moderate, and a third severe. So, as we look at this information, I look at it very seriously, because no one knows if that mild episode is going to progress to a severe, life-threatening episode at the onset of symptoms.

I appreciate the paucity of data that you keep referring to, but that data also really does not give me a whole lot of comfort, particularly

when you are making statements about people who suffer with a serious disease as if they can be lumped into these categories.

To Dr. Gay's comments, the number of canisters scanned does not equal the number of canisters used. Could that be a correct assumption?

DR. BERLIN: Well, the purpose in scanning is just to tell you how many units are sold. It doesn't mean that someone actually uses the product, it just says that they bought it, and it doesn't say whether they have used all or a portion of the product.

It is just a way of giving us some calibration to answer the specific question that the FDA asked, was how many canisters are sold, and that is the best way we can approximate the answer to that question.

MS. SANDER: Okay. So, we don't know if these patients are going oh, my gosh, this is not working, this is not having the effect intended, and if they are tossing them away or not, we don't

know that, right?

DR. BERLIN: Well, we actually do know that, and I mentioned that data, and maybe we could show the consumer survey backup data. I am not sure we even have that slide.

We asked in one of the surveys--and I am sorry, I don't remember exactly which one--we asked the consumers a question, okay, because we are in a business, we communicate we consumers frequently to find out whether they like our products and use our products, and how they do that.

So, we asked them to rate the use of their inhaler as excellent, very good, good, fair, or poor. The answer that we got is that more than 90 percent or approximately 90 percent rated it in the top three categories, which is good, very good, or excellent.

So, we have some direct information from them which indicates that they think that the product is working for them. We also have two other pieces of information which I think are very interesting, and that is, that when we asked why

sole users used the product, and we asked dual OTC and Rx users why they used the product, they actually gave us a comment about efficacy, and they said because it works better than their

prescription medicine.

What is interesting about that, and, you know, that's the answer, that's the answer that they gave us, so let me just go through this, and the answer that they gave us was that they thought,

this is perception, that it worked better than their prescription medication.

I think that the only message that we can take away from that is, in general, anyone who is sick values getting better faster, and the last

thing, and I think the most compelling piece of information is the paper that Dr. Hendeles published in December.

That was the paper I showed you which compared metered dose epinephrine to metered dose

Alupent, the gold standard for bronchodilators, and Dr. Hendeles, in his abstract, in his paper, actually says that these are, in his eyes, so I am

not making the judgment, I showed you the data, that these are very similar in effect.

I think that when he started to do the study, I think he may have shared the view that, in fact, epinephrine wasn't as effective. So, I think we have data from consumers, asked in a variety of ways, that they value the product, and we have hard clinical data which also suggests that the product is similar in efficacy to Alupent.

MS. SANDER: I have several things to go through here, so hopefully, we can move through them pretty readily, but the point being that canister scans do not equate to canisters used.

The data that you refer to, you have also said you don't have very much data, and the product that has been out for 40 years, you know, and you just said a moment ago you are used to being in conversation with the consumer, I would expect that we would have more information to review, that would talk about goals of therapy, are goals of therapy being met.

When you look at NIH guidelines, those

have been developed over 15 years, and, you know, a lot of scrutiny goes into the recommendations that are made, and I don't recall, being part of that committee that looks at all that, I don't recall

any recommendation for asthma to be self-treated, self-diagnosed, self-managed outside of a written asthma management plan.

I don't know of any instance where it says in the middle of the night, it's a good idea to get

up and go to a pharmacy or some other channel are the words you used as opposed to seeking medical attention.

I know that for any disease where you are ill, if you call your physician any time of the day

or night, there is someone who is going to answer that call and make sure that you have what you need. That is true for any person.

So, having an exclusion, so that people can get up in the middle of the night and say, oh,

I am having an asthma attack, the best place for me to go is to the pharmacy, you know, it doesn't necessarily impress me.

I guess my next question would be, well, statement would be, AMA, you referred to, and I don't speak for AMA, but you referred to or suggested an endorsement from AMA, and there is

three recommendations that were published, and these are recommendations of AMA that were published in the Chest journal, that says AMA says strengthen your labeling.

It encourages FDA to re-examine whether

OTC epinephrine inhalers should be removed from the market. It has nothing to do with CFCs. In the event that these products continue to be marketed, further information should be obtained to determine whether OTC availability is a risk factor for

asthma morbidity and mortality.

I need clean information and I need for it to be balanced. You know, we are talking about people who have a life-threatening disease, and when you can't breathe, you know, you are not

looking for a stopgap. You are not looking for the least amount of time for that relief. Twenty-three minutes is what this product provides of relief

according to the data that you gave us.
          You know, how does that compare? You know, albuterol, Xopenex, you have up to six hours. I think that in the middle of the night, people

want to use an inhaler and go back to sleep.
          DR. BERLIN: I really understand your concerns. In fact, you were quoting some of the information from that Chest article. We did strengthen the label. The data from Hendeles

wasn't available at the time that was written.
          Every piece of information we share with the consumer recommends consultation with the doctor. I want to show a study, and it is not to disagree with you in any way, but to show that you

have a perspective, but there are people who are in situations where if they try to access the physician, it just doesn't work as well as you fortunately are able to achieve.
          So, if I could show the data from Crain.

This is I think an instructive study. There are plenty of others like this. What this group did is they actually went out and interviewed caregivers

who had children with asthma, and you are right, as a parent with a child who has had some sicknesses, it is always a very challenging situation, you want to do your best for your kids.

So, they went out, and they interviewed these folks, and these were inner city kids. So, this was inner city Baltimore and inner city Washington, D.C. What they did is they had a hypothesis. They thought that having insurance was a surrogate for having good medical care, and so they went to this population and more than 90 percent of them had insurance of some sort, the majority Medicaid, but there was also some private insurance.

So, they asked a lot of questions, and one of the questions they asked was what do you do when your kid has an asthma attack, and 75 percent of these people, although they had a doctor, their primary place of getting care was the emergency room.

Then, they asked some questions about how easy was it for the caregivers to get to access

care, and so one of the things, the message was that when these caregivers were asked, they said that 53 percent of them perceived a significant barrier to access for care, and this was for acute asthma episodes.

I won't go through this whole list, but they indicated, in fact, a whole series of issues.

Slide off.

Now, I showed you some data about the demographics of the people who used the product, and about a third of them have an income of less than $20,000 a year. I want to try to put that in perspective, because I think it's important.

According to the U.S. Census Bureau, that qualifies as poverty for a family of four. So, if you can't take off from work, and if you don't have a car, and if you can't get child care, and even after you have Medicaid, you can't get access to the system, and by the way, in that study that I was referring to, 50 percent of the people reported that despite the insurance, they had to pay for all--I am sorry, not all--for some portion of their

health care.

I guess my point about this is when I started, I said we have to consider what the realities are. We try to be responsible and

encourage people to consult with their physician. We are highly successful in doing that. Ninety percent of them, in fact, have been seen and diagnosed by a doctor, and the reality is not everyone is as well served as you and your family,

and they deserve to have an option.

MS. SANDER: If I may finish. Our organization, Allergy and Asthma Network Mothers of Asthmatics, looks at that list and sees opportunities, opportunities to fix our system and

opportunities to help families, and we do that every single day. We don't say to them here's a medication that is going to last 23 minutes.

When you talk about patients' poverty level, spending money on Primatene Mist, the cost

per puff and for duration of action is far more for Primatene Mist than it is for the most recent bronchodilator to be approved, HFA to be approved

on the market, and that is Xopenex.

I also want to ask you one more question, and that is, do you plan, in your HFA formulation, to have dose counters, integrated dose counters on your inhalers, because that is part of the recommendation also by FDA or the guidance from FDA for all newly reformulated MDIs?

DR. BERLIN: I want to respond to one of the comments, and then I will come to the question that you asked, and I understand and support the commitment that you and your organization have to working with asthmatics.

I want to show the cost slide, please.

These are the costs that someone sees when they have to pay for the product, so I have shown you the average cost for Primatene, about $15 for the small size, and that is the size, about 90 percent of the sales are for the small size.

The thing that I have drawn a red line through is generic albuterol CFC, because that product will cease to be available. It still costs more, but for the sake of completeness I put it

there, and then I have X'd it out because it won't be available.

Then, I have shown the cost of these other products. They are more expensive. I would also

point out that the cost of the product is not the totality of the cost. There is a factor of having to access someone to get a prescription, and if you have to go see a doctor, the time and money it costs to go see the doctor, so there are other

factors involved in cost and other than just directly what the prescription costs.

Slide off.

DR. WOOD: I think the point Ms. Sander is making is that the poorer you are, the more

important it is that you spend your limited funds on the best available and most effective therapy.

Is that a fair summary? I mean amongst the other points in terms of the financial issue.

MS. SANDER: Yes, that is correct, and

also, you have to look at it, not just the canister price, but also the duration of action of each puff, and all things being equal, Primatene Mist is

far more expensive.
DR. BERLIN: Just to perhaps--
DR. WOOD: I am going to let you off the hook for the moment, because we want to take a

break. I know there are other people who still have got questions to ask, and then we will come back, and then we also will, before lunch, try and go through the public comment period, so the people who are here for the public comment period should

prepare to launch earlier than planned.
[Break.]
DR. WOOD: Let's get back to where we were. Dr. Schatz, you have a question?
DR. SCHATZ: Yes. One of the points made

is that the labeling fits with mild, intermittent asthma, but as was brought up, that diagnosis depends on normal pulmonary function tests.
If only 26 percent have been seen in the prior year, then, the other patients couldn't

possibly be known to have mild, intermittent asthma and the severity changes. Even those under a doctor's care may or may not have had pulmonary

function.

I guess the question is in the surveys that you have done, do you have any sense as how many of the single users have had pulmonary

function tests done?

DR. BERLIN: The best data that we have are the pulmonary function testing that was performed by Kuschner. That was the study where they advertised to find asthmatics, and they found

that the sole users all comfortably fit into the PFT definition of mild, intermittent asthma, in other words, they had an FEV of approximately 90 percent, and a peak flow variability of approximately 10 percent.

Now, in the rest of the survey data obviously, we were unable to ascertain what their actual pulmonary function tests were. It is interesting that you mentioned the issue about what gets done in the doctor's office, because when you

look at the performance against the NAEPP guidelines, one of the things that is really quite striking is how few of the patients have actually

had pulmonary function testing.
DR. SCHATZ: Again, the Kuschner data were 50 patients.
DR. BERLIN: Yes. The numbers are

limited, but at least it confirms that when someone indicates to you that they have mild asthma, at least in general, that is directionally correct. They seem to be able to estimate that, and it is corroborated I think also by the use of the

emergency room and other corollary measures.
DR. SCHATZ: I would point out in obviously not these data, but there are actually quite a bit of other data to suggest that people who think they have mild asthma don't. I mean I

think there are substantial data to suggest that people underestimate the severity of their asthma.
DR. BERLIN: Right. In no way am I disputing that. We understand that there is an issue and that the best way of our serving this

public is to provide guidance to them in terms of having been diagnosed by a physician, because theoretically, once they have been seen and

diagnosed by a physician, they have had that contact and we don't really have control at that point about what the physician does with that.

I pointed out that it was interesting that even the sole user, 28 percent of those sole users had seen a physician for their asthma during the preceding year. So, even for the sole users, they had some contact, and more than 90 percent had been diagnosed.

Again, for the vast majority of the people who use the product, we are talking about 2 out of the 3 million, these are people who are under the care of a physician. They are dual users and they are using this as stopgap.

So, the responsibility of what level of care is provided to those people is contingent upon what the physicians do in terms of appropriately educating and treating the patients and also what the patients do in terms of compliance with those instructions.

DR. TINETTI: I have two questions as a non-asthma expert. [Inaudible. No microphones.]

DR. BERLIN: Perhaps the best way that I can answer that question is to show a slide from the core presentation, that is, the Hendeles study, because I think it provides some useful data in answering the question.

One thing is if you have your symptoms relieved, did they come back or did they recur. So, when you look at this study and it has probably got lost, the last time point is 7:00 a.m. in the morning. So, these people were treated. They went to sleep, and they woke up in the morning.

Dr. Hendeles makes a specific comment that people did not re-awaken with symptoms. If you look at this chart, the FEV1 at 7:00 a.m., when they woke up, was comparable between the two groups.

DR. TINETTI: [Inaudible.]

DR. BERLIN: I want to go back and show some corollary data from our consumer survey about how sole users use the product, and again from the core talk.

I have tried to be as open as I can with

folks about--this is a challenge for us, because we are going back and trying to reassemble data here, and it comes in ways that, you know, we are not necessarily all of us as scientists used to looking

at, but it doesn't mean that it doesn't all fit together.

So, if I could have, from the core talk, the sole users, the one using it as a reliever. It's from the survey data. Sorry, it is taking us

a second to bring this up. That's not the one.

DR. TINETTI: While we are getting that, I am going to ask my second question.

DR. BERLIN: Sure.

DR. TINETTI: When we are talking about

adverse effects of the epinephrine, we can talk about the direct effects we thought might be related to the epinephrine, but the other side of the equation is, of those 5,000 people that you say die each year from an asthma attack, do we know

what percentage of those people were sole users of epinephrine versus prescription medications?

DR. BERLIN: If it's okay with you, I will

finish answering the first question, and then we can come back to your second question. I am sorry it took us a moment to get the slide up.

Again, we went out and we asked folks how do you use your medication. So, we wanted to know how many attacks, and this comes back to some of the questions that have been asked about, well, you know, is this mild, intermittent asthma, do patients know, how do they know, and on average, over a three-month period, they treated about four episodes. I have shown the 95 percent confidence interval there, so between three and five episodes.

DR. TINETTI: But that wasn't my question. It's if they have an episode, this medication lasts 23 minutes. Do they frequently have to re-dose during that episode?

DR. BERLIN: Right. The other slide, which I wanted to bring up after this, is the one that talks about how many puffs the sole users use, and I think I can give you the approximation of the data even if we don't get the exact slide up and number.

That is that about 80 percent only use two puffs, that they had adequate relief with two puffs, so what they are telling you--and again I acknowledge it is a little bit indirect--they are

telling you that they are able to treat their episode satisfactorily with two puffs, and then the last piece of data, so 81 percent, I am sorry, I was off, 81 percent indicate one or two sprays.

Slide off, please.

In the last piece of data, which again goes to whether you relieve an episode or whether it comes back, and whether people get adequate relief, so we asked what would be typical in a consumer setting, how do you rate this drug, do you

rate it excellent, very good, good, fair, or poor, and as I was painting the picture before, when you agglomerate those scores, you wind up with a score of 90 percent.

So, let's see now how this all fits

together. We have a controlled clinical trial albeit in a small number of patients, where the author specifically comments that people didn't

reawaken and that the FEV1 was comparable at 7:00 a.m. in the morning.

We have consumer data that says they treat the appropriate number of episodes, and when they

treat them, that a very, very large percentage of them only use two sprays, two doses, which would indicate that they have gotten relief.

Third, we have a further corollary which helps to cement that together, because when you ask

people to rate how well this product worked for them, and the only reason they are taking it is for their symptoms, and they tell you, 90 percent of them tell you it's good, very good, or excellent.

DR. TINETTI: My second question related

to the number of the 5,000 deaths that you say occur each year with asthma. Do we have any idea what percentage of those are sole epinephrine users?

DR. BERLIN: The best data that we have to

answer that question are the cases that are reported to us or to the FDA, and as I indicated, when we tried to look at those data, what we find

is that over this 40-year period, including data--
DR. TINETTI: That's a different question.
DR. BERLIN: But there's a primary drug that is associated with those reports. I have no way of knowing exactly--
DR. TINETTI: Okay. So, you don't know. Thank you.
DR. BERLIN: I have no way of knowing exactly, but what happens is when they are reported, they do get categorized as related either as a primary suspect drug or a secondary suspect drug, so we would still wind up getting those out of the database.
So, for example, if someone--I just want to pursue this for just a second, if I might.
DR. TINETTI: That's enough. That wasn't my question, but you answered the question that we don't have the data. Thank you.
DR. BERLIN: Thank you.

MS. SCHELL: I just have a comment or I guess a question. You keep reiterating that appropriate uses was used on over-the-counter

medications, and with your labeling, that helps that, but in practice, in my field, many of our patients do not use their prescribed drugs appropriately even with the extensive labeling the FDA does.

So, I just wondered how you came up with the fact that they are using it appropriately.

DR. BERLIN: I am sorry. I am not clear on what the question is.

MS. SCHELL: You stressed in your slides that they used the drug appropriately due to the labeling and that the patients reported appropriate use, but how do you know that, because my comment is that most patients need re-instruction on the use of the medication, and visiting the physician and getting that education is a vital part of all asthma medications, and I don't understand how you can say that they are used appropriately without any data.

DR. BERLIN: The basis for our making that statement was that one of the key label elements is that you shouldn't use the product unless you were

diagnosed by a physician, and both academic surveys, albeit in limited numbers, and our survey data indicate that 90 percent or more of the patients had been diagnosed by a doctor.

So, that is one element of the label. The other element of the label says that you should use this in a particular fashion. You should use two puffs, for example, and the consumer data, the survey data suggest that, in fact, the vast majority of consumers are using it that way.

The question is, you know, do they use this as a reliever medicine, not for maintenance therapy, and again the data that I shared with you says that 90 percent approximately use the medication as a reliever.

So, we did try to support all of the statements that we made, that the consumers actually have--what I have to admit is a fairly surprisingly high level of compliance with the label.

We take some comfort in the fact that all of the sources of information we provide to the

consumer really stress these kinds of messages - be diagnosed by a physician, use the product appropriately, how to use the inhaler, all of those things, and we are gratified that the message seems

to be getting across so clearly to the consumer.

DR. WOOD: Dr. Kercsmar.

DR. KERCSMAR: I have two comments. I feel compelled to clarify the Crain data that you showed, which is from the National Cooperative

Inner City Asthma Study in which I participated.

You are correct in saying that over 90 percent of the patients had insurance and could identify a primary care provider, and that about half of them identified problems in accessing it.

Their access were problems and didn't prevent them, it just hindered their care, and it was not just for acute care. It was for problems in accessing chronic care.

Also, in that study, the vast majority of

the patients had medication prescribed including albuterol as part of that study, and it was from seven inner city locations, not just from Baltimore

and Washington, and it was on school age children, which are probably, as you said, not using this product, but probably certainly could use this product.

I want to make one other comment, too, that I think Dr. Brantly asked about, relief of symptoms, not just FEV1, which I would agree you can study almost any bronchodilator and show an improvement in FEV1, is this a drug that will also control symptoms.

If you go to the Hendeles paper, which is again 8 patients, the relief of symptoms actually was greater and with fewer puffs with albuterol than it was with the epinephrine, a very small data set.

But I think the interesting comment that Dr. Hendeles makes actually, you know, gets to the issue of because this drug is effective, it does have an abuse potential, as does any bronchodilator, and, in fact, may cause patients to not seek medical care, because they do get at least very temporary relief.

It seems to me that this should still be a concern in that you have very little data including--I don't know what you already presented--that this drug, because of its ready availability over the counter might continue to cause patients to seek adequate medical attention due to the relief that they do obtain.

DR. BERLIN: Thank you. If I might, can we show the symptom data from Hendeles, please? I think it's useful to look. I tried to separate the initial graph we showed in terms of recommended versus exaggerated doses, because I think no one is proposing that anyone use 8 puffs of either bronchodilator, and the recommended use is 2 puffs.

So, the first set of bars on this, and you are looking at cumulative numbers of subjects who were symptom free, and the way Dr. Hendeles defined symptom free was that you had a symptom score of 1 or less out of a potential 30 points, which included wheeze, coughing, and chest tightness.

What you see on that first bar is the comparison of albuterol with epinephrine, and you

are right, there is a difference, but it is also important to note that there was a difference going into the study, at the beginning of the study, in terms of the symptom score.

For epinephrine, it was 10. For albuterol, it was 9. After the first dose, it was 4.1 for epinephrine and 2.8 for albuterol, and if you subtract the difference that was there at the beginning, you wind up pretty close.

What Dr. Hendeles also says is that his sample size is too small to draw a conclusion about that, but I wanted to clarify that point.

Slide off, please.

The second point that you raise had to do with medication and its use in inner city or from not even inner city, but other asthma-treated populations, and I think there are a variety of papers that look at what percentage of people with severe asthma actually are on the appropriate inhaled corticosteroid, and, in general, the number is somewhere around 50 percent give or take.

The last thing I think that you made a

comment about had to do with access to care, and whether we felt that we were diverting patients from care. I think it might be useful for me just to go over just a few points about this. Ninety

percent of the people who use the product had been diagnosed.

The label recommends that if you are not responding, or if there is a problem, that you go see the doctor. That is in the insert, too, that's

on the website, and that is what we tell them from the 800 number.

So, I think our intent is not to divert people from a physician, but to provide a resource to them and also a form of education that says you

really should access a physician for your diagnosis, and if you are not responding to the medicine appropriately, you should also access a physician.

DR. WOOD: Okay. I guess one other point

before we let you go, in addition to the problems with lack of evidence of long-term safety, lack of evidence of efficacy, and it's customary when

looking at data that shows the patients understand the label for an actual use study to be presented, or a label comprehension study to be presented rather than just a consumer survey.

Did you think about doing that before you came here, and if so, why didn't you do it?

DR. BERLIN: One is that there are many products that are safely used OTC on the market that have not had formal label comprehension studies done since that is a more recent development.

The second comment that I would offer is that when we learned about this advisory committee, it certainly didn't afford us adequate time to go out and do a label comprehension study.

The third comment that I would make is that I think in the label comprehension study, we would consider some of the key elements to test, in other words, whether they understand. We have presented data I think that illustrates that for key elements of the label, that consumers do understand the label albeit that we don't have a

formal label comprehension study, I think the performance of the consumers actually demonstrates that they do get it.

DR. WOOD: Are you aware of any other drugs over the counter for the treatment of a disease with this kind of mortality?

DR. BERLIN: Well, I am not aware, and, you know, I think that when we look at the data, the record indicates that this is a fairly safe drug, so I think that the condition with appropriate instruction to the patient and with appropriate warnings on the products, has demonstrated that it can be used safely in this population OTC.

DR. WOOD: Thanks. Let's move on to the public hearing. I am sorry, Neal, I beg your pardon.

DR. BENOWITZ: There is one issue that I would just like to comment on, a statement that you made showing the Hendeles data as relieving symptoms all night long. I really don't think that is a fair comment.

DR. SCHOENFELD: Is anybody there? I can't hear very well.

DR. BENOWITZ: Can you hear now?

DR. SCHOENFELD: A little bit better.

DR. BENOWITZ: The question is you commented that epinephrine has the potential to relieve symptoms all night long, but the Hendeles study involves 14 actuations, and your package insert is labeled for no more than 2 in 3 hours, so

I really don't think it is fair to extrapolate that.

The other thing I am just curious about, you had said before that Australia was the only country that had over-the-counter bronchodilators.

DR. SCHOENFELD: I can't hear.

DR. BENOWITZ: The AMA document actually referred to that, and they cite three studies from Australia where there is a concern that over-the-counter bronchodilators result in

inadequate treatment, and these were studies that were published between 1993 and 1995.

I am just wondering why you haven't

pursued that question, 10 years, and the concern is obviously there. You must have thought about it when you saw those papers 10 years ago. Why have you not looked at that question and done some

research on that?

DR. BERLIN: I would like to respond first to the comments you made about the Hendeles paper, and just point out that the comparison is also with an unapproved excess dose with albuterol, so both

agents were given.

And then just one other point in passing in terms of the efficacy with epinephrine, given the fact that it has such a short half-life, in fact, even after those exaggerated administration,

we are talking about approximately an hour into the study where they got the last administration, and then they slept through the rest of the night.

So, your point is well taken. It wasn't simply with the two puffs, but the comparison was

with more than two puffs of albuterol, and the second is that, in fact, it is very short acting, so that even if you are in an hour, the symptoms,

you know, there is no epinephrine remaining, and the symptoms were still relieved.

Again, I will acknowledge fully, very small numbers confounded by the fact that there were additional doses.

DR. BENOWITZ: When you give a large dose, and this has certainly been seen with local anesthetics, with a vasoconstrictor, you can prolong the effect disproportionately, and the comparison with albuterol is not really relevant.

You basically said that when you use epinephrine, it has the potential to relieve asthma all night long, and that has just not been demonstrated with the labeled use.

DR. BERLIN: I didn't actually say that. I said that the best data we have to try to look at this was the Hendeles data, and we don't make a claim, directly or indirectly, that it lasts all night long.

I was simply trying to give you the best data that we have that calibrates that, and we recognize, and I think we were pretty clear about

stating upfront what we think the duration of action is based on the studies of about 20 to 30 minutes.

DR. BENOWITZ: Right, but, you know, it could be that your label is really insufficient. I mean maybe people should be using six doses or eight doses to have an effective amount. I don't know, but I think it is a problem when you present data that is not according to what you tell people to use.

DR. BERLIN: In consideration of that, we obviously didn't design this study. I don't think most people would propose using eight puffs of albuterol either, and the way I tried to present the study is I divided that slide, so that the left-hand side of the slide really spoke about what was the label dose for both product, and then I was very clear to segregate anything that happened after as being related to exaggerated doses.

So, we have been as explicit about what the strengths and the weaknesses are.

I do want to make a comment. You are

right, there was a reference to three papers, two by a group involving Henry and one by Camino, and I would actually like to show the results from the Camino paper, because I think it's important to look at that, because there are two ways of looking at things.

One is sort of what happens, and then there is the second question, which may be more important, is what are the outcomes of what happens.

So, maybe we could begin with the methodology first, because I think--

DR. WOOD: Let's be fairly quickly. You have had 50 minutes to present it, and you could have presented it then, so be fast.

DR. BERLIN: Why don't we skip the methodology. They simply surveyed people who basically either used only OTC, they purchased it, or they got their medication through the physician.

So, let's go to the number of physician visits.

Can we go to the number of physicians? The next one. I want the number of physician

visits, please.

Yes, thank you. This is in direct response to your question. Sixty-eight percent of those who bought their inhaler OTC saw a GP in the past 12 months versus 86 percent who went to see a physician. It is sort of what you would expect, that difference is statistically significant, but I think the important question is what about the outcomes.

So, let's look at the outcomes, and I think there are two or three slides. I will go through them very quickly, that look at the outcome.

This is hospital admissions on the top, 5 percent for those who bought via OTC, 8 percent for those who got it through their physician. ER visits, 4 and 8 percent. Currently used peak flow meter, 14 and 15 percent. Doctor measured lung function, 37 and 42.

Doctor wrote action plan, 16 and 18. Possesses action plan, 7 and 9. So, there are all not different.

Next slide, please. There is one other. Okay.

So, this is just another way of looking at it in terms of some medication, preventive medication, 54 percent and 60. It is a little bit lower in the OTC group, but it is not statistically significant.

When you break it down by the specific medications, 52 percent inhaled steroids in the OTC group, 57 percent in the prescription-only group. Frequent symptoms, less frequent in the OTC group, and that difference versus the prescription is statistically significant.

Admitted to the ER, 5 versus 8, and attended an emergency room department, 4 and 8 percent.

Slide off.

Those are similar data to the ones that Henry also found in the British Medical Journal paper.

DR. WOOD: Ruth.

DR. PARKER: Just one other comment

relating to the lack of label comprehension or actual use study. I would caution about making an assumption that the label is understood and used, particularly adequately in a disadvantaged

population and one that might have decreased or probably does have decreased access to chronic and acute care, which seems to be one of sort of posed reasons for considering this, disadvantaged people, this is what they can get ahold of, this is what

they can use.

There is one study in Chest from a couple of years ago, the late author Williams, that looked at the ability to understand and use inhalers among low literacy patients, and showed a very strong

correlation with literacy level and ability to correctly use inhalers even after being taught one on one with health educators about how to use it.

So, I think more information on that would be really useful, especially if access to care for

an underserved population seems to be a factor in consideration.

DR. WOOD: Dr. Brantly.

DR. BRANTLY: I just wanted to make one more point about Dr. Hendeles study, and that is, the typical history of nocturnal asthma is that their FEV1 returned to close to normal by the time

of the early morning, so that we may not even be looking at a drug effect at all.

DR. WOOD: Any other pressing comments? Then, let's go on to the public comment.

Thank you.

DR. BERLIN: Thank you.

Open Public Hearing

DR. WOOD: Let me read the statement first.

Both the Food and Drug Administration and

the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the

context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing presenter, 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 group that may be affected by the topic of this meeting.

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

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

The first speaker is Manuel Mirabel. Not here? Okay, we will go on to number two.

Sandra Fusco-Walker.

MS. FUSCO-WALKER: Good morning. My name is Sandra Fusco-Walker. I am Director of Government Affairs for the Allergy and Asthma Network Mothers of Asthmatics.

We are a leading grass-roots family education and advocacy, nonprofit organization, and all expenses associated with my presence here today have been paid by AANMA.

On behalf of AANMA and the 20 million Americans diagnosed with asthma, thank you for the opportunity to speak here today.

The question of whether this product is a public health benefit can be answered easily if we focus on what is best for patients. No, it should not. Asthma is a potentially life-threatening disease that requires medical diagnosis and strategic management.

Self-treatment of asthma may lead to inadequate or delayed therapy that can lead to complications or deaths that could be prevented.

Since the transition to non-CFC MDIs began, concern for patient safety has been paramount. Manufacturers have spent hundreds of millions of dollars developing non-ozone-depleting alternatives, and patient and medical professionals have spent the last nine years committed to

ensuring a safe and fair transition.

We heard today that people who do not have insurance coverage and those who do not qualify for government assistance programs use this medication.

We also heard that lower income families will be harmed if the option of an OTC epinephrine is not available and patients must use prescription albuterols.

However, if we are going to look at the

price of this medication, we need to look beyond the cost at the store. AANMA has compiled a brief chart detailing the costs of two puffs of three HFA medications presently on the market and Primatene Mist.

It is coming up quickly--it is not coming up. It is included in the handout.

When we look at the duration for each of these medications, we find that the most recent HFA on the market, Xopenex, has a total cost of 60

cents for six hours duration.

DR. WOOD: It is up now.

MS. FUSCO-WALKER: I used six hours

because four to six hours is recommended, and I used 30 minutes for Primatene Mist, because 20 to 30 minutes duration is recommended.

So, in applying the same duration period to Primatene Mist, and recognizing that the two puffs will last no longer than 60 minutes, we see it costs a total of 72 cents for six hours duration. It is not a bargain.

Six years ago, a Chest study stated that gross misuse of OTC epinephrine could cause severe adverse reactions including death.

The study recommended FDA re-examine whether OTC epinephrine inhalers should be removed from the market, and that if these products continued to be marketed over the counter, further information should be obtained to determine whether OTC availability is a risk factor for asthma morbidity and mortality.

It is six years later, and the only study we were able to find regarding OTC epinephrine since then was published last month with eight patients. If this medication is so essential, why

hasn't there been any follow-up over the last six years?

AANMA contacted a small group of physicians who treat patients from a variety of socioeconomic levels, and we asked the following questions:

Should epinephrine inhalers for asthma continue to be available over the counter? Do you tell your patients to use over-the-counter epinephrine? Do you think asthma should be treated over the counter? Are there any life-threatening diseases that are treated over the counter? All of the answers to these questions were no.

I would like to share one of the comments from one of the physicians. He stated the risk of having patients buy over-the-counter medications for asthma is that they may simply increase their use of inhaled bronchodilators, thus, not consulting a health care professional to treat the underlying inflammatory process. Progressive and uncontrolled inflammation can lead to serious and undesirable outcomes in patients with asthma.

Today, this committee is not just reviewing whether an OTC inhaler with CFCs should continue to be available, but more importantly, you are reviewing the way our society deals with

critical health issues that affect all Americans including poor people.

Our job here is to help patients transition, not to create a population of patients for whom the medical guidelines don't apply. What

you are deciding here today is if asthma, which kills almost 5,000 people a year, and affects over 20 million Americans, should be treated over the counter.

I urge you to ask yourself the question

you did at the July 13th committee meeting. Do you think you can care for patients if this drug is gone?

Thank you.

DR. WOOD: Thank you.

We will go back to speaker one. Manuel Mirabel, if he is here now.

MR. MIRABEL: Thank you. Good morning.

My name is Manuel Mirabel. I am the President of the National Puerto Rican Coalition, a public policy organization based here in Washington, D.C., which has worked on issues of

health and other important issues affecting the minority community for the last 25 years.

I am also here today representing a number of our sister national public policy organizations which have signed on to our statement today. They

include the Cuban American National Council, the League of United Latin American Citizens, MANA, a national Latino organization, the National Council of Laraza [ph], the National Hispanic Medical Association, the ASPIRA Association, and the

Dominican American National Roundtable, all national public policy organizations working on various issues and particularly concerned about the impact of asthma on their communities.

I would like to begin by saying that we

have no relationship with the sponsor or product, or any competitor of the products being discussed here today.

My testimony is about the need and the use of OTC inhalers by the Latino community. I would like to note that the second criteria in your Federal Register states that this designation will be provided to a product and this product has been shown to have an otherwise unavailable important public health benefit.

It also says that you are particularly encouraging comments on the second criteria regarding the public health benefit derived from the availability of these products in the OTC setting.

The vital importance of the public health benefits of continued availability of OTC asthma inhalers, as described in the Federal Register, is why I am here today.

While we are all in favor of removing CFCs from the air, we also believe that the public health needs of people with asthma overrides the impact of the relatively small amount of CFCs which may enter the atmosphere from the use of OTC inhalers.

Not everyone has access to professional medical assistance to help manage their asthma and other medical conditions, because many do not have medical insurance for financial and other reasons.

This is, in fact, the case for many Hispanic Americans who depend on OTC asthma inhalers. These inhalers are all that in many cases stands between them, as an asthmatic, and the emergency room or worse.

I am presenting today because of this, and because we believe that the effect that the OTC inhalers have on the environment is minor compared to their value to people suffering from asthma.

In the U.S. today, the burden of asthma falls disproportionately on the minority community, African-American and Hispanic, and particularly the Puerto Rican community. Many poor, uninsured, have unfortunate outcomes including emergency room visits, hospitalizations, and death, with children suffering the most.

For many Hispanics, access to medical services is further complicated by language

barriers, lack of cultural competency, and misinformation. The most recent report by the Agency for Healthcare Research of HHS states that the disparities for Hispanics in access to health

care has widened and is continuing to widen.

One particular statistic that they reported in their report that was issued just this month states that for Hispanics, the lack of access to health and medical services is 88 percent higher

than for non-Hispanic white community.

This is in the 2005 National Health Care Quality and Disparities Report recently issued.

Hispanics already have limited access to health insurance and prescription drugs largely due

to their employment in job sectors where insurance is not offered and high poverty rates.

Currently, Latinos are the largest ethnic group in the U.S. with the greatest proportion of uninsured. According to an August 2004 census

report, the uninsured rate for Latinos is close to 33 percent as compared with blacks at 19.5 percent or non-Hispanic whites are 11.1 percent.

Therefore, it is essential that low-cost generic drugs remain available to this population. Puerto Ricans living in the United States mainland and in Puerto Rico disproportionately suffer from asthma.

Of all the age groups, children are the most affected by asthma, and of all Latino subgroups, Puerto Ricans have the highest rate of asthmatics. The American Lung Association reports that two-thirds of the estimated half million Latino children showing asthma symptoms are Puerto Rican.

Asthma has been estimated to affect as many as 20 percent of the mainland Puerto Rican children, 6 months to 11 years of age. Puerto Ricans had the highest annual asthma mortality rate, 40.9 percent.

Puerto Rican children have the highest prevalence of active asthma, 11 percent, of any group of U.S. children, significantly surpassing African-Americans at 6 percent, and white at 3 percent.

In Puerto Rico, asthma in children stands at an alarming 32 percent.

We are concerned that if restrictions are placed upon the usage of bronchodilator inhalants, they could have a negative impact on our community. Should the various store brand bronchodilator inhalants be removed from the market, we anticipate serious public health implications will occur, specifically and especially for the Latino community that cannot afford to purchase more expensive medicines.

The potential removal of the product is not a safety issue. Epinephrine is deemed safe by the FDA, and has been effective and has a long history. This is an issue of maintaining access to medication that may be required by a patient at a moment's notice.

While we strongly encourage the pharmaceutical industry to abide by a standard of seeking out newer technologies that are not environmentally damaging, we believe that there are currently no OTC alternatives since these products

support medically underserved populations and since they serve an important rescue role. They provide an important aspect of public health for our community.

Due to the public health needs and to ensure that asthma medicines are readily available to those without access to medical professional services, for monitoring their asthma at the time of an attack, we urge the FDA to grant OTC

epinephrine an essential use designation and continue to make it available to the public until a reformulated OTC product is available.

Thank you.

DR. WOOD: Thank you very much.

We will go on to the last speaker, Martin, Bryan.

DR. MARTIN: My name is Bryan Martin. I am a practicing allergist here in Washington, D.C., and a member of the United States Army. I have no

direct financial interest in the matters discussed today.

My presentation is a joint statement from

the American College of Allergy, Asthma, and Immunology, and the American Academy of Allergy, Asthma, and Immunology. These two organizations represent the majority of the allergists and

immunologists in the United States.

Asthma is a very serious, potentially life-threatening illness that affects an estimated 17.5 million Americans. While prevalence rates have increased and continue to rise significantly,

of even greater concern is that nearly 5,000 patients die from this illness every year.

The quality of life of patients with asthma is severely compromised with sufferers often unable to participate in typical daily activities

and annually, missing 14 million days of work and 14.5 million days from school.

While studies have shown that health care professionals experienced in managing patients with asthma will improve outcomes, patients are not

availing themselves of this service, and are self-treating.

As a result, there are two million

emergency department visits and 500,000 hospitalizations for asthma yearly, while the annual combined direct and indirect costs for caring for this disease has now escalated to $16 billion.

Although asthma affects all ethnic groups, the morbidity and mortality amongst the African-American population, where self-treatment is very common, is three times greater than that among Caucasians.

In addition, a delay in the early introduction of prescription anti-inflammatory asthma therapy could lead to the development of irreversible lung damage.

Our primary interest is in the well-being of our patients. Of concern is the potential impact of the FDA's recommendation regarding the OTC availability of metered dose inhaler epinephrine and eventually metered dose inhaler albuterol. Neither of these therapeutic agents has anti-inflammatory properties, nor does either have any favorable long-term effect on the natural

course of asthma.

On the other hand, inappropriate use of, or abuse of, these inhaler medications could lead to deterioration of asthma control and, in some circumstances, lead to death.

The FDA's decision regarding the status of CFC epinephrine and HFA albuterol MDIs must be the result of careful review of evidence based on medical literature, however, we would strongly urge this body to recognize that outcomes will be optimal if patients delegate their asthma management to trained health care professionals who can help them in identifying the asthma triggers and counsel them on environmental avoidance measures plus the appropriate use of ongoing anti-inflammatory medical regimens.

Patients must be discouraged from self-managing their asthma and using over-the-counter bronchodilators and/or the hospital emergency department as their sole source of treatment.

It is our profound hope that the FDA will

strongly consider the well-being of our patients in determining the status of metered dose inhaler bronchodilators, and will act responsibly in making a decision that will afford asthma patients the greatest opportunity for optimal asthma control.

DR. WOOD: Thank you very much.

That is the last public comment. Let's turn to the committee and start the discussion.

Are there points of discussion that you would like to raise? Yes.

Committee Discussion/Questions

MS. SANDER: Could we ask any questions of the speakers?

DR. WOOD: Of course.

MS. SANDER: Manuel, could I ask you to come back up. I appreciate your comments very, very much, and we work with many of the organizations listed in your comments.

My question would be, out of your organization and the organizations that you work with, do you refer patients to free sources for medical care and for prescription medications?

MR. MIRABEL: That's a complicated question to answer, and let me begin by saying for the last eight years, our organization and the other organizations listed are supporting the

statement, have all worked together to develop public policy help agendas, which we have presented to the various Secretaries of HHS, to the CDC, and the various other Federal Government agencies that address providing medical services whether they are

free or not to the communities that we serve.

We, in our organizations, try to enroll as many children in public health services plans, make sure that families understand the benefits, that they are available to, and encourage and recommend

that they see a medical doctor about issues, a number of issues, but particularly asthma, because asthma, although it has been studied, frequently, for the Puerto Rican community, and a little somewhat less so for the Mexican-American

community, there is practically no other data for any of the other Latino community, and we are talking about 43 million Hispanic-Americans in the

U.S. today, and the Puerto Rican community makes up about 8 million of them, and a portion of the Mexican-American community for which asthma studies have been conducted, that we have on record, is

very, very minimal.

So, more needs to be done about this. The one thing that we do know is that many families, for one reason or another, never get to that doctor even though they or their children are completely

eligible for free medical assistance, they don't get to that doctor, and there are other cultural and systemic barriers that affect their being able to get services when they need them including, unfortunately, although everyone today seems to

have a cell phone, there are many families who don't have a phone at all.

Particularly, when you get to poorer families, this becomes more and more likely. So, there is a lot of misinformation, much inability to

communicate with medical practitioners that can give them good advice.

DR. WOOD: Try and focus just on answering

the question.
MR. MIRABEL: One of the things that we know would assist is getting to a doctor, so we don't recommend that, but that is not always the case for these various reasons that we have stated.
MS. SANDER: So, it is safe to assume that the patients that you are describing are patients who are probably using Primatene Mist in a manner not indicated for its use on the label. These should be physician-diagnosed patients, and these should be patients who have seen or are under a doctor's care if one to interpret the labeling correctly for Primatene Mist, right?
MR. MIRABEL: That is entirely possible.

MS. SANDER: Pharma companies have programs for these families that I know in our office, we work to channel patients into those programs, but I don't know if Wyeth offers similar programs that you have been able to channel for patients.
MR. MIRABEL: I happen to be familiar with the Patients' Prescription Assistance Program.

MS. SANDER: Right.

MR. MIRABEL: I am one of their lead spokespersons. We rolled the program out in Puerto Rico, in New York, in Washington, D.C. over a year ago, and we are continuing. I know in my community alone, more than 120,000 families have signed up for one of these free programs. Yes, asthma is part of that.

MS. SANDER: Is Wyeth part of that program? I don't know if someone from Wyeth could--

MR. MIRABEL: I have to say I remember seeing it on the list. There are 2,400 medicines, but we did look at asthma, and, yes, Primatene was one of those medicines.

DR. WOOD: Other discussion? Robert.

DR. TAYLOR: I wanted to get some clarification of the scope of the committee's work. It seems from Dr. Meyer's initial discussion that we were to concentrate primarily on the CFC issue, but it looks like we are headed down a--you know, casting a broader net.

Is that the intent of the FDA for us to do that?

DR. WOOD: Before he answers that, I am not sure how we can avoid doing that. As a read the instructions, we are supposed to consider the essential use of this drug and whether it provides a public health imperative.

I don't see how we can do that without considering the public health implications.

DR. TAYLOR: Well, I have my interpretation of it, and I perhaps agree with you, but I want it from the FDA standpoint to have them on record on that.

DR. MEYER: The question posed about the continued essentiality of this drug does obviously closely relate to the larger issue of having this or any other such drug available OTC.

The intent of this meeting is really to focus in on this question, but I think we are fully cognizant of the fact that it raises larger issues. I would say that we are not particularly interested in getting into discussions beyond epinephrine in

the OTC setting, in other words, whether albuterol should be there, those kind of questions.

But obviously, the question about whether OTC epinephrine continues to be a drug that

provides an important public health benefit that is not otherwise available is the question, and it raises some of these larger issues.

DR. WOOD: Other comments?

DR. SCHATZ: In the questions that have

been asked, there seems to be some consensus. I don't think there is anybody here who isn't concerned and aware of the disparities that exist.

I don't think any of us, though, believe that the best approach to that or have any data to

suggest that over-the-counter epinephrine is a help in that arena, and we would be concerned that perhaps it is, in fact, a worsening of that situation.

But I think that I am hearing a lot of

consensus, I believe, that that concern exists, but this is far and away not the most appropriate approach or even an effective approach to that

problem.
DR. WOOD: Any other comments? Yes, Sonia.
DR. PATTEN: Yes. Could someone just clarify for me, please, what other asthma treatment products are available over the counter?
DR. WOOD: Sounds like one for the FDA.
DR. GANLEY: Could she repeat the question?

DR. WOOD: What other asthma products are available over the counter?
DR. GANLEY: As I noted in my introductory slide, there is several products available over the counter through the monograph, and the one, it's ephedrine is the only oral single ingredient. Technically, it's not over the counter, it's behind the counter, because of DEA regulations.
There is an allowance for ephedrine plus guaifenesin. There was a rulemaking published in July 2005 that proposed to remove that from the OTC market, because it was not used as rational therapy. The only other product available would be

the epinephrine solutions by bulb nebulizer.
We are not clear, as I think someone else had noted, whether there are actually some products marketed there. Even when you do an Internet

search, you don't find a lot of products being advertised for that.
DR. WOOD: Marie.
DR. GRIFFIN: I guess being swayed by the fact that we have just an inferior medicine, that

we all think is inferior, although we don't have good data on efficacy and safety, but we think it is inferior to what is available by prescription.
I think when I originally thought about this, I didn't think of it in terms of children,

but the idea of children with asthma being cared for by their parents is kind of frightening to me, because children should be seen to get their immunizations and to get other health care, and their parents should make sure that children that

have asthma see a physician.
I think that the other inhalers that are available by prescription, I mean it is an expense,

but it is not $40. If a child truly has mild, intermittent asthma, or an adult, they should only be using one or two inhalers a year. So, although that is an expense, it doesn't seem unreasonable.

So, I think I am just being swayed by what I have heard, and that the United States is really the only country where this type of medicine is being used currently.

DR. WOOD: Dr. Brantly.

DR. BRANTLY: I just wanted to reiterate I think the point that basically, it is probably not appropriate to have any OTC asthma medications and the potential risk that is associated with that long term and initially, and I would like to just

make the point that we are hearing that minority and poor people have the greatest impact, but I think that it may be that by having these medications out on the market, that it also has a significant impact on their health and well-being.

DR. WOOD: Mary.

DR. TINETTI: I certainly agree with everything that has been said, but again, in terms

of framing the debate, in the ideal world, we are talking about this less effective medication versus clearly more effective care, but it is still not clear to me with all the discussion that we have

had today, and I think because we really don't have the information, is are we in some cases talking about a less than effective medication versus no treatment, and I think we need to bear that in mind, and none of us have data to answer that

question, but I think it is the unspoken piece that I think we need to remain cognizant of.

DR. WOOD: Terry.

DR. BLASCHKE: Well, I agree with what Mary said, and I think we are also hearing, which I

think bears some further discussion, that all asthma is moderate or severe, and I think with most diseases, one has a gradation of severity, and that certainly in circumstances where access to health care is limited or unavailable, that it may be

quite reasonable for such individuals to have access to an over-the-counter formulation.

I would also mention that we have sort of

dismissed the idea that it is important about the finances or the delay, but, in fact, that was exactly the same rationale that we used a year or so ago with Plan B, where the issue was rapid

access to a medication that was important, and the cost of going through a physician to get a prescription as opposed to the cost of simply the medication itself.

So, I think it is not as optimal

obviously. I think there is no disagreement that ideally, health care would be provided through the physician, but I think we need to recognize that that isn't always possible, and I don't see necessarily that--we all know there is huge

disparities, and as mentioned by one of the speakers, increasing in terms of disparities in health care amongst minority populations.

I don't know that pulling something off the market is the way to cure that disparity.

There are other mechanisms that we need to obviously be working on.

DR. WOOD: Dr. Gay.

DR. GAY: I think we have to be clear to emphasize what the appropriate utilization of this medication should be. Even as physicians, there is fairly clear data in the literature that says that

we have difficulty making the distinction of what is mild, intermittent asthma.

We do not do it extremely well, and many of those patients lack pulmonary function criteria in addition to an appropriate analysis of their

symptomatology to do this. I think to consider that patients can do it as well puts those patients at significant risk.

Although this medication seems to be from the data that they have presented and from the fact

that we, as the FDA, had approved it so long ago, reasonably safe, that was clearly under different criteria for the treatment of asthma.

The hallmark of treatment for asthma at this time is clearly a controlling medication that

requires anti-inflammatory therapy, and it is actually a markedly smaller population of asthmatics that can clearly be managed by the PRN

dosing of a short-acting beta agonist, or short-acting bronchodilator, period.

Because of this, I think that we, as a committee, basically, are being asked two questions. Yes, whether or not this fulfills an appropriate public health need, and in light of knowing what the guidelines are, no, this does not fulfill an appropriate need. We are undertreating and inappropriately treating asthma if individuals are using this as their sole medication with self-diagnosis to maintain and take care of their asthma.

DR. HU: Hello.

DR. WOOD: Go ahead. Speak.

DR. HU: Hi. I am Linda Hu. I am a medical officer in the Office of Nonprescription Drugs.

There is a listing on the Consumer Health Care Product Association website that states what the legal classification of selection ingredients are worldwide, and in the listing, they list epinephrine for asthma as OTC also in Canada and

New Zealand, and also for salbutamol, it possibly is OTC for China and Korea.

In some other countries, it is listed as pharmacy dispensed only, and that would include

Australia, or pharmacist dispensed only, but for the China and Korea locations, they don't specify how, but it is a possibility that it is also available as an MDI inhaler there, as well.

DR. WOOD: Okay. Any other discussion?

Nancy.

MS. SANDER: I think what we all are looking for is a compassionate way to address all populations affected by asthma, and certainly, you know, pulling a drug off the market is always a

frightening idea to anyone including especially patients.

But the transition, the word itself is meaning over time, and it can happen, and a strategy that is considerate of a number of

factors, one important one being that CFCs are going away. They are going away.

Everyone with asthma must make a

transition to an HFA or other non-ozone-depleting substance. We have three HFA, or four is it now, medications on the market, and the prescriptions for these medications are not what they should be

considering that CFC MDIs are going away.

The nation needs to pay attention to this transition and start making the transition. That means prescriptions need to be written for the HFA products, and patients need to be encouraged to try

them now before the CFCs are gone away.

With regard to Primatene Mist and other OTC bronchodilators, you know, I guess I am shocked that there wasn't more clinical or scientific evidence to give us reason to say that there were

certain populations of patients that, you know, their lives were going to be dramatically altered in such a negative way that they should have access to these medications, you know, in light of the absence of that information, and also just surfing

the Internet, just looking for what patients say about Primatene Mist. You know, you are not finding anyone who is saying that this has saved

their life, it is what they need, it is what they want.

In fact, you find quite the opposite, people recommending that, you know, I used one puff, I will never use it again, and that could account for the number of canisters, and, you know, discrepancy that was noted earlier by Dr. Gay.

I also think the example of if you are in a car accident, and both your arms are broken, you don't go to the pharmacy and ask for an ace bandage. You wind up getting the help that you need for the broken arms.

We are talking about broken lungs. Breathing is vital to life. It is not an OTC type of disease. It is one that needs to be treated seriously and with great consideration.

Thank you.

DR. WOOD: Dr. Schoenfeld is on the phone and has a comment.

DR. SCHOENFELD: Excuse me, and I am getting an echo, but I will try to talk through it. Where I am having trouble is that the information

about what happens when you withdraw something like this from the market hasn't been presented.

So, you know, we are considering whether to withdraw something that a lot of people are using, and it may not be the best thing for them to use, but there are lots of things that keep people from getting optimal health care.

You are making the assumption that by withdrawing it, people will get optimal health care, and I just haven't seen evidence. I think that needs to be looked at carefully before something like this is withdrawn.

DR. WOOD: My understanding--and the FDA should comment on this--is that the next step will be a rulemaking notice.

Would you want to comment on that, Bob?

DR. MEYER: Yes, that is actually a point I did want to circle back and make.

If the recommendation of the committee is, in fact, that it remains essential, then, there is no regulatory action that follows except perhaps that we reconvene this committee at some future

date to revisit the question, whether other circumstances would change that recommendation.

If the committee recommends that the drug is no longer essential, for us to effect that, we would have to go through notice and comment rulemaking, so we would propose, based on that recommendation, under that hypothetical, that the drug is no longer essential, and we would then have a public comment period.

It is possible that that might even involve an advisory committee meeting during that public comment period or as a part of that.

So, the vote of the committee today will help inform our further action, but if it's to take the drug off the market, if that is the vote, then, there is further regulatory processes that we need to go through that importantly entail public commentary.

DR. SCHOENFELD: I don't know that public commentary answers this issue, because I guess the real issue is whether, in fact, when these kinds of things happen, OTC products are taken off the

market, whether, in fact, that does increase how many people go to doctors, how many people get different treatments, or whether it simply means people without treatments, which I am afraid is

what is going to happen.

DR. WOOD: That is not the question that is on the table. The question that is on the table, is this an essential medicine. We are not going into solving uninsured treatment and all

these other issues today.

DR. SCHOENFELD: Well, it's public health we are talking about, not medicine, so we are not talking about what is the optimal treatment for asthma. We are talking about whether the drug

provides an unavailable public health benefit, that is, so that says that the public health will remain the same at least when it is withdrawn.

DR. WOOD: Dr. Schatz.

DR. SCHATZ: I absolutely agree, and I

don't think any of us, who at this point may favor having it not available think that automatically, that is going to improve health care access.

But on the other hand, I would emphasize what Nancy said, and what would undoubtedly happen is there would be a transition, and this transition I think would give us an opportunity for an

increased targeted education and perhaps access program that might, in fact, lead to better care of the population formerly using this drug during that transition period.

DR. WOOD: Dr. Swenson.

DR. SWENSON: Yes. First question to the FDA officials, Dr. Meyer possibly. If Wyeth comes back in five years with an application for now an HFA delivery of epinephrine, would they come in as an OTC, or would it now be a prescription drug,

because I think we really have two almost separate questions here.

Are we talking about the CFC environmental issue, or are we talking more about the global problems with our health care system and our

ability to deal with something like asthma?

DR. MEYER: Let me address that by referring back to in your background package, under

Tab B, is the final rule from July 24th, 2002, which includes the preamble, and in that preamble, on page 48375--I am not making that up--on the right-hand column, there is actually a paragraph

that speaks to the issue of OTC epinephrine.

That paragraph ends with the sentence that says, "FDA further notes that any re-examination of the appropriateness of continuing the OTC status for bronchodilators is quite separate from the

determinations on the essential use status of the epinephrine CFC MDI."

So, what we are focusing on here today, again, is the issue of the essentiality of the epinephrine OTC. Although I understand it closely

interrelates to the larger question, we are not asking that larger question today about the advisability of having anything OTC.

DR. SWENSON: What I fear about making a decision on this is simply that we may risk taking

a step backward in the present level of health care for asthma in this effort to move forward with better control and better management of asthma, and

we simply don't have the data to let us know to what extent these drugs are critically important, and it would seem to be vital that Wyeth in particular should mount the necessary studies to examine that question if it's central to their wish to continue with this.

I think an issue like that, given today's modern powerful tools of informatics, could probably come up with some type of answer on that.

DR. MEYER: The one comment I would make in that regard is that I think the gentleman from Wyeth correctly pointed out that the lead time they had for coming to the committee today limited the amount of work they were able to do. They did a fairly extensive presentation, but it certainly limited the amount of work they were able to do particularly if they were going to be doing some kind of more explicit research.

A public rulemaking process might afford more ability for Wyeth or other concerned organizations or peoples to make a more extensive effort, I guess, to address some of these issues.

DR. WOOD: Any other comments?

MS. SANDER: Just a question. Does the Federal Government look at the public health impact of this medication independently of any other, you know, pharmaceutical or consumer product company?

DR. MEYER: I am not sure I understand your question.

MS. SANDER: I am not sure I phrased it very well. You know, so does the Federal Government look at--because we are looking at this as a public health benefit--we, as a nonprofit organization, don't have money to go out and study what is happening to patients from a patient perspective, does the Federal Government, on behalf of patients, have any funding for that kind of thing?

DR. MEYER: I am not sure I could definitively answer your question in terms of whether we have any funding for that kind of activity, but I can say with regard to the rulemaking, the 2.125, and continued essentiality, and so on, what we are relying on in making those

decisions is the expert advice of the advisory committee that we have convened today, as well as public commentary, and that public commentary may involve substantial data submitted by interested

parties, but it generally would not involve the FDA specifically doing such studies.

DR. WOOD: Okay. Any other comments?

[No response.]

DR. WOOD: In that case, let's call the

question, and the question, as you will recall, is: Given the current practice of medicine and overall treatment goals and therapeutic strategies for asthma, does the use of CFCs in epinephrine MDIs available without a prescription remain an

essential use at the current time?

Why don't we start with Marie.

DR. GRIFFIN: No.

MS. SANDER: No.

DR. PATTEN: Yes.

DR. KERCSMAR: No.

DR. TINETTI: Yes.

MS. SCHELL: No.

DR. SWENSON: Yes.
DR. WOOD: No.
DR. TAYLOR: Yes.
DR. SCHATZ: No.

DR. PARKER: No.
DR. CLYBURN: No.
DR. SNODGRASS: No.
DR. BLASCHKE: Yes.
DR. BRANTLY: No.

DR. BENOWITZ: Yes, but I would like to make a comment that it's a temporary yes, because I think that there are people relying on this product, but I think that its continued status as a yes should require data on efficacy at the labeled

dose, label comprehension, and also on appropriate studies to look at the question about whether its over-the-counter status is resulting in undertreatment of some people.
DR. GAY: No.

DR. SCHOENFELD: Hello.
DR. WOOD: Yes, Dr. Schoenfeld?
DR. SCHOENFELD: Yes.

DR. WOOD: Darrell didn't get the votes, so let's do it again.

DR. GANLEY: Alastair, can I just remind you that also it is important when people vote is to explain their vote, and I don't know if you want to do that on the go-around or after the vote.

DR. WOOD: Let's finish the vote for Darrell, and then we will go around again.

DR. GRIFFIN: No.

MS. SANDER: No.

DR. PATTEN: Yes.

DR. KERCSMAR: No.

DR. TINETTI: Yes.

MS. SCHELL: No.

DR. SWENSON: Yes.

DR. WOOD: Okay. You got it? All right.

DR. SCHOENFELD: Am I supposed to vote again? I voted yes, David Schoenfeld. I just don't know what happened, because I am not sitting there.

DR. WOOD: Let's start at the other side and go around for comments.

DR. GAY: At this time, there are other beta agonists currently available, although they are by prescription, with a small increase in effort, that are appropriate for therapy as rescue medication for asthma.

With the improvements in technology, if you have a prescription in a pharmacy, you can pretty much go to any other pharmacy and get it refilled and renewed, and I think with the availability of these other beta agonists on the market, I do not believe that inhaled epinephrine by a metered dose inhaler carves out a significant or unique niche in caring for individuals with asthma.

DR. BENOWITZ: As a person who works in San Francisco, which is a city with a lot of illegal immigrants and people without insurance, I am concerned that there are many people who rely on these products.

So, I am concerned about removing them from the market, but on the other hand, I think the continuation of this on the market should be

contingent on an assessment as we would do for other over-the-counter drugs.

So, I would like to see that the dose, as labeled, is effective. I would like to see label

comprehension studies, and I would like to see appropriate studies to look at the question about whether the availability of over-the-counter bronchodilators results in inadequate treatment of asthmatics, failure to see physicians, failure to

use inhaled corticosteroids.

DR. BRANTLY: My vote was no, and there are a couple of different reasons why. Number one, after more than 50 years on the market for this particular drug, the fact that we don't have

efficacy studies that demonstrate its efficacy sort of suggests that it is unlikely that they are going to appear in the near future.

It is clearly not optimum therapy, and I think suboptimal therapy is a disservice to our

patients.

DR. BLASCHKE: My yes vote was, as usual, based almost exactly on what Neal has said. I

think there is a population who really does need and likely does benefit from the availability of this drug, and I certainly don't disagree with the need for some additional information about the label, the actual use type of data.

DR. SNODGRASS: I am sympathetic to the perceived need issue, but I can tell you after 30 years of dealing with young children and adolescents that I have never seen in large children's hospitals, and I am unaware of a single case where there has been worsening of asthma requiring hospitalization due to the lack of availability of this type of product.

I am aware of several cases where the use of this kind of product delayed therapy and did result in hospitalization.

DR. CLYBURN: I voted no, and as I read through this, said otherwise unavailable important public health benefit, and I think that the benefits are available otherwise.

Also, I started thinking as someone who practices in a medically underserved setting

predominantly, is this part of my armamentarium, is it something that I use regularly, and it is not, and, in fact, it is something that we discourage our patients from using, because we are trying to minimize beta agonist issues.

DR. PARKER: No, based on basically, insufficient evidence to convince me that it fit the criteria for essential use. Though, indeed, some may benefit, and I have great care for the underserved, I feel like there is a lack of evidence to say that a greater number are not being harmed by it.

DR. SCHATZ: I am not sure I have anything totally different to say. The way I look at it, we were asked are there data, is there evidence that this product improves the public health.

I think we have learned that it is used, but I don't think that we have heard anything that tells us that it improves the public health, and I think some points have been brought up to concern us that, in fact, it may adversely affect.

I do have confidence, although I agree

with the people who are concerned about the somewhat uncertain impact of removal, I will repeat what I said before, that I am convinced that the transition that would be absolutely part of it and

the education opportunity that would be provided, I think could, in fact, improve the public health.

DR. TAYLOR: I would like just to say that in a perfect world, I would vote no, too, and I don't see that perfect world and providing access

and a plan to address those folks that are underserved, and I see an emerging problem, for example, with Medicare Part D.

This is just another lack of planning on our part, so in the absence of that, I have to vote

yes.

DR. WOOD: I vote no, and what I also am very concerned about, the access and care for underserved populations, and I am equally concerned that we should start a system that says that

underserved populations should be assigned to drugs for which there is no evidence of efficacy and/or safety, and that seems to me a slippery slope that

we probably ought not to step onto, and I hope we don't step onto.

DR. SWENSON: I voted yes. I wish I could vote no. If it were a new drug application, I

certainly would, but the fact is that for 40 years, people have been using this drug. I am sure there are some that benefit, and I don't know what the cost to them will be if it's withdrawn, and we desperately need that data.

I would prefer that this decision be deferred until that data could be made available, but I think that given the inequities of our health care system and its inefficiencies, this is just possibly another example of the poor and

underserved bearing the burden of that system when they already are under such a burden anyway.

So, it's a yes with real reservation.

MS. SCHELL: I voted no primarily because I am concerned of the inappropriate use of the

medication over the counter, and I, too, have seen the consequences of inappropriate use of this particular drug, and I think that we are doing a

disservice to our patients when we don't educate them on the proper treatment of asthma and the management through education and the proper use of medication.

DR. TINETTI: I voted yes for many of the reasons that have been stated. I think nobody doubts that more appropriate would be for these people to be under care and getting appropriate treatment, but I think it's naive on our part to think that if this medication went away, that these people would access appropriate care.

I also wish there was more evidence of effectiveness, but as we well know, that lack of evidence is not evidence of lack, and because this predated the need for new drugs, unfortunately, the company hasn't had the impetus to study it. Perhaps knowing that it is going to be pulled from the market if they don't will be the impetus they need to provide some data.

DR. KERCSMAR: I voted no predominantly for reasons that have already been stated, but I would agree that all patients, regardless of their

ethnicity or economics, deserve the same high standard of appropriate care, and that we should work to transition those patients to appropriate state-of-the-art care rather than what might be

risky, disease-progressive care.

DR. PATTEN: I voted yes, and my reasons are very similar to those of Neal's and Mary's. I am thinking particularly of undocumented workers. There is large numbers of undocumented workers in

my state who are reluctant to seek care from a physician. They are on my mind.

I would be very reluctant to pull from the market something that 2 to 3 million people are using apparently feeling that they are getting

benefit from it unless I had better evidence than what has been presented to us now, that that is absolutely essential.

MS. SANDER: I voted no, which I am sure is no surprise. In New York City, in 2002,

Primatene Mist and all the other OTC bronchodilators were removed from the market due to, according to this article, manufacturing

problems, and they found--I have lost my spot here--that they weren't counting or doing something right, anyway, in the post-production process.

New York City survived according to this article, and when we talk about transition, again, it should be done thoughtfully. I think that is what we have all worked so hard to do in preparing for the transition of prescription medications, and I think we have to apply that same care to transition of OTC epinephrine.

Increasingly, patients are being exposed to health risks associated with unapproved nebulizer medications that are being swapped out. They are taking their prescriptions and turning them in, and having them swapped out with unapproved medications.

The patients don't know that this is happening, but one of the arguments the manufacturers give is--actually, several of them were the same ones that were given today, you know, we are helping the poor, we are helping save money. You know, it's the same, it does just as good.

I feel like we need to be careful that we don't put to the lowest common denominator in our health care and that we think thoughtfully, that we don't try and solve problems of access with

inferior products, and also knowing that the challenges that pharma companies have had in HFA development, I think the timeline that was given by Wyeth is a little bit ambitious for HFA transition.

DR. GRIFFIN: I voted no. I think that

it's an inferior medicine and I think our view of treatment of asthma has changed, so that the treatment has moved more towards anti-inflammatories than bronchodilators, and there is continuing emerging evidence about concern about

the harm of epinephrine-like drugs.

So, I think there will be some people who won't get their symptomatic relief, but I think as far as preventing morbidity and mortality, we are not losing anything by losing this medicine.

DR. WOOD: Dr. Schoenfeld.

DR. SCHOENFELD: I voted yes, and the main reason is, first, there is, in fact, no other

available substitute being another available over-the-counter, short-acting beta agonist.

So, there is--excuse me, the echo is making this hard--there is no available

alternative, and I think that without some knowledge as to what the effect of pulling this off the market would be under the current medical system, or the political will to make the kinds of changes necessary to make other things available, I

think we can't really take this off the market.

DR. WOOD: Yes, George.

DR. GOLDSTEIN: I wonder if I may make a couple of comments, and I will try not to repeat some of the things that were said here today.

Despite any cynicism that may exist, pharmaceutical companies are made up of people who have friends, parents, relative, et cetera, and they do, and do every day, try to do the right thing. So, there should be no cynicism on that

point.

Secondly, Dr. Ganley pointed out earlier that in view of the timing of this meeting, the

sponsor did not have adequate time to prepare an appropriate, at least in the judgment of the panel, presentation.

I submit to you that the panel could effect or could ask the sponsor and the agency to meet, and also, in view of the mixed vote that took place here today, to resolve some of those issues in discussions that are ongoing between sponsors and the agency every single day.

I resonate to Dr. Tinetti's comment about the--I think she used the word "naivete," of expecting if things are pulled off the market, it will suddenly thrust every patient into doctors' offices.

I should tell those on the NDAC Committee and the Pulmonary Committee that I was a practicing pediatrician for 17 years before going into the industry, and I have been in this industry for 30 years, in everything - OTC, Prescription, Regulatory Affairs, and you name it. I am now retired.

But I think the best interests of the

patient regardless of who they are or what they are, as Dr. Schoenfeld and others have pronounced, must be paramount, and I cannot bring myself to believe that withdrawing this product from the market would contribute to that, certainly in the short term and perhaps never.

I think the agency and the sponsor should get together, carefully consider every comment made here today, and out of that, a plan should emerge to resolve some of the outstanding issues, and I won't repeat them. We all know them too well.

But never, ever be in doubt that the right thing is paramount in our considerations.

DR. WOOD: Okay. Ted.

DR. REISS: I want to make just one brief comment, and I think that whatever the decision is, if the decision is to keep the drug on the market and to move things forward through the process, as Bob Meyer had outlined, I think it has to be a data-driven decision.

Those were my thoughts as I was sitting here, that really, to make an adequate decision for

all of the reasons that were put on the table, there has to be more adequate information on the effect of this drug.

DR. WOOD: A good point to end on.

Anything else? Charley?

DR. GANLEY: If this is the conclusion of the meeting, I just want to reiterate thanks to both committees for participating in it. It really serves an important mission for us in terms of

moving this process forward, and I just want to thank you again.

DR. WOOD: It is the conclusion of the meeting, Charley, unless there is something else you want us to debate.

Thanks a lot.

[Whereupon, at 12:22 p.m., the meeting was adjourned.]

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