DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE

Thursday, June 10, 2004

8:03 a.m.

Holiday Inn Gaithersburg
The Ballroom
Two Montgomery Village Avenue
Gaithersburg, Maryland

PARTICIPANTS

Vernon Chinchilli, Ph.D., Acting Chair
Shalini Jain, PA-C, MBA, Executive Secretary

MEMBERS

Carolyn M. Kercsmar, M.D.
Fernando D. Martinez, M.D.
Theodore F. Reiss, M.D. (Industry Rep)
Michael Schatz M.D., M.S.
Karen S. Schell, RRT, (Consumer Rep)
Erik R. Swenson, M.D.

SPECIAL GOVERNMENT EMPLOYEE CONSULTANTS (VOTING)

T. Prescott Atkinson, M.D., Ph.D.
I. Marc Moss, M.D.
Wayne Mitchell, M.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order and Opening Remarks

DR. CHINCHILLI: Good morning, everyone. This is a meeting of the Pulmonary-Allergy Drugs Advisory Committee. We are here today to discuss whether the use of chorofluorocarbons as propellants in albuterol-metered dose inhalers in no longer an essential use under the criteria as set forth in the Code of Federal Regulations 12 CFR 1.125.

My name is Vern Chinchilli. I am the Acting Chair today for the committee. So we will have some opening remarks. The first thing I usually do is introduce--I will ask each committee member--we will go around the table--to introduce themselves. Please make sure you hit the microphone button so it is on.

Why don't we start with Dr. Reiss. Oh; he is not here? Dr. Atkinson?

DR. ATKINSON: I am Prescott Atkinson, Allergy and Immunology at University of Alabama in Birmingham.

DR. SCHELL: Karen Schell, Consumer Representative from Kansas.

DR. MARTINEZ: I am Fernando Martinez from the Arizona Respiratory Center, University of Arizona.

DR. SCHATZ: I am Michael Schatz, Allergy and Immunology, Kaiser Permanent, San Diego.

DR. KERCSMAR: Carolyn Kercsmar, pediatric pulmonology, Rainbow Babies and Children's Hospital in Cleveland.

DR. MOSS: Mark Moss, Pulmonary and Critical Care, Emory University in Atlanta, Georgia.

DR. CHINCHILLI: Vern Chinchilli. I am a biostatistician from the Penn State Hershey Medical Center.

MS. JAIN: Shalini Jain, Exec Sec, Acting, and, at this point, for this meeting for the Pulmonary-Allergy Drugs Advisory Committee.

DR. SWENSON: Erik Swenson, Pulmonary and Critical Care Medicine at the University of Washington in Seattle.

DR. LUTTER: Randy Lutter, Economics, with the Office of the Commissioner in FDA.

DR. MITCHELL: Wayne Mitchell, Office of Regulatory Policy in the Center for Drug Evaluation and Research. I am the draftsman on the rule.

DR. SULLIVAN: I am Gene Sullivan. I am the Deputy Director of the Division of Pulmonary and Allergy Drug Products at FDA.

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

DR. CHINCHILLI: Thank you, everyone, for attending.

Next, Shalini Jain will talk about the Conflict of Interest Statement.

Conflict of Interest Statement

MS. JAIN: The following statement addresses the issue of conflict of interest with respect to this meeting and is made part of the record to preclude even the appearance of such at this meeting.

Based on the agenda, it has been

determined that the topics of today's meeting are issues of broad applicability and there are no products being approved at this meeting. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions. All special government employees have been screened for their financial interests as they may apply to the general topic at hand.

Because there has been reported interest in pharmaceutical companies, the Food and Drug Administration has granted general-matters waivers to the special government employees who require a waiver under Title 18, United States Code Section 208 which permits them to participate in today's discussion.

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. Because general topics impact so many entities, it is not prudent to

recite all potential conflicts of interest as they apply to each member, consultant and guest speaker.

FDA acknowledges that there may be potential conflicts of interest but, because of the general nature of the discussion before the committee, the potential conflicts are mitigated. With respect to FDA's invited industry representative, we would like to disclose that Dr. Theodore Reiss is participating in this meeting as an industry representative acting on behalf of regulated industry. Dr. Reiss is employed by Merck.

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

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

upon.

Thank you.

DR. CHINCHILLI: Thank you, Ms. Jain.

We are ready to start the regular part of the agenda. Dr. Meyer, the Director of the Office of Drug Evaluation II, will have some opening remarks.

Opening Remarks

DR. MEYER: Good morning. Although I service Director of the Office of Drug Evaluation II in the Center for Drugs, I, for many years, served for the Center Lead on issues related to the Montreal protocol and phase-out of CFCs from FDA-regulated medical products, specifically MDIs for asthma and COPD.

So, on behalf of the FDA, I wish to welcome all the participants in today's meeting of the Pulmonary and Allergy Drugs Advisory Committee. I want to thank you in advance for your time and your efforts and your thoughtfulness in your discussions and advice.

When we were originally planning this

meeting, we had hoped the meeting would coincide with the open public comment period of a proposed rule to delist albuterol as an essential use of ozone-depleting substances, specifically CFCs. This is now, indeed, the case although the rule just went on display at the Federal Register and, subsequently, on our web page yesterday afternoon. I believe you have been provided copies.

I would point out that, although the proposed rule is posted on these sites, it is not officially published until June 16 so what you have in hand is a pre-publication version that means some dates are missing and the pagination will change when it is officially published in the Federal Register.

I would also point out that the six-day comment period starts on the day of official publication which will be June 16 although, clearly, the discussions today will be considered as part of the docket for us to consider in coming to the final rule.

We particularly look foreword today to

input from the public in our public hearing portion of the meeting and I thank those individuals and organizations who are presenting or have otherwise submitted materials for the record.

All of the presentations, submissions and the deliberations of the committee and advice given today will be entered into the docket, as I said, and will help us to move forward towards finalizing this rule with a target of Summer of 2005.

I would note to the committee that we are not seeking any formal votes today on a particular question but do, very much, seek your counsel on the matter at hand whether the use of CFCs in albuterol metered-dose inhalers remains an essential use under the provisions of our regulations.

We will have three speakers from the FDA today. I will first speak, giving a history of the Montreal Protocol and FDA's regulations regarding essential use of CFCs. Dr. Eugene Sullivan, from the Division of Pulmonary and Allergy Drug Products, will then follow with considerations

related to the current situation with albuterol and its essentiality as well as some related issues.

To close FDA's presentations, Randy Lutter, who is FDA's Chief Economist in the Office of Planning, will speak on economic considerations related to the potential for delisting albuterol as an essential use.

Again, we would like to thank you for your time in being here and look forward to today's discussion.

DR. CHINCHILLI: Thank you, Dr. Meyer.

I believe you are on the agenda next for your presentation.

History of the Montreal Protocol and 21 CFR 1.125

DR. MEYER: Good morning, again, from this venue. When I arrived at the agency about ten years ago this July, I can assure you that I never envisioned I would be standing here representing the FDA on the issue of ozone protections. As a pulmonologist, it was not something that entered my mind at that point.

But life is full of happy occurrences.

This picture on my title slide is from NASA's web page and shows the largest recorded ozone hole over the Antarctic which actually was shot last September of 2003. This serves as a fitting graphic to start a talk on the history of the Montreal Protocol as well as the FDA regulations that related to chlorofluorocarbons and ozone-depleting substances.

The stratosphere is a region of the earth's atmosphere that begins roughly ten to fifteen kilometers above the earth's surface, depending on the particular part of the earth one is focused on, and extends up to 50 kilometers. Most of the ozone, over 90 percent of the ozone, in the atmosphere is in this stratosphere where it acts, in part, to filter ultraviolet B radiation by absorbing this band of wave length from sunlight.

Increases in UV-B reaching the earth's surface are detrimental to human health in a number of ways as well as to other life forms and to synthetic materials. The human consequences of most note are increases in skin cancer as well as

cataracts and alterations in immunity. Those skin cancers are both of the melanoma type as well as non-melanoma.

This, then, is the background as to why there is a worry about protecting the ozone layer. Also, by way of background, since we are talking about regulations, I would like to explain how rules are made. The FDA operates under laws or statutes, most notably the Food, Drug and Cosmetic Act, as well as other statutes.

However, no matter how well written or detailed a law may be, it cannot provide sufficient detail to inform the specific process of regulation. This is accomplished by the writing of rules which, when finalized, have the force of law behind them as it represents the agency's implementation of the respective law that we are operating under.

The usual pathway for reaching a final regulation or rule is by what is called Notice and Comment Rulemaking. Formally, that involves the FDA publishing a Notice of Proposed Rulemaking, or

NPR, in the Federal Register such as will shortly occur for albuterol.

An NPR typically has a comment period between 60 and 90 days--again, that, for the rule at hand is 60 days beginning on June 16--during which time comments from the public, including the regulated industry, are solicited. These comments are then individually considered and addressed in reaching a final rule. Rulemaking is an integral part of the CFC non-essentiality determinations. I will speak more on this later.

The purpose of my talk, then, this morning, is to give a history and background of the Montreal Protocol and to FDA's regulations with regard to ozone protection. The timeframes for these, as they developed, overlap and, obviously, the efforts intersect. So I will interweave the two topics in my talk.

Back in the mid-1970s, two scientists operating out of trial University of California at Irvine posited that chlorofluorocarbons were reaching the stratosphere were UV radiation slowly

would cleave off the chloride atoms that, in turn, catalyze the destruction of ozone. This work was by Molina and Rowland, who later was awarded the Nobel Prize.

At the time that this article came out, chlorofluorocarbons, or CFCs, were ubiquitous in use in multiple applications. They became widespread for a number of reasons. Amongst these were that CFCs are quite non-toxic which, parenthetically, makes them excellent for use in inhalers, very stable and had physical-chemical properties that were advantageous for use in refrigerant systems, air conditioners and aerosols.

The stability of these gasses is, in part, why they are so devastating to the stratosphere. They have a very long half-life when they reach the stratosphere and, therefore, damage the ozone layer for many, many years.

In 1978, really in a fairly remarkably short time after the seminal publication by Rowland and Molina, the U.S. Government acted to address the issue of CFCs and to place a general ban on the

use of CFCs as propellants in consumer aerosol products. This was accompanied by a rule from FDA in the relevant chapter of the Code of Federal Regulations or what we call the CFR, and that, for the FDA, is the 21st Chapter, banning the use of CFCs in all regulate products except for those deemed as essential uses.

This rule is now called 2.125 because that is the citation where it is published. That is how we will be referring to it throughout much of the day. Notably exempt at that time were broad classes of asthma and allergy products such as a nasal steroids, the inhaled steroids, and adrenergic bronchodilators.

In 1987, as the science of ozone depletion advanced and as there was further evidence accumulated about ozone reductions, a global treaty known as the Montreal Protocol on substances that deplete the ozone layer was initiated. At that time, 27 nations, including the USA, were signatories.

I would note, just to make this topical to

sort of current events, that this was during the latter years of the Reagan Administration. The original protocol now has at least 184 signatory countries. As of the time that I queried the web page for the Secretariat of the Ozone Efforts about a month, it was 184 countries. Countries are also called parties under the terms of the protocol.

This is widely considered a successful example of global, environmental cooperation. Indeed, there is evidence that the chloride levels in the stratosphere have stabilized in recent years and it is expected that the stratospheric ozone layer will slowly recover to levels that were seen in the early 1980s by the middle part of this current century.

The original phase-out of CFCs was slated for the Year 2000. That was taken in London in 1990. This was moved up, however, by meeting of the parties in Copenhagen which occurred in 1992. It was moved up to 1995, at the end of '95, because of increasing evidence of marked ozone depletion, particularly over the extreme southern hemisphere,

as you saw in my first slide.

This phenomenon is commonly called an ozone hole. It is not really a true hole but an area of extreme depletion. I should point out that, although it is a depletion that is particularly prominent over the southern hemisphere, it has occurred globally.

I should also point out that, while we are focussing on CFCs today because that is the relevant topic for the FDA, the protocol, itself, has controls on many other ozone-depleting substances such as halons, HCFCs, methylbromide, carbon tetrachloride and other substances.

So, while the CFCs are an important issue to FDA and, indeed, to the Montreal Protocol, I do want to be clear that the protocol is a much broader effort in scope than simply the chlorofluorocarbons.

In accordance with the Copenhagen Amendment to the protocol, the production and importation of CFCs became illegal in economically developed countries including the United States as

of January 1, 1996. The rest of the world is expected to have phased out new CFCs by 2010. Metered-dose inhalers, or MDIs, for asthma and COPD are currently considered as potentially acceptable essential uses of CFCs. I say potentially acceptable because there is a nomination process that parties undergo if they want to produce or import CFCs for use in MDIs.

These nominations have to be done annually and the process generally begins nearly two years prior to the year in question. So, for instance, the U.S. had to submit its nomination for 2006 in early 2004.

I would also point out that nominations are historically approved by consensus of the parties to the Montreal Protocol but, actually, if the consensus process fails, there is a mechanism within the protocol to default to a two-thirds majority decision.

I wanted to go through sort of how the protocol has evolved over time This is a decision of the parties from the Copenhagen meeting.

Decision IV, or this IV, means that it was from the fourth meeting of the parties and it was the 25th decision taken at that meeting. This was the definition at the time that they decided the phase-out would begin on January 1, 1996, or the ban on CFCs, that stated that, "All essential uses of CFCs would have to be based on products being necessary for public health and that there were not adequate alternatives." The failure to have adequate alternatives could either be based on technical problems or economical problems.

But this was macroscopic in terms of both this determination as well as the general use. In other words, it was widely accepted at that point in general that the uses of CFCs and MDIs for asthma and COPD could be considered an essential use.

However, over time, the protocol evolved so that, as the phase-out progressed, as alternatives became available, this sort of more generally and broad interpretation of what was an essential use became narrower and narrower in

scope.

In Beijing, at the twelve meeting of the parties in the Year 2000, another decision was taken that said that any product approved after December, 2000, must individually meet these criteria for essentiality under Decision IV-25. So, in other words, it is not just a general consensus any longer that the use of CFCs for asthma and COPD was acceptable but, in this case, any new product would have to individually meet this.

So this was a product-centered determination of essentiality that essentially precluded new CFC generics and, actually, many other new CFC products. It essentially was shutting the door, for all intents and purposes, except under extraordinary circumstances for any new CFC MDIs.

This past year, in Nairobi, a further decision was taken by the parties that became even more narrow and specific in scope. It stated that essential-use nominations from parties which, in

the past, had been lumped and general and not parsed out for the purposes of the protocol's evaluation, or the Montreal Protocol evaluation.

Now it stated that essential-use nominations have to be specific; for example, a country might say they need some undetermined--well, they would have to give a specific number, but some number of tons for albuterol. No quantity of essential-use CFCs would be authorized for albuterol. This is, I think, particularly germane today--that no quantity of essential uses of CFCs would be authorized, period--actually, this is a little bit of a misstatement in the way this is terms--if a country does not submit to the meetings of the party--beginning of the open-ended working group, excuse me, in the summer of 2005--a clear plan for when albuterol, specifically, would no longer be essential.

Let me go through that again, because this is key. Countries who request essential uses, including the United States, will have to submit to

the Ozone Secretariat of the Open-Ended Working Group in the summer of 2005 a plan or a date-certain for when albuterol will no longer be considered essential. If parties fail to do that, including the U.S., we will not receive and essential-use allocation at all.

Now, turning a little bit from the evolution of the Montreal Protocol back to our rules and regulations, the Clean Air Act Amendments of 1990 codified the Montreal Protocol into U.S. law. The implementing EPA regulations specifically call for FDA to define what is an essential medical use and refers to our 2.125 as the source of the listing of those essential products.

I remind you, however, that 1.125 was finalized before the Montreal Protocol existed and before the Clean Air Act Amendments.

The rule, as promulgated in 1978, stated that a CFC-containing product regulated by FDA was misbranded or adulterated under the FD&C Act; that is, it would be illegal under our authority unless deemed essential and listed in 2.125. The

definition of essential was that there would be no technically feasible alternatives; that the use of CFCs in that particular product provided substantial health, public or environmental benefit; and that the release of the CFC was small or justified given the public-health benefit.

Notably, the FDA rule had no mechanism to determine when things were no longer essential and, therefore, to delist them. It did have ways to add new classes of drugs to the list and, in fact, that was done over the years. But it had no specified way for delisting things.

Another important feature of the rule that needed to be correct is that many drugs, including albuterol, were not specifically mentioned as essential uses but, rather, there were broad definitions of drug classes, if you will, such as albuterol and other beta-agonists being under the general term of adrenergic bronchodilators for human use.

So, realizing that we needed to correct some things about this rule that was written prior

to the Montreal Protocol and the Clean Air Act, and specifically to develop a mechanism for delisting things that were no longer essential, FDA, in 1996, undertook revisions. Because of wanting to do these revisions in the very most public and informed manner, the FDA took an additional step to the steps that I gave you earlier for the publication of a rule, doing something called an Advance Notice of Proposed Rulemaking which, actually, starts with another cycle of notice and comment.

This effort proved very successful if measured by the number of comments. We got close to 10,000 comments to this Advance Notice of Proposed Rulemaking, many of which, I would point out, were actually patient-based comments sparked by lobbying efforts.

We then took all 10,000 comments and reviewed them and responded to them. I would note that there were many fewer substantive comments but still all of the comments were carefully reviewed and considered. That resulted in the publication

of a Notice of Proposed Rulemaking in 1999.

That proved to be less controversial in many ways and it received many fewer substantive comments and comments overall and, as I said, had seemingly much less controversy. So FDA moved forward with amending 2.125 in July of 2002 and this went into effect six months later.

The 2002 revisions did a number of things. First of all, it listed essential uses as individual moieties. I would point out that, to coincide more correctly with the Montreal Protocol, it no longer referred simply to chlorofluorocarbons but to ozone-depleting substances. But, for the purposes of today and for all intents and purposes, most of FDA's activities, you can consider ODS, or ozone-depleting substances, as being synonymous with CFCs in terms of this discussion.

So, for instance, albuterol is now separately listed rather than there just being a broad class without any citation of individual moieties.

The revisions also added a higher hurdle

for investigational new drugs to be developed with CFCs and it raised the bar for new listings of essential uses as well. There was also a list of criteria, importantly for today, for determining when individual uses were no longer considered essential.

One other revision I would point out that is not on this slide was that we shifted the rule, because of the re-write of the Clean Air Act, to state that if something was no longer essential, it would be considered illegal to market it under the Clean Air Act and not under the Food, Drug and Cosmetic Act.

Let me go through these important nonessentiality criteria. I would point out that Dr. Sullivan will revisit these in his talk specific to albuterol, but I think they are worth hearing a couple of times.

For a specific moiety to be considered nonessential, there would have to be at least one non-ozone-depleting-substance product--in other words, a non-CFC product--with that same active

moiety, and here I am only talking about a moiety where there is only one marketed-brand product or one marketing strength, so, at least one active moiety with the same indications, same route of administration--in other words, oral albuterol would not be considered an alternative under these criteria--and about the same level of convenience.

We stated in the preamble to the final rule that, although dry-powdered inhalers might fit this description, we felt that MDIs would most neatly do so and, I think, most logically do so.

In addition to this, these alternatives would have to have adequate postmarketing data to prove that they are not only safe and effective for approval purposes but will serve as an adequate alternative in the marketplace. Importantly, there would have to be production capabilities and supplies that are adequate to meet the needs of patients who depend on the use of this moiety for the treatment of their asthma or COPD and patients who require the CFC product are adequately served.

I would state, and I am sure that Gene

will bring this up as well, that, under the considerations for adequately served, is the issue of price in that--not so much whether there will be any impact on the price to the patients but will patients be disaffected or unable to get the medicine if there is a price differential.

We didn't build that in as an explicit consideration, the cost issue, but it was mentioned in the preamble because many of the comments to the ANPR and to the PR as we developed this re-write of 2.125, brought up the issue of affordability.

Now, specific to albuterol which has--actually, this should say one branded product available and three generics marketed--for moieties with more than one available product or strength such as albuterol, you would need at least two non-ozone-depleting-substance products with the same active moiety, the same indication, route of administration, about the same level of convenience, and the other criteria were the same.

So, in other words, if the moiety was represented in the marketplace by different

strengths or different numbers of products from different manufacturers, we felt it important that there be sort of at least--if not a full match to the range, at least alternatives that represented some choice.

Let me just show you, to wrap up this background, where all this has led over time. This is a graph of the global situation for CFC essential uses. Let me go through the two lines here. This is 1996. The open space is actually the year, not the hatch mark, so we go from 1996 out to 2006 on the X axis. On the Y axis, we are talking about metric tons. A metric ton is 2200 pounds, so these are metric tons of total CFC used for essential-use allowances in these developed countries.

The red line is the amount that was exempted--in other words, the amount that was nominated and approved by the parties. The blue line is the amount that was actually used over time. The green line is the stockpiles. So these are the amounts held by the countries that don't

represent new production.

You can see that the peak of the use worldwide, or at least in these developed countries that were putting in essential uses, was just about 9,000 metric tons occurring in the 1997-1998 range. This has fallen by 2003 down to just a little bit over 4,000 tons. One would project from the amount nominated, which generally has been historically higher than the amounts actually used, that this will further fall in the coming two years rather dramatically. So the amounts nominated in 2006 are down below 3,000 metric tons.

I apologize for this being a little harder to see. I could not manipulate this as easily as the last one. But this is the situation for the United States, itself. Again, this is metric tons per year on the Y axis, years on the X axis. I know that will be very difficult for people in the audience to see but the main point here is this is the blue line, which is the amount used for metered-dose inhalers in the United States.

You can see, for the most part, that it

has been reasonable stable from the pre-Montreal-Protocol years through the time period of the Montreal Protocol, although there was a rather substantial fall in the last couple of years--this goes out to 2002--at which time the total use was just a little bit over 1500 metric tons in the United States. I would point out that the use for albuterol is a substantial portion of the United States nomination.

Let me also now talk about the transition within the United States, itself. What we have here is a slide that attempts to display the original listings under the 2.125 and then the specific listings under 2.125, and then to display changes over time.

So, originally, 2.125 had the broad class of beta-adrenergic agents: inhaled corticosteroids; nasal steroids; the cromones--cromolyn and nedocromil were actually separately listed; ipratropium; atropine, which was actually approved for use in Desert Storm; a combination product, albuterol and ipratropium.

I think it is important for me to point out, if Dr. Sullivan does not and if it is repeated, I think it is still and important thing; we are not talking about a combination product today. We are only talking about those products that solely contain albuterol as their active ingredient; and then a number of other products, many of which were actually, as you can see, not MDIs. So we had talc, contraceptive foams, rectal foams, ergotamine MDIs, polymxin, anesthetic drugs including those that directly use CFCs, and nitroglycerine.

When the re-write of 2.125 was finalized in 2002, those products listed in red were taken out, many of these because they either did not meet the criteria any longer or were not considered essential under the Montreal Protocol, or they were no longer marketed.

So, at the time of the finalization, isoetharine, isoproterenol, the nasal steroids as a class, contraceptive foams, rectal foams, polymyxin and nitroglycerine all came out and were not

separately listed in 2.125.

The products in yellow could be considered as potential for delisting soon, these because they are no longer available, marketed as CFC products. One of the things in 2.125 re-write that was said was that, if a product was not marketed for a substantial period of time, one could consider it to be not essential. Those would include bitolterol, salmeterol, which was discontinued by the manufacturer, dexamethasone, talc, ergotamine MDIs and anesthetic drugs.

Beclomethasone is no longer marketed, the MDIs, at least not newly produced MDIs, and there are alternatives. So that is another potential delisting. Albuterol, I guess I did not put in yellow here because that is what we are here to discuss today is whether that has met the criteria that we laid out in the revisions of 2.125.

So, to conclude my talk, the U.S. Government moved proactively to address the issue of ozone depletion shortly after the development of the ozone science, and the U.S. Government had a

key role in the formation and the conduct of the Montreal Protocol. The Montreal Protocol is considered a successful treaty that has led to important reductions in CFCs and other ozone-depleting substances and, as I mentioned, there are data to suggest that the recovery of the stratospheric ozone layer is in the early stages.

Now, the Montreal Protocol, as I pointed out from the evolution of some of the decisions taken, is increasingly moving towards control in its specific essential uses, notable amongst those would be albuterol.

Just as a transition slide, I chose another picture off the NASA web page of the ozone depletion. Remember that I said we would recover to the early '80's levels by the mid part of this century. This shows the Antarctic region in 1983 and the Antarctic region in 1993. You can see the difference where the white is the thicker ozone. You can see the difference in the ozone layer in that decade.

So, thank you very much.

DR. CHINCHILLI: Thank you, Dr. Meyer.

You finished a few minutes early so let's see if there are any questions from our committee members. I have one, Dr. Meyer. What was the rationale behind the decision about not pursuing this with the--not considering the dry-powdered inhalers as a similar moiety?

DR. MEYER: What we said was that we thought they could serve as an alternative but it would not be as automatic as an MDI. So, in fact, I think if there were an albuterol dry-powdered inhaler that met those criteria otherwise, we would consider it.

I think, at the time we were writing it, we had considerations such as, at that point, albuterol was available in a capsule, an individual capsule, rotohaler-type device where one would place it in, turn it and breathe. We did not feel that that had sort of the same level of convenience and portability and so on as an MDI. So I think we wanted to not exclude all dry-powdered inhalers out of hand but say that they would have to meet

certain levels of convenience and patient acceptability.

Again, the presumption in the preamble to rule was that the MDIs would most neatly do that because they are very much similar.

DR. CHINCHILLI: Dr. Martinez?

DR. MARTINEZ: Dr. Meyer, in your multicolored slide, there was some products in white. I presume those will continue to be available by way of CFCs and includes epinephrine, for example; is that correct?

DR. MEYER: Some of those products in white are, in fact, under development in that are alternatives being developed. Some are not. One of the provisions in the rule that I didn't bring up today because it wasn't fully germane but I would be happy to answer as a part of your question is the fact that, beginning next year, we will have the ability to call this body into meetings, have the advisory committee come to meetings, to discuss those products that remain on the list that are not being reformulated and whether they remain

essential.

I think, just parenthetically, epinephrine will be something that will be important for us to discuss at some time in the future.

DR. CHINCHILLI: Any other questions from the committee? If not, thank you, again, Dr. Meyer.

I guess we will move forward with Dr. Sullivan, the Deputy Director of the Division of Pulmonary Drug Products.

Medical Considerations

DR. SULLIVAN: Good morning. I am Gene Sullivan. I am a pulmonologist. I am also the Deputy Director of the Division of Pulmonary and Allergy Drug Products at FDA. For the next twenty or thirty minutes, I am going to be discussing some of the medical considerations in regard to this proposal to remove albuterol from the list of drug substances that are considered essential uses for CFCs.

Following my talk, you will hear from Dr. Lutter, as Dr. Meyer mentioned. Dr. Lutter will go

into more depth in regard to the economic aspects of this question. Then, following that, you will hear some very important information from interested parties who will be speaking during the open public hearing.

So this slide provides a background overview of my talk. Dr. Meyer has just given a very nice background on the overarching issues about the Montreal Protocol and the FDA Regulation 2.125, so my background remarks will be brief. Then, also, briefly, I will review the currently marketed albuterol MDI products. But the bulk of my talk will be in this section specifically looking at the criteria that Dr. Meyer mentioned that are included in the Amended 2.125, so the currently existing regulation, and specifically examining those criteria in regard to how they apply in the case of albuterol.

Then, finally, I will touch on a couple of other issues which, although they are not directly responsive to the criteria laid out in 2.125, I think are clearly important issues to consider when

deciding on a path forward with regard to albuterol.

So, again, Dr. Meyer has provided very nice background on the Montreal Protocol and on the FDA regulation concerning the essential-use determinations, that being 21 CFR 2.125 and, as Dr. Meyer mentioned, I will be referring to it as 2.125 from now on.

As you know, the agency is currently considering whether albuterol, in fact, has met the criteria that are listed in 2.125 for removal from the list of essential uses. This process that we are embarking on is in keeping with the goals of the Montreal Protocol, specifically, the goal of phasing out production and importation of ozone-depleting substances including chlorofluorocarbons.

I think the step forward with albuterol is an important step in that direction particularly because approximately half of the annual essential-use CFC allocation in the U.S. is for albuterol. We are moving forward in this direction

in light of the fact that there now exist two alternative, non-CFC albuterol metered-dose inhalers on the market in the U.S., that being Proventil HFA and Ventolin HFA.

In addition, in 2003, the American Lung Association submitted a citizen petition on behalf of a group of organizations, collectively referred to as the U.S. Stakeholders Group. That petition requested that the agency move forward with this rulemaking process in order to remove albuterol from this list.

That citizen petition is included in your background materials. Your background materials also include other communications we received from the Stakeholder's Group as well as the submissions to the public docket that were submitted by various interested parties and organizations in response of the citizen petition.

So what are the currently marketed albuterol metered-dose inhalers? Obviously, they can be divided into those that contain CFCs, which are ozone-depleting substances, and those that

don't contain CFCs. In terms of the CFC MDIs, there are several. First of all, there is the branded product, Proventil, marketed by Schering-Plough. This was approved in 1981. In addition, there is a product marketed under a Warrick label which is marketed under the same NDA.

Then there are several generic versions. Actually, four have been approved. The first of these was approved in 1995. Currently, three of these are being marketed. As you may know, in 1981, there were actually two branded albuterol CFC MDIs that were approved, the other one being Ventolin. That is not listed here because it is no longer marketed within the U.S.

Now moving to the non-CFC MDIs or, and I will use the shorthand, as alternatives, these don't use CFCs. Rather they use HFA 134A which is a substance that does not affect the ozone layer. There are two of these HFA products; Proventil HFA, which was approved and initially marketed in 1996 and, more recently, Ventolin HFA, which was approved in 2001 and was marketed in 2002.

So this is the regulation, obviously, that is at the heart of today's discussion, 2.125, called the Use of Ozone Depleting Substances in Food, Drugs, Devices or Cosmetics. Among a number of thing, one of the things that it does is it lists specific drug moieties for which the use of CFCs is considered essential.

In addition, as Dr. Meyer mentioned, it sets forth criteria. There are four such criteria that must be met in order to remove a drug moiety from the list of essential uses.

I will run through these again. Dr. Meyer has been through them. I will run through again, though, because I think they are the heart of today's discussion. First of all, and here I am referring to active moieties represented by two or more NDAs which is the case, as I mentioned, with albuterol.

The first criterion for removing a drug from the list of essential uses would be that at least two non-ozone-depleting-substance products that contain the same active moiety are being

marketed with the same route of delivery for the same indication with approximately the same level of convenience as the ozone-depleting product.

The second criterion is that supplies and production capacity for the alterative must exist or be expected to exist at levels that would be sufficient to meet patient need.

The third criterion is that adequate postmarketing-use data should be available for the non-ozone-depleting products. Again, as Dr. Meyer mentioned, that is to provide some reasonable assurance that no unanticipated limitation of the alternative product emerges during the postmarketing, so real-world experience that was not detected prior to approval.

Then, finally, the fourth criterion is that patients who medically require the product would be adequately served by non-ozone-depleting products containing the same active moiety and other available products.

So now I am going to walk through each of these criteria and look at how they apply to

albuterol. The first criterion; again, at least two products containing the same active moiety, the same route of delivery, the same indication and approximately the same convenience of use. So, clearly, the alternatives that we are discussing, Ventolin HFA and Proventil HFA, both have the same active moiety, albuterol. Both are delivered by the same route of delivery, oral inhalation, and carry the same indication, prevention and relief of bronchospasm and patients with reversible obstructive airway disease and prevention of exercise-induced bronchospasm.

I should point out the initial NDA, Proventil, was approved down to the age of 12 and Ventolin was approved down to the age of four. Both of the alternative products are approved down to the age of four.

Finishing up with the first criterion, the final bit of it is the same level of convenience. Now, when we looked at the same level of convenience, we described, in the Preamble, various aspects of what we might mean by that. We looked

at things like portability, preparation before use and the physical effort of manual dexterity that might be needed to administer the drug.

The CFC and HFA MDIs are quite similar and so have very similar portability and require similar degrees of physical effort and dexterity to use. I should mention, in regard to preparation before use, that, in the early experience with the first HFA that was approved, the Proventil HFA, we became aware that there were occasional instances of clogging of the actuator if they were not cleaned properly.

Now, the CFC and the HFA inhalers have actually very similar cleaning instructions. It is just evident that patients using the HFA inhalers need to pay more attention to the cleaning instructions that are already in the label for both products.

The second criterion is a little bit more difficult to definitively establish at this point. This is the criterion that states that supplies and production capacity for the alternatives need to be

at levels that would be sufficient to meet patient needs. At least in part, because of the price differential between the generics and the currently marketed FHA products, the market share for the HFA products, at this point in time, is much smaller in comparison than the market share of the CFC products.

So, if the CFC products were to become unavailable suddenly today, the current supplies and production capacity of the HFA alternatives are not sufficient to meet patient need. That is because, simply, that the manufacturers would need time to ramp up production. However, GlaxoSmithKline, in its statement in response to the citizen petition submitted to the docket and included in your background package has stated that it is confident that additional internal and external capacity can be installed to insure adequate supplied and production capacity for Ventolin HFA and that this could be accomplished within twelve to eighteen months.

In addition to this statement in the

docket, GlaxoSmithKline and, also, Schering-Plough, will be speaking today and I expect that at least a portion of their comments may address specifically this criterion.

The third criterion that we are applying is that adequate U.S. postmarketing data be available for the alternatives, again, looking for unexpected real-world problems with the alternatives. At this point in time, we have Proventil HFA which has been marketed for seven years and Ventolin HFA which has been marketed for two years.

Apart from the early reports of actuator clogging that I mentioned, the available postmarketing use data does not suggest any problems in terms of safety, efficacy, tolerability or patient acceptance of these two alternatives.

Perhaps the most difficult of the criteria to address is the fourth. This is the criterion that states that patients who medically require the ODS are adequately served by the alternative. This term, "adequately served," is fairly broad and it

encompasses a number of things.

Clearly, the most important is that the available data on the alternatives must demonstrate sufficient efficacy and safety and tolerability and so forth such that the alternatives could be considered reasonable replacements for the CFC MDIs. This type of data was submitted with the NDA and has accumulated in a postmarketing period and seems to imply that the alternatives do meet these criteria.

But there is a further subtlety to the adequately served phrase here and that is cost. As Dr. Meyer mentioned, during the process of the ANPR and the proposed rule, there were comments about the effect of this rule on the price of medications. In the Preamble, in the Federal Register, the Preamble to the 2002 Amendment where these criteria were established, the FDA clearly stated that it will consider cost in determining whether the alternatives meet patient needs.

So I am going to take a couple more slides to just look at this cost issue a little bit in

more depth. As with most drugs, branded CFC products cost more than their generic counterparts. As it turns out, in this very complicated healthcare system that we have in the U.S. in which the specific price of a medication varies according to a number of factors including who is paying, it is somewhat difficult to arrive at "the" price of a drug.

Therefore, it is somewhat difficult to arrive at a clear statement of the differential between the cost of a branded product and a generic product. Dr. Lutter will go into this in a little bit more depth and talk about the various sources of data that are available for the price of a medication and how complicated that issue is.

I have provided on this slide some data from an FDA website that highlights the cost savings to a patient that can be achieved with generic products. The web address is in your handouts. On this site, data on the average national retail price, which was data from IMS Health, were used to generate this information so

that the retail cost per day for an asthmatic patient who used Ventolin would be $1.44 whereas the CFC generic would be 69 cents per day.

Of course, this is a comparison between a CFC generic and a CFC branded, so it is important to note the branded HFAs, in general, are priced comparably to the branded CFC products although not exactly the same price.

The other element to this is that there are a number of existing patents and, due to these patents, there are currently no generic HFA products available. These patents are listed to expire, the first one in 2010 and the final patent in 2015. So, given the current realities, the removal of the essential-use status of albuterol would result in an increase in the price of albuterol MDIs.

The public-health consequences of such an increase in price are not known and are, in fact, very difficult to predict. One possibility would be that patients who are prescribed albuterol metered-dose inhalers may be either unable or

unwilling to pay for that and so may not purchase the albuterol inhalers.

It is also possible that an increase in the price of an albuterol MDI, which is an acute-reliever drug from which patients, as you know, perceive an immediate benefit, might result in them forgoing filling prescriptions of other medications such as asthma-controller drugs from which they don't receive the same immediate feedback. But, as you know, controller drugs are quite important in the appropriate management of asthma.

So, as I mentioned, Dr. Lutter will discuss in greater depth these economic aspects including descriptions of the various sources of price data that are available and means for estimating how changes in the price of albuterol MDI might affect the utilization.

As I mentioned, that is a difficult task in and of itself, how will an increase in price of an MDI translate into a change in utilization of albuterol and, even if we were able to establish

that firmly, the next question that begs answering would be how does the change in utilization translate into important health outcomes. Of course, that is an open question as well.

So, before I close, as I mentioned, I want to bring up a couple of other issues that are not directly responsive to the criteria in 2.125 but, nonetheless, may be quite important in considerations regarding a path forward on albuterol. Both of these issues relate to the future availability of chlorofluorocarbons.

The first issue has to do with production facilities. Currently, the only source of pharmaceutical-grade CFC 11 and 12 for use in the U.S. is Honeywell's plant in the Netherlands. CFC 11 and 12 are the particular chlorofluorocarbons that are contained in the albuterol CFC MDIs.

The Dutch Government has informed Honeywell that CFC production at that factory will no longer be permitted after 2005. So that might jeopardize the supply of CFCs that are necessary for the manufacture of albuterol MDIs but also all

of the other MDIs that use pharmaceutical-grade CFCs. However, Honeywell has stated in its submission to the docket in response to the citizen petition that it will begin production of pharmaceutical-grade CFC 11 and 12 at a U.S. plant and will be able to supply CFCs beyond 2005. Honeywell will also be speaking during the open public hearing session today.

The second issue that touches on the future availability of the CFCs refers to potential actions that might be taken by the parties to the Montreal Protocol. So, as Dr. Meyer mentioned, each year the U.S. and other countries who request to manufacture CFC MDIs, go through a nomination process whereby specific quantities of CFCs are requested of the parties.

Thus far, the parties have respected the U.S. determination that albuterol is, in fact, essential and have granted the volumes requested by the U.S. However, more recently, the parties have very pointed noted the availability of two non-CFC alternatives within the U.S. and some have

questioned the continued need for chlorofluorocarbons for this purpose. It is not at all clear how long the parties will continue to grant CFC requests for use in albuterol MDIs.

So, with that, I will close. I have listed on this slide the questions or topics for discussion that have been provided to you in a handout format. Essentially, the agency is asking you to discuss the extent to which you believe the criteria that are established in the 2.125 for removal of a drug substance from the list of essential uses of CFCs have been met in the case of albuterol. Beyond that, we are open to hearing from you any suggestions of additional data, additional information or other issues you think should be considered as we move forward in this process of determining the essential-use status of albuterol.

With that, I will close.

DR. CHINCHILLI: Thank you, Dr. Sullivan. Again, we are ahead of schedule so we can take some questions from committee members if there are any

questions. Yes, Dr. Atkinson?

DR. ATKINSON: Can you comment on whether the existence of the patents on the new HFA devices are going to preclude the development of any generics until that time period? Are there any pending applications for generic devices?

DR. SULLIVAN: Of course, we can't comment on any pending applications. The analysis of patents is a complex issue that the FDA doesn't really directly do. Companies claim they have patents which protect them. If a generic firm wants to challenge that patent, they can. I think, beyond that, perhaps I will invite Wayne Mitchell to comment more specifically, if he can.

MR. MITCHELL: I really can't say much more. We don't have any institutional expertise on patent law. Patents are listed in our Orange Book. The patents are listed through 2015. That is about all we really can say.

DR. CHINCHILLI: Any other questions? Dr. Sullivan, I have a question. In one of your slides, when you talked about Proventil HFA, you

said that early reports of actuator clogging were available. Does that imply that there are no longer reports of this problem? Were there modifications to the device? I just was confused by the word "early" reports of actuator clogging.

DR. SULLIVAN: That refers to the fact that when the product first went on the market--and it is not unusual to get more reports on a particular drug when it first hits the market, but the agency became aware that patients were having problems with the clogging of the actuator and an effort was made to better publicize the necessity of cleaning these products because, although the cleaning instructions were included in the CFC versions, they may not have been followed by patients.

It was determined that if the instructions are actually followed, there are fewer reports. I believe that the number of such reports has declined. That was sort of an early phenomenon.

DR. CHINCHILLI: Thank you. Any other questions? Okay; if not, then we will move on to

Dr. Lutter.

Economic Considerations

DR. LUTTER: My name is Randy Lutter. I manage a small economics group within the Office of Policy and Planning, Office of the Commissioner at FDA. It is my pleasure to be here.

I would like to talk to you today about the question of whether or not delisting albuterol will have effects on--whether the patients will be adequately served by delisting albuterol.

Let me begin by giving you an overview. The key conclusion is that delisting albuterol CFCs will deter the use of a number of prescribed MDIs that is large in absolute terms but small relative to the market. Our analysis is ignoring an announced giveaway by GlaxoSmithKline of 2 million MDIs per year because we lack a basis to evaluate that quantitatively. We also find that the effects on public health are too uncertain to quantify.

Let me give you some brief institutional background of how an economist ends up in the position of speaking before a group of esteemed

pulmonary and allergy advisors to FDA. There is an executive order, 12866, signed by President Clinton in '93 and it actually follows one signed by President Reagan in '81. It directs the agencies to assess the costs and benefits of all regulatory actions developed through the notice and comment rulemaking that Dr. Meyer described earlier.

The office that I had at FDA develops the economic analyses required by that executive order. The method of economic analysis that we developed follows the constraints of OMB Circular A-IV which is the latest in a series of circulars developed by the Federal Office of Management and Budget directing agencies on how to conduct economic analyses.

The executive order directs agencies to assess the cost and the benefits and to take regulatory actions which are cost-effective but economics also is reflected in the decisions of the Montreal Protocol. Drs. Meyer and Sullivan have mentioned the term "essential," and "essential use," turns on whether there are available

technically and economically feasible alternatives or substitutes that are acceptable from the standpoint of environment and health and that is in Decision IV-25. Section 2.125 uses the phrase "adequately served." As described by Dr. Meyer, that has economic content.

So there are actually three institutional reasons why economics matters for the current decision.

A brief discussion of economic fundamentals. The issue here is that delisting would remove albuterol MDIs with CFCs. Those are currently the only generic albuterol MDIs on the market. Therefore, one would anticipate on that basis an increase in the price. So the broad question is whether or not that increase in price has effects on whether or not patients are adequately served.

To comply with the executive order, we need to assess the benefits of delisting and, in particularly, a relatively earlier delisting as opposed to a later one, and also the costs of

earlier delisting.

The benefits come in four separable categories. The first is a controlled transition. You have already heard presentations about the nature of the international cooperation and the way that that might affect the availability of CFCs by offering a relatively--by proceeding with this rulemaking, FDA hopes to establish an opportunity for a controlled transition to CFC-free MDIs.

The second category of benefits is clearly the environmental ones that Dr. Meyer has described. Reduced emissions would lead to reductions in skin cancers, cataracts and UVB-related ecological benefits. For this, our proposal, FDA has not been able to quantify the benefits in terms of skin cancers, cataracts or UVB-related ecological benefits.

Some analysis in quantitative terms has been conducted previously by other federal agencies including the EPA. The difficulty that we face is in translating their estimates of aggregate benefits to the benefits from the much smaller

reductions of CFC emissions that might be achieved from this rulemaking, and we haven't been able to do that for this proposal.

A fourth category of benefits pertains to international cooperation. Dr. Meyer did not understate in any way the importance of the Montreal Protocol. It is a flagship treaty for successful international environmental protection and it enjoys wide respect and esteem for that reason.

A final category of benefits is that this rulemaking may encourage innovation in environmental safe technologies.

In terms of the costs, I would like not to focus on the increased spending associated with a higher price of MDIs but, instead, focus on a related question of whether or not the increased prices may deter appropriate usage. I think that is the appropriate issue for this panel and that is the one that I am going to devote the rest of my time to.

Also, by way of background in economics, a

key notion is what are we comparing the world to when we do our analysis. We need to describe what is the baseline relative to which we are assessing the effects of delisting. The baseline in this instance is the continued availability of generic CFC albuterol. So the analysis that we are conducting is relative to a world in which the CFC albuterols continue to be available and, therefore, the generic CFCs also continue to be available.

What I am going to focus on is a relatively standard and conventional economist approach to estimating the response to higher prices. It really focuses, in particular, on the estimated quantity of metered-dose inhalers that may not be consumed as a result of the increased price. It interprets this as the product, really, of three things. One is the price increase in percentage terms. The other one is a measure of the consumer sensitivity to the price increase, a measure the economists typically describe using the word "elasticity," and, lastly, the MDIs sold in the baseline to price-sensitive

consumers. So these are three parameters that I will draw your attention to.

With respect to the price increase, the prices are, of course, variable in a particular way. The vary with market conditions and they vary also in response to the marketing decisions made by the different companies marketing the products. As a result, the assessments of the price are difficult not only because of the data deficiencies but also because, ideally, we need to be looking forward to what the price difference might be between a world where the albuterol CFCs are delisting and a world where they would continue to be available.

That forward-looking approach requires and association of these prices that takes the variability into account. For the purposes of our analysis, that is too complicated and we are, instead, going to take the current price differences as a measure of the price increases from the delisting. The merits of this approach are simplicity, transparency and also consistency

with an announced policy of GSK that it would freeze wholesale prices through December, 2007.

Where does one go for information on prices? In the modern day, Google comes to mind as a source of all information. If you go to Google and look for prices, you come to drugstore.com. It listed generic MDIs with albuterol on the 24th of March for $14. HFA at drugstore.com sold a Proventil. The Proventil HFA was sold at $39.61 and Ventolin HFA sold at $38.99. Those prices I have checked twice and they were relatively unchanged in the recent period.

That gives an increase of about 180 percent just comparing the generics to the HFA. But these web-based prices are really unrepresentative. They neglect the brick-and-mortar outlets. They neglect shipping costs. Ideally, what one would want are average retail market prices for the cash-paying customers who would be sensitive to price increases.

We have not acquired these idea data for the analysis that we have conducted for this

proposal. So, instead, I am going to talk to you about data we have acquired which are the best available proxies at this moment.

The Medical Expenditure Panel Survey of the Agency for Healthcare Research and Quality provides some information on prices. This survey assesses expenditures by the noninstitutionalized people age less than 65 in the non-Medicare population. It provides information on the average retail prices among all payer types, the insured and the uninsured alike, for CFC albuterol inhaler prescriptions 2000 to 2001.

The information is that the generics are a little bit less than $25. I also report here the standard error. The brand is $39. You have heard Professor Sullivan mention that the branded price of the CFC tends to be close to the branded price of the HFA. In this instance, the data on the HFA prices are too rare to report.

We also looked using the MEPS survey at a sensitive population that lacks insurance or has only private non-group insurance which, in the

judgment of experts at ARC would typically exclude coverage for drugs. We looked among this group at people with incomes less than 400 percent of the federal poverty level. This was a convenient cutoff, given the data constraints of MEPS.

Within this group, the estimated average retail prices were $22 for the generic inhalers and, again, in this instance, the data on the branded inhaler prices were too rare to be reportable. This group had about 2.8 million albuterol prescriptions annually.

A second source of data on prices that we consulted is proprietary information from IMS Health, their national prescription audit for the first quarter of 2004. Note the distinction in dates. The MEPS is 2000-2001 and this is 2004. There is no more recent information on MEPS. For the IMS price information, we have prices measured using the average pharmacy's revenues from uninsured customers, insured customer and Medicaid beneficiaries alike. So this is basically across all payer types.

This includes chain, independent, food-store pharmacies. It excludes the Internet. It excludes mail-order and long-term-care pharmacies.

Information on prices from IMS suggests that the median price for the generic albuterol MDIs is $19.70 and for the albuterol HFA MDIs, the price is $43.00, the price difference of about $23.00. This suggests an increase of about 120 percent.

It is important to view these data as approximate for a variety of reasons. I have acknowledged the proxies for the conceptually correct measure. In addition, the HFA prices have been changing. The MDI data suggests that there has been an increase of about 18 percent over the twelve months preceding the sample of the first quarter in 2004. Again, these prices reflect the full price for the insured and the uninsured alike.

The next part of the puzzle is to assess the response to the increase in price that one might expect among consumers. In general, there is

an extensive economics literature that reports small effects of price increases on consumption. It rarely distinguishes, however, among drugs. There is a very recent article by Dana Goldman of Rand in JAMA that surveys more than a half million people in 52 health plans over four years.

interestingly, it reports responses to increases in co-pay among different categories of medicines. With respect to anti-asthmatics, as the average co-pay for anti-asthmatics doubles, the average number of days of treatment supplied fell by more than 30 percent. The authors report that albuterol was the most common anti-asthmatic including albuterol sulfate.

They also assess the effects on public health. Let me back up a moment. They also assess for drugs with no OTC substitutes, the set that presumably includes albuterol MDIs. The response in utilization described as I just did in the average number of days of treatment supplied is 0.15. So there is substantial uncertainty about what would be the relevant number.

With respect to average co-pay for anti-asthmatics as a group, the response is 0.3. But, if one then looks at drugs with no OTC substitutes which would also include albuterol, the effect is 0.15.

The authors go on to talk about the effect of these increases in co-pay on ER visits and on hospital days for the class of drugs diabetes, asthma and gastric-acid disorder together, ER visits grew by 17 percent and hospital days by 10 percent when co-pays doubled. The authors acknowledge that these results are "not definitive" for reasons of data limitations.

As a result, we are unable to quantify any effects on public health because of the nature of the limitations to the data.

Let me offer a summary of what we know about the response to a price increase. I have mentioned that an analysis would have, really, three parts. With respect to the MDIs sold to a price-sensitive population, MEPS suggests that there are 2.8 million MDI albuterol prescriptions

going to the uninsured patients with incomes of less than 400 percent of the poverty line who are not Medicare eligible and under age 65.

If one takes, instead, data from the National Health Interview survey and combines that with data on the distribution of MDIs as described in the proposal, one ends up with a larger number of MDIs that would be used by the price-sensitive population.

With respect to the price increase, we really have two estimates. One is 120 percent increase. That is from the IMS National Prescription Audit reflecting average prices for all payer types including those that are insured. We also have the 180 percent which reflects the Internet information.

A key question pertaining to the analysis is the estimated elasticity, or the nature of the consumer response. JAMA, as I mentioned, reports two numbers that may be plausible. I think the 0.15 is one that we focus on. That reflects their estimate of the response to increases in co-pay for

drugs with no OTC substitutes. I think that is also consistent with other economics literature.

The next question pertains to the interpretation of these. The JAMA paper really focuses on consumer response for insured patients to higher co-pays. They report an average co-pay of a little bit more than $12. So that co-pay and the increase are roughly the same order of magnitude as the price and the price increase that one would anticipate for uninsured patients.

So, if one applies that increase in price implicit in both the IMS data and in the Internet data and the consumer response implicit in the JAMA paper to the MDIs sold in the price-sensitive population, then it is reasonable to infer a quantity response among the uninsured population in the high hundreds of thousands. It is very difficult to be more precise. This is a daunting exercise with data that are imperfect, as we have acknowledged. But the numbers that we have presented in particular are 0.4 million to 1 million. These are clearly approximate.

Let me offer some empirical caveats. I have neglected the response of insured patients to any increases in co-pays. The JAMA paper measured these and we know that the co-pays for branded products are much higher than co-pays for generics. But this delisting of albuterols would have no direct effect on the co-pays. The co-pays may change only in response to the changes of the insurance companies. We, therefore, believe these are too uncertain for us to quantify at this time.

Let me reiterate that the estimates of the price-sensitive population of the price increase and the consumer response, or the elasticity, are all relatively uncertain.

There is another caveat with respect to the interpretation of these estimates. GlaxoSmithKline wrote to FDA on May 3 of 2004 stating that 2 million complementary samples of Ventolin would be made available each year to physicians who may choose to reserve these inhalers for their lower-income patients.

We are unable to assess quantitatively

what this might do for any reductions in utilization because of the uncertainty associated with how they might actually be distributed in physicians' offices. The GSK letter also said that it would freeze wholesale acquisition costs or prices thereby suggesting that the eventual HFA prices at the retail level would also be relatively constant. As I have mentioned, that is an assumption that we maintain.

The giveaway, in general, may significantly offset the loss of canisters provided it is well targeted to the most price-sensitive patients.

Thank you for the opportunity to talk. I would be happy to take questions.

DR. CHINCHILLI: Thank you, Dr. Lutter. Are there any questions from the committee? Dr. Schatz?

Questions from the Committee to the Speakers

DR. SCHATZ: My question is the relationship between elasticity and over-the-counter substitutes. I gather that, with

more over-the-counter substitutes, then elasticity is theoretically increased?

DR. LUTTER: Yes.

DR. SCHATZ: Then I would submit that there may be an over-the-counter substitute which is Primotine so that I think that, in consideration, one might have the higher elasticity and that patients doing that might be not as well served.

DR. LUTTER: Lacking your medical expertise, I will leave the judgment and the discussion about the substitutability of the OTC to you. Let me simply say that the availability of OTC substitutes would affect the response in that way.

DR. SCHATZ: And it could make the higher value that they found more relevant than the lower value potentially.

DR. LUTTER: Yes.

DR. CHINCHILLI: Dr. Martinez?

DR. MARTINEZ: Certainly with the caveat which we may discuss later, but Primotine is not

albuterol and, thus, a potential consequence that has not been thought of is that individuals who cannot afford albuterol anymore will start using over-the-counter Primotine which is associated with a completely different set of side effects which need to be seriously considered.

DR. CHINCHILLI: Ms. Schell, you had a question?

MS. SCHELL: Yes, thank you. I just have a question about the shift of production of the CFC to the United States from the Netherlands in 2005. Do you project an increase in the CFC MDIs' cost with that shift of production coming to the U.S.?

DR. LUTTER: That is not something we have taken into account in the analysis. We have no information on which to assess that question.

MS. SCHELL: Thank you.

DR. CHINCHILLI: Do any of the FDA representatives want to respond to that or the previous question?

DR. MEYER: I think, as far as that question--I don't think we have data that could say

one way or the other. Not the least of the considerations there is how much in the price does the actual cost of CFCs play, and I don't think we know that.

As far as the earlier question and point, I think it is something we can certainly consider as we consider all the input from today.

DR. CHINCHILLI: Dr. Swenson, you had a question?

DR. SWENSON: Yes. Regarding that JAMA article, did you pursue at all the cost implications of this greater ER and hospitalization rate that might arise from some of these shifts that you have postulated?

DR. LUTTER: No, largely because of the uncertainty in quantifying those increases. As I mentioned, there were three categories of therapeutic classes that they grouped together only one of which was asthma. Albuterol is only one treatment for asthma and, therefore, we thought that inferring--that the judgment of the applicability of those estimates to this delisting

appeared to--is that we have no basis to accept those estimates to predict quantitative reductions, quantifiable reductions, in the ER visits or days in the hospital. So, therefore, we don't really want to estimate either the cost of reductions or increases associated with those either.

DR. CHINCHILLI: Dr. Moss?

DR. MOSS: I work at Grady Memorial Hospital which serves an indigent-care patient population. About 40 percent of the patients there are self-pay which means they don't have insurance. It is nice way of saying that. One of the big problems in the hospital is the in-hospital pharmacy costs. Do you have any information or is there a way to figure out how the changing cost of inhalers would affect operating at a hospital that serves indigent-care patients or is there a way to figure that out?

DR. LUTTER: There probably is a way to figure it out. It is not something we have done.

DR. CHINCHILLI: Dr. Kercsmar?

DR. KERCSMAR: The transition to HFA

inhalers has been made in a number of other developed and industrialized countries. Are there any data that are comparable to that that has been published in the JAMA article? You referenced that might give other insight into the elasticity problem, changes in morbidity, lack of prescription refills or, because of the difference in economic structure and drug reimbursement in these countries, are there no data available? Are there lessons to be learned from countries that have already made the transition?

DR. LUTTER: It is a good question. We thought of that. Other countries lack the uninsured population that exists in the United States and generally control prices. In particular, the price discrepancy that I have described here is unusual if not unique.

DR. CHINCHILLI: Any other questions by the committee members for Dr. Lutter?

MR. MITCHELL: Just before the break there is something I would like to say.

DR. CHINCHILLI: Yes; please go ahead.

MR. MITCHELL: This is addressed to the people who are watching this procedure through the webcast. The proposed rule that we have been discussing is available on FDA's website if you go to www.fda.gov. In the middle column, you should see FDA advanced display. If you click on that, you should be able to see another link which goes to advanced publication display. Click on that and you should see something about a special filing, publishing, on June 16, 2004. That should get you to the Notice of Proposed Rulemaking.

Thank you, Mr. Chairman.

DR. CHINCHILLI: Thank you, Dr. Mitchell. Yes; Ms. Schell?

MS. SCHELL: I am not sure who to direct this question to, but I have a question. Several of you talked about what the ozone depletion does in cataracts, skin cancer and that, but no one has mentioned how it affects asthmatics of COPD patients, the depletion of the ozone layer and how that would increase, if we didn't do something now, how the ozone depletion would affect asthmatics in

the future. Would we be causing more asthmatics to have problems with their breathing?

Thank you.

DR. MEYER: I will try to answer that. I think it is unclear to us that asthma or COPD patients would be differentially affected in terms of the environmental consequences of ozone depletion. You were not asking this, but, for the public, I think it is hard for them to understand that ozone in the lower regions of the atmosphere is bad for asthmatics, particularly, and probably for COPD as well. But ozone in the stratosphere probably has no bearing on the development of asthma and COPD that we know of.

So we would assume that the consequences to the asthmatic and COPD population would be the same as to consequences to other populations. One could perhaps try to parse that out more closely in that it is potential that inhaled corticosteroids, for instance, may somewhat increase the predisposition to cataracts. Whether that would be even more the case in the circumstances of a

thinned ozone layer, who knows. But, again, we have no basis at this point to believe that there would be a differential effect on those patients.

DR. CHINCHILLI: Any other questions from committee members for our FDA representatives? Yes?

DR. MEYER: I just wanted to make the point--I realize that the people sitting around this table probably are fairly well versed in this but, for the purposes of the public, I realize that we didn't really sort of step back and make this point. But albuterol has really become a prime drug for both the treatment of asthma, in particular, but also for COPD in a way that, even when we began the advanced notice of proposed making in '96, I don't think we have fully anticipated.

It is now clear that approximately 50 million or more canisters of albuterol are necessary to treat patients with asthma and COPD in the United States. It is, again, by far and away the bronchodilator or short-acting reliever of

choice in patients with asthma and COPD.

Again, I think the people around the table know this but, for the matter of the public record, I just wanted to get on the table the kind of numbers we are talking about. This is a very important drug that is sold widely and is really critical in the asthma armamentarium and very important in the COPD armamentarium as well.

DR. CHINCHILLI: Thank you, Dr. Meyer. Dr. Martinez?

DR. MARTINEZ: I have one question regarding worldwide distribution of sales. What is the situation in the underdeveloped world? Which are the products that are sold there and what are the projected consequences of this regulation in that particular market?

DR. MEYER: From the FDA perspective, I don't think we have a lot of information on that. I also am involved in the Montreal Protocol on a working group on aerosols, medical aerosols. I can say that the United States actually exports relatively few of its MDIs as opposed to the EU

where much of their production is exported.

So most of what we are talking about here is for domestic consumption and will not really have much bearing on the rest of the world. I would parenthetically note that there is a lot of attention paid in the Montreal Protocol about how this phase-out in the developed world will affect that in the developing world because it is a very important issue.

Unfortunately, in much of the developing world, the use of MDIs is not very common because they are--although they are cheap per dose, to actually buy one requires you to buy a certain number of doses as opposed to oral medications which may be more expensive per dose but cheaper where you can just buy a few.

So there is probably undertreatment in the developing world in general and specifically there is not a lot of use of MDIs relative to the developed world.

DR. CHINCHILLI: Before we proceed with other questions, I would like to welcome Dr. Reiss

to the committee. Would you turn on your microphone and introduce yourself to everyone?

DR. REISS: Sure. I apologize for being late this morning. I am Ted Reiss from Merck Research Labs. I am the industry non-voting representative on the committee.

DR. CHINCHILLI: Thank you. Any other questions? Yes; Dr. Swenson?

DR. SWENSON: Dr. Meyer, a couple questions. I didn't see anywhere in the data, either in the background information, if you could go back to the initial signing of the protocol. At that point, how much CFC was being produced and now, of that amount, what does the present use of CFC in albuterol represent in a percentage term or absolute amount?

DR. MEYER: I am sorry that I don't actually have those particular figures available. I can say that the use of CFCs for MDIs when the protocol was signed was a relatively small proportion of the CFC use because CFCs were then used in refrigerators, auto air conditioners, home

air conditioners, foams and so on.

Now that the provisions of the Copenhagen Amendments went into place, the use of CFCs for MDIs in the developed world is the large majority of these CFCs but it is still a small fraction compared to what was the total in 1987.

Albuterol in both the United States and in the rest of the world has been a prominent use of CFCs. As I mentioned, for the United States, it amounted to about half, or does amount to about half, of our essential-use denomination. So I am not giving you specific numbers, but I hope I am sort of giving you a qualitative feel.

DR. SWENSON: Okay. The next question I have then is, on Slide 24 or one of the similar slides that you had in your talk, was the projected return, or this idea of a projected return, of normal stratospheric ozone levels by mid-century based on the present use right now which includes our use of CFCs or was that based on complete elimination of CFCs?

DR. MEYER: Those projections, and just to

be clear, they are actually projecting the recovery to early 1980s levels which was still not normal but a recovery nonetheless, are based on the successful conduct of the Montreal Protocol. So it is based on the Montreal Protocol as currently amended being successfully carried out into the future.

DR. CHINCHILLI: Ms. Schell?

MS. SCHELL: I am sorry. I would like one more question on the 50 million uses of Ventolin or albuterol. Have you looked at the overuse of albuterol and the underuse of the anti-inflammatory? Is there any look at overuse? As we know, asthmatics, a lot of the time, don't have the proper education in the use of the anti-inflammatory so they overuse their albuterol. Are there any numbers reflecting that?

Thank you.

DR. MEYER: We do not have such numbers. It is certainly something that we considered. As Dr. Lutter said, there are a lot of things we would wish to consider in an ideal analysis. One of the

complications of projecting a public-health consequence of some drop in the number of albuterol MDIs distributed or used relates to these questions, relates to the possibility that when beta-adrenergic bronchodilators are overused that that might, itself, have detrimental effects.

But these things, although clearly we think about them, are not something we can reasonably quantitate. So we have not.

DR. CHINCHILLI: Any other questions from the committee? If not, I want to thank the FDA for enlightening us on these issues. We are scheduled for a break at 10:00. We are about eight minutes before that, so we will take the break early. But I would like to reconvene at 10:10.

Thank you.

(Break.)

DR. CHINCHILLI: I do have one announcement and that is if you have a cell phone and it must be on, it would be preferable if you put it on vibrating mode and then, if it does go off, that you take your call outside the room.

Thank you.

Before we go on to the open public hearing, the first session that we will have this morning, I just want to make sure that the committee members don't have any other questions for the FDA representatives. Are there any other questions from the committee? Any final comments from the FDA?

If not, then we are going to move into the open public hearing.

Open Public Hearing (Session 1)

DR. CHINCHILLI: One other announcement I am supposed to make. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning

of your written or oral statement, to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

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

So that is important for our open public hearing speakers to recognize that and to make acknowledgments. I probably will repeat this statement when we start the afternoon session as well.

We are ready for our first speaker during the open public hearing. Please be sure to introduce yourself and pay attention to the

statement I just made.

MS. WEXLER: Good morning. I am Pamela Wexler. Since 1997, I have served as attorney and advisor to the U.S. Stakeholders Group on MDI transition. I have no financial interest in any of the companies or participants today.

I would like to start by telling you a little bit about the U.S. Stakeholders Group. It is a consortium of nine leading patient and medical professional organizations. Members of the organizations include patients with asthma, chronic obstructive pulmonary disease and other respiratory diseases. Collectively, the member organizations represent and reach 25 million Americans who suffer from asthma and other respiratory diseases and they include organizations that educate and advocate for individual patients and their families through local chapters.

Members of the Stakeholders Group also include physicians, respiratory therapists and other healthcare professionals who specialize in respiratory care and they are recognized leaders

among the healthcare community. The stakeholders, as a group, and its member organizations individually collaborate with various other interested organizations in the U.S. and around the world.

In the eight years since the Stakeholders Group has acted formally, neither its membership nor its procedures have changed. The American Lung Association convenes the U.S. Stakeholders Group. The member organizations elect representatives to the stakeholders process and these individuals meet, in person, once or twice a year and communicate regularly.

Oftentimes, the leadership of these organizations attends stakeholder meetings and participates in the deliberations. Other times, the government and the private sector are invited to attend as well and make presentations. Any action taken under the name of the stakeholders is approved by each member organization.

Now, I would like to turn to our petition. Eighteen months ago, we petitioned FDA to consider

albuterol essentiality. The petition was not precipitous. It, in fact, was requesting the agency merely consider essentiality. It was FDA, itself, in a rulemaking process that started in 1997 and lasted five years that set up these essentiality criteria, the conditions under which any drug substance would be delisted and no further CFCs would be available.

The stakeholders petition asserted that the criteria had been met or, with the case of manufacturing capacity, that the criteria could be met or that information could be ascertained and, hence, it was time for FDA to consider removing the essential-use designation.

Now, there are a number of reasons why the stakeholders petitioned FDA. I will just take a moment to touch on them. First and foremost is the environmental imperative. I won't spend too much time on this because I think that the importance of repairing the ozone layer is well established, both by the Montreal Protocol and the U.S. Clean Air Act on which, by the way, the U.S. has been a leader

since the beginning on the international process. FDA, in its July, 2002 Final Rule establishing the essentiality criteria actually offered a very concise and clear explanation of why every use of CFCs must be eliminated, even seemingly small amounts like those used in MDIs.

I won't spend too much time on the second sub-bullet either because a physician from one of our member organizations in the next session, later this afternoon, will present more on the opportunity to improve disease management. But let me just say that, from its inception, the stakeholders position on the potential of transition has not changed and that is that we understand the potential of a switch in medication and we have worked, and we hope to continue to work, to ensure that that experience provides an opportunity to improve patient care.

On the third and the last, and probably the most pressing, issue for patients and physicians is the issue of CFC supply and how it might affect the availability of medications. As I

am sure you will hear more about today, the future of CFCs to make MDIs is uncertain and fundamentally the stakeholders want FDA to sufficiently plan for that and for CFC-free medications to be available and widely accepted before CFC supply can have any impact on product availability or price.

Since the petition was filed, in the eighteen months since the stakeholders filed the petition to consider albuterol essentiality, a lot has changed and we have learned a lot more. As to supply, anyone who follows this knows that, in the past three to five years, there has been a lot of new and often conflicting information about where PhRMA-grade CFCs were going to come from after December 31, 2005.

Remember, that is an issue simply for the U.S. market because, for the most part, developed countries will not need these chemicals after that date. They are on pace to phase out the use of CFCs in MDIs.

The stakeholders have never had full information on the future of CFC supply. We heard

originally, maybe two years ago, there were going to be two plans, one in Europe and one here. They we heard that that wasn't going to happen. Then the issue of certification was raised, that plants had to be certified, the CFCs produced had to be certified, and that the production that would replace the production that is going to be lost in Europe would be a different kind of production and that different specifications would be required.

We heard, now, recently, despite a letter from Honeywell indicating its stated intent to supply CFCs at a plant in Baton Rouge, Louisiana, that we still had questions about certification as that was not mentioned in the letter and we have never heard anything further about FDA on what, exactly, that requires.

So the stakeholders, themselves, have limited information on which they could base a conclusion that the CFC supply would be without problems. Recently, a non-governmental organization, NRDC, wrote the EPA suggesting that it would be illegal to produce CFCs in Baton Rouge.

So, again, we are faced with not a lot of clear information on how we will go forward.

As to the second sub-bullet, even if the Baton Rouge plant is not a problem, we certainly see an increase in pressure on the part of the international community to limit future supply of CFCs especially where there are alternatives as in the case of albuterol. We heard recently that the U.S. request that was recently put into the parties was approved but with the strong suggestion that the U.S. come back to the parties after this rulemaking was complete since it wasn't clear that those quantities would be needed.

So it is obvious that the parties are signalling the intent to stop authorizing new CFC production for MDIs, again, in the case of a drug like albuterol where there are safe alternatives.

Also, since the petition was filed, we have, in the FDA docket, an independent analysis conducted by National Economic Research Associates, NERA, that provided us a much better picture of the albuterol market. I expect that we will hear more

about the NERA analysis this afternoon, but it gave us a very good picture of how the market is supplied, how patients who rely on albuterol pay for their drugs.

It estimates the price and what the market might look like once HFA alternatives are introduced. More importantly, NERA projects how the increased costs might be distributed and allocated among the different classes of patients, managed care and other payers including Medicare and Medicaid.

Now, you know, the stakeholders are medical and patient advocates, medical professionals and patient advocates. We are not economists. So we aren't here to speak to the specific numbers in the NEAR report but we do believe that the general thrust of the report comports with what we have always believed about the albuterol market and our understanding of how increases, not just in medications but in all sorts of other medical procedures and services rise and are absorbed in the healthcare system.

Now, there is no mistake about the need to ensure patient access to medication. In our petition to FDA, we were clear that FDA needed to take into account price and how it would affect patients and their ability to obtain medication and comply with their treatment regimens. But we think that, between the manufacturers, the stakeholders and FDA, collective, we can adequately protect the potentially at-risk subgroups and we can do it in a variety of ways.

On the part of the manufacturers, we have one submission already in the docket from an HFA manufacturer outlining what it intends to do. We would hope that we would see similar commitments from other manufacturers as we move forward about increasing the number of samples and enhancing patient-assistance programs.

On the part of the stakeholders, our member organizations are committed to working with the agency and the manufacturers to develop an educational strategy for communicating the availability of free and discounted albuterol. We

can work with our member organizations and our network to deploy these messages in advance of transition to patients, to specialty, general physicians and the rest of the healthcare community.

As for FDA, we think that there also might be mechanisms that the agency can consider to protect, again, these potentially at-risk populations. One thing we have discussed within stakeholder meetings is for FDA to monitor the patient compliance or access to HFA albuterol and reserve the right to allow a certain number of CFC MDIs to be sold in the case of a real emergency so, if you will, a phase-down process that allows the potential--and that is the potential in both CFC supply and manufacturing capacity to not be gone before we are out of transition, so a phase-down period that protects that at-risk population.

I think that if FDA acts in a relevant timeframe, there would still be enough stockpile to be able to incorporate such a mechanism.

Last, I would like to turn to the timing

of transition. There has been a lot of talk about when the right time is. Now, it is no secret that the stakeholders have long supported December 31, 2005 as the effective date for removing CFC albuterol from sale in the U.S. As early as 1996, in fact, before we had ever heard the word "TEFA" or "WEERT," we embraced the idea of a target date.

We embraced the eventuality that these chemicals as slated for elimination. We understood that it was useful to have a target date so that manufacturing capacity could be put into place. That idea of an aim, a target, a goal, has proven successful as is evidenced by the fact that the rest of the world or the rest of the developed countries also adopted that date and or on pace to meet it.

We saw transition as an opportunity to educate physicians and patients about the learning that has been done, especially in the last decade, regarding asthma treatment and management.

But, in 1996, we saw December 2005 as a goal, not an imperative. Eight years later, we now

know that WEERT will close. We know there are additional uncertainties regarding the Baton Rouge facility. We know that there are two alternatives ready to go and a third on the way. Given that, December 31, 2005 makes a lot of sense.

Again, I just want to go back to mechanisms for actually proceeding through transition. Ending at December 31 is sensible and it is achievable and, most importantly, it is near-term enough that any problems with HFA production, any problems with patient access, any problems with affordability, compliance, any unforeseen consequences, can be discovered and addressed before CFCs are unavailable and before the capacity to produce additional CFC products is gone.

Thanks very much.

DR. CHINCHILLI: Thank you very much.

We will move on now to our second speaker.

DR. JONES: Good morning. My name is Elaine Jones and I am Vice President of U.S. Regulatory Affairs at GlaxoSmithKline. On behalf

of GlaxoSmithKline, I would like to thank the advisory committee and the agency for opportunity to present our commitment to the transition from albuterol CFC-free metered-dose inhalers, or MDIs, which are ozone-depleting to albuterol HFA MDIs, which are non-ozone-depleting.

Principally, during this presentation, I will address the two questions that have been posed to us by the agency that relate to the FDA's criteria for transition.

The first question concerns our manufacturing capacity for Ventolin HFA and the second, what GSK programs are, or will be put in place to help ensure that patients are adequately served during the transition from albuterol CFC to albuterol HFA and thereafter.

To set the stage for discussion of the two principle questions, I would like to review the timing of Ventolin HFA development in relation to implementation of the Montreal Protocol. Development of Ventolin HFA started before the Montreal Protocol was ratified and resulted in

submission of a new drug application in 1998. Filing of this NDA was the result of over ten years of research and development including a technically challenging reformulation effort under comprehensive clinical program.

After gaining FDA approval, GSK launched Ventolin HFA in 2002 and stopped the sale of Ventolin CFC. Currently, GSK sells Ventolin HFA in 165 countries around the world which has resulted in over 20 million patient years of experience. Also, in 2002, FDA published its final rule outlining the criteria for transition from CFC MDIs, which was the culmination of a lengthy process that took five years to complete.

Quoted on this slide is one of the criteria for transition from the 2002 Final Rule. FDA has asked us, as one of the manufacturers of the replacement products for albuterol CFC MDIs to address this criterion which relates to the issue of adequate supply and production capacity. Specifically, the question is, can GSK, in conjunction with other manufacturers of the

replacement albuterol product, manufacture sufficient quantities to satisfy patient demand after the CFC products are no longer available.

To help answer this question, here is a graphical representation of GSK's manufacturing capacity over time in relation to the overall albuterol market. Other manufacturers can be expected to contribute to the supply as well. At present, patient need for albuterol MDIs is about 50 million per year, as shown by the yellow shading in this graph. This demand has remained fairly constant over the past five years and is expected to remain constant into the future.

The blue shaded portions of the graph represent two distinct components of GSK's ability GSK's ability to contribute to meeting this demand with CFC-free MDIs. The darker shaded blue area reflects currently installed capacity and the lighter shaded blue area reflects expansion capacity. The sum total of both components is about 30 million MDIs per year, or about 60 percent of the expected market.

Now, I would like to discuss in detail our current capacity. GSK manufacturers Ventolin HFA at a facility in Zebulon, North Carolina, which has a long history of manufacturing MDIs including the now discontinued Ventolin CFC. At this facility, we already have installed the capacity to manufacture 15 million Ventolin HFA MDIs. At present, since transition has yet to take place, we are utilizing only 2 percent of our installed capacity.

Production of up to 5 million MDIs could be achieved immediately and this could be progressively increased to the full 15 million MDIs within six to twelve months. To achieve this capacity is a relatively straightforward process. We would need to hire additional staff and reconfigure existing space.

As illustrated on the graph I presented earlier, GSK is prepared to increase production capacity by an additional 15 to 18 million MDIs. This would entail significant capital investigation on the part of GSK, would take approximately twelve

to eighteen months to complete and would require the installation of additional manufacturing equipment and securing of MDI components.

This could be undertaken simultaneously with a previous increase in production. This expansion, in addition to our current capacity, would deliver a total of approximately 30 million MDIs.

I would now like to address the second question posed to us by the agency which concerns another one of the criteria in the 2002 Final Rule on Essential Use Determinations and is reflected on this slide. The issue is whether a high-priced, non-ODS, product is effectively unavailable to a portion of the patient population because they cannot afford to buy the product.

Payers, and the healthcare system overall, may experience higher costs as the market transitions to CFC-free albuterol. But the relevant question under FDA's 2002 Final Rule is how individual patients will be impacted by this transition, specifically whether they will have

adequate access to CFC-free formulations of albuterol.

The larger policy questions regarding a balancing of societal cost against environmental benefits have already been resolved by the Montreal Protocol.

In order to assess the economic impacts of an albuterol transition, GSK commissioned a study by the National Economic Research Associates. The analysis proceeded on the basis of data collected from a variety of sources as shown on this slide. Although the economic report examined impacts on payers as well as patients, our focus today is on the impact a transition will have on the access to albuterol HFA MDIs for individual patients.

To understand the impact on patients, one must appreciate that albuterol is dispensed to patients in different settings including retail pharmacies, hospital pharmacies, clinics and federal healthcare facilities. As represented by the large green slices of pie chart, 84 percent of dispensing takes place at retail pharmacies. The

remaining 16 percent takes place in other settings; for example, a Veterans Administration Hospital where financial impacts on patients, of changes in drug prices, are likely to be quite limited.

The pie chart on the right reflects a further breakdown of the retail-pharmacy segment. Within the retail portion, 72 percent of MDIs are covered by private drug insurance and 15 percent are covered by Medicaid. About 13 percent of albuterol MDIs dispensed by retail pharmacies go to patients who pay cash. GSK recognizes that it is within this group of patients that the greatest concern exists regarding access to albuterol MDIs after a transition.

As we consider the patients who pay cash for their prescriptions, it is important for us to emphasize our long-standing dedication to helping those in need obtain access to our medicines. For over two decades, GSK and its Heritage Companies have been committed to helping patients without public or private drug insurance to get the medicines that they need. To this end, we have had

in place various patient assistant programs.

I will now describe Bridges to Access, the GSK program which is directed at patients of all ages who require financial assistance. For those who qualify, GSK offers its medicines, including Ventolin HFA, at no cost or at a minimal retail-pharmacy dispensing fee.

Individuals with annual incomes up to $25,000 or families at or below 250 percent of the federal poverty level are eligible for Bridges to Access. Patients who enroll can receive their medication the same day that it is prescribed. This program also includes a spend-down option that allows patients to deduct medical bills from their income for purposes of determining eligibility requirements.

Patients are not required to be U.S. citizens to qualify for Bridges to Access. Patients who apply also receive assistance in finding additional healthcare programs for which they qualify such as Medicaid, AIDS drug-assistance programs, state children's health insurance and

state elderly drug-assistance programs.

In this visual illustration, we use the federal poverty level as a baseline to compare the income eligibility levels for Medicaid and Bridges to Access. The yellow line represents the federal poverty level income for households of different sizes ranging from one to four members. The blue lines represent the average income eligibility ceiling for Medicaid which is 135 percent of the federal poverty level.

Each orange bar represents the maximum qualifying income under Bridges to Access for a household of that size. This maximum qualifying income level is $25,000 for households with one individual or 250 percent of the federal poverty level for households with more than one individual.

I might add that certain patients who do not meet Medicaid's eligibility requirements despite meeting the income requirements could potentially qualify for Bridges to Access. For lower-income patients who do not have public or private drug insurance, for whatever reason,

Bridges to Access is, thus, a valuable resource.

GSK's experience with Bridges to Access for Ventolin HFA from June 2003 to May 2004 illustrates the program benefits for patients. We have distributed nearly $3 million worth of product representing approximately 100,000 inhalers to nearly 14,000 patients. During this period of time, the total amount of Ventolin HFA distributed was approximately 400,000 MDIs which means that one out of four Ventolin HFA MDIs went to a Bridges to Access patient.

GSK has generated awareness of this program through various avenues including half a million letters sent to advocates at the launch of the program, training for healthcare providers and partnerships with public agencies and professional associations. In addition, we maintain a public website with extensive information about our program including application forms.

These activities represent some of the significant efforts GSK has made to raise awareness of the program and we look forward to continuing

our outreach efforts. We are committed to provide Ventolin HFA to all eligible patients in the event of an increased need at the time of transition. In order to show more clearly the estimated financial impact of a transition to CFC-free albuterol on individuals, I would like to now illustrate how a lower-income patient might fare in a transition both with and without the benefit of Bridges to Access.

Our hypothetical patient is an individual who makes less than $25,000 a year and, thus, qualifies for Bridges to Access and who also uses four albuterol inhalers. To make this calculation, we compared the current average wholesale price of Ventolin HFA to the mean of the average wholesale prices for the three top selling generic albuterol inhalers.

Average wholesale price, or AWP, is commonly used as a pricing reference point for distributors and payers in the healthcare system and is calculated and reported by commercial data vendors. GSK does not set an AWP for its products

or sell its products according to AWP and we recognize published AWPs are different from actual prices paid in the marketplace.

Based on the AWP comparison, the current difference in price between Ventolin HFA and generic albuterol is $9.49. Therefore, in our example, if the patient did not enroll in Bridges to Access, the extra cost per month would be $3.16 or $37.96 a year.

With assistance from Bridges to Access, the cost of Ventolin HFA would be limited to a one-time charge of $10.00 for the patient's first 60-day retail pharmacy fill. The patient would then experience no added cost for further prescription. In fact, the medicine would be entirely free from that time forward.

Keep in mind that this hypothetical patient, if not enrolled in Bridges to Access prior to the transition, would previously have been paying out of pocket for that generic albuterol.

For seniors or disabled persons, in addition to Bridges to Access, GSK offers the

saving programs, Orange Card and Together Rx to help make GSK medicines more affordable. The GSK Orange Card was the first of its kind. It is available for Medicare beneficiaries without any prescription-drug insurance and incomes of up to $30,000 for an individual and up to $40,000 for a married couple.

Orange Card offers savings on GSK products including Ventolin HFA to eligible Medicare beneficiaries of up to 40 percent depending on a pharmacy's usual and customary price for the medicine. The program, Together Rx, is a multi-company savings program and, as such, provides access to a larger number of medicines. This program was modeled after the GSK Orange Card and has similar eligibility criteria.

Although the arrival of a Medicare drug benefit in January 2006 should substantially lessen the need for assistance of this kind, GSK's commitment to helping patients access our medicines will remain.

In addition, GSK has committed to provide

at least 2 million professional samples of Ventolin HFA each year beginning a transition. Although samples are distributed to physicians with no conditions attached, we understand, anecdotally, that many physicians do take medication-access considerations into account in allocating samples among their patients. Furthermore, GSK has committed to freeze the price of Ventolin HFA from November 5, 2003 until December 31, 2007.

In summary, GSK is committed to and has global experience in transition to ozone-friendly formulations. GSK has currently installed production capacity to produce 15 million Ventolin HFA MDIs per year. We are prepared to expand the total capacity to approximately 30 million MDIs per year.

GSK has demonstrated an abiding commitment to helping patients gain access to our medicines and, towards this end, has patient-assistance programs in place to help ensure access to Ventolin HFA at transition. Finally, GSK has committed to provide professional samples and freeze the price

of Ventolin HFA.

We expect that the criteria for transition, as outlined in the 2002 Final Rule, will be met with the support of all currently approved albuterol HFA suppliers. Therefore, GSK supports a transition date of December 31, 2005 which would allow for a smooth and orderly transition for patients.

I would like to conclude by, once again, thanking the advisory committee and the agency for allowing GlaxoSmithKline the opportunity to present today.

Thank you.

DR. CHINCHILLI: Thank you, Dr. Jones.

Let's have our third speaker for this morning.

DR. GARUTTI: Members of the committee, Food and Drug Administration, invited guests, ladies and gentlemen, good morning. My name is Dr. Ron Garutti. I am a pediatrician and I am Group Vice President of Global Regulatory Affairs at Schering-Plough Research Institute.

On behalf of Schering-Plough Corporation, I want to thank the FDA for the opportunity to address the advisory committee today.

Let me say, at the outset, that our company firmly supports the principles of the January 29, 2003 petition of the U.S. Stakeholders, which you have heard about, which requests an end to the exemption for albuterol CFC-based in inhalers. As pointed out, this exemption, after all, was never intended to be permanent.

Now, I will not devote any of my discussion today to the rationale for removing CFCs from albuterol inhalers as I believe that that rationale is well understood and accepted by most interested parties as the right and necessary thing to do.

In so removing CFCs, the United States would be accomplishing the transition to a non-CFC environment that has already successfully been implemented by most of the European Union, Canada, Australia, Japan and other countries.

So the important question, then, today,

for the committee is not if the transition should be done but when. It can be done as soon as FDA, in conjunction with the healthcare community and the industry, is prepared to initiate the transition.

It has been pointed out that in July, 2002, the FDA issued a final rule which set forth the conditions that would have to be met before an essential-use designation for albuterol inhalers could be removed. Both Drs. Meyer and Sullivan have noted them. Schering believes that all of the necessary elements to remove the essential-use designation can be met as early as December 31, 2005.

We acknowledge the proposed rule distributed today and we are pleased to learn that FDA plans to publish this on June 16. We are hopeful that today's discussion will lead to the establishment of a firm date.

As a company with more than twenty years of respiratory experience and the first with our partner 3M to introduce an HFA inhaler to the

United States, Schering understands that we, in conjunction with all of you and other members of the professional asthma community, will be asking millions of patients to change their behavior.

We recognize the significance of this transition to patients and providers alike and we are sensitive to the fact that ongoing communication efforts will be essential elements to ensuring that the transition is smooth and successful.

To accomplish this effectively, however, it is critical that FDA establish a clear timeline to end the exemption because we believe that only in doing so will there be the necessary stimulus to drive the kind of provider and patient-behavior change that will be required. Schering's contribution, as well as that of others, to effecting a successful transition hinges on implementing the various elements of the transition at the right time in relation to the effective date.

In the absence of such a date, it will be

difficult to manage these various aspects efficiently. For example, patients may not be receptive to targeted communication efforts until a fixed date has been established. It has been pointed out, in addition, that significant planning decisions and resource commitments required to increase current production capacity need to be made and, for us, we need about eighteen months in advance of a known effective date.

That being said, Schering is poised to play a part in a planned orderly transition and we could be ready for an HFA-only environment as early as the end of next year. We believe that for the FDA to remove the exemption, certain assurances are required. These are that safe and effective alternatives are available, that patients and providers are knowledgeable about and comfortable with the use of the inhalers and that industry can adequately meet the demand.

In the next few minutes, I will point out that we do have safe and effective alternatives right now and Schering will have educational

programs ready so that patients and providers will be knowledgeable about and comfortable with their HFA alternatives and that we can have an adequate supply and production capacity of Proventil HFA available again as early as December 31, 2005 or within eighteen months of an established transition date.

Now, regarding the safe and effective alternatives, following the issuance of the Montreal Protocol in 1987 and after years of research and development, Schering was the first company to market, in collaboration with our partner 3M, a non-CFC inhaler in the United States in 1997.

Industry researchers had created HFAs that were more environmentally friendly than CFCs. These HFAs were then extensively tested to ensure that they possessed the desired characteristics of an MDI propellent. A wide range of toxicology studies, comparable in scope to that for a new molecular entity and consisting of acute, chronic reproductive genetic and carcinogenicity

evaluations, established that certain HFA molecules were, in fact, suitable candidates to replace CFCs in inhaled delivery systems.

The new technology was then applied to Proventil and, after a comprehensive clinical program established that Proventil HFA was both safe and effective, the FDA approved the product for marketing clearance in 1996. In addition to the clinical studies that were included in the NDA, 3M also conducted a robust observational postmarketing program which studied more than 6,000 patients.

In the nearly eight years of postmarketing patient experience to date, more than 17 million prescriptions for Proventil HFA have been written. Spontaneously reported adverse events, as you have heard, have been consistent with the product's labeling and similar in nature to that of its CFC counterpart.

Taken together, available data clearly support the established safety profile of Proventil HFA and so, yes, we do have safe and effective

non-CFC alternatives available right now and, in fact, with Glaxo's HFA product, there are, as said, two such products available.

Let's turn now to another assurance required before removing the exemption, that relating to education and communication. Schering is committed to playing its part in communicating important information around the transition to both patients and providers. Including in that important information is reiteration of the message that HFA inhalers are as safe and effective as the CFC inhalers to which most patients are accustomed. The HFA inhalers are also similar in size and shape and as convenient to use.

Now, we all recognize, especially those who treat asthma patients, that there can be a significant psychological and emotional component to asthma and its treatment. Asthma patients come to rely on their inhalers and expect a certain type of experience in using them. They tend to associate activity of the drug and subsequent relief with the forceful sensation of the spray

from a CFC inhaler has on the back of the throat.

I would point out that, with an HFA inhaler, however, there is a softer spray and less sensation although, of course, the active drug is still effectively delivered to the lung. This fact must this communicated to patients to ensure the appropriate use of the product. Patients will also need to be comfortable with the fact the drug from an HFA inhaler may taste and smell slightly different than that from a CFC inhaler.

Schering has always had educational programs in support of our respiratory-care business and messages such as those I have just noted will be included in our developing multipoint communication and awareness programs intended to facilitate a safe and orderly transition.

Educational information will be accessible via many channels including informational websites, written materials available in physician's offices and through our professional sales representatives. Schering has traditionally had strong collaborative working relationships with relevant national

medical associations including both the American Academy and the American College of Allergy, Asthma and Immunology, the Academy of Family of Physicians. We will continue to work with these associations and others to develop appropriate educational materials for patients and providers.

We especially appreciate the efforts of organizations such as the allergy and asthma network Mothers of Asthmatics in their own commitments to educating and supporting the needs of asthma patients.

Schering is also one of the founding sponsors of the National Patient Safety Foundation and has held a seat on its board of directors since 1997. This group is dedicated to improving patient safety through educational programs and initiatives and Schering will continue to provide input and leadership on issues related to safe medication use.

As I stated in my introduction, the impact of an expanded successful patient and provider education campaign will be highly dependent on

implementing the various elements at the right time in relation to a proposed effective date. These programs, to be maximally effective, will need to be timed in coordination with the transition date established by FDA so that the asthma community can be optimally prepared.

On other point related to the transition, it is, unfortunately, a fact and well known that many asthma patients do not regularly visit their healthcare provider. Schering believes, in agreement with the U.S. Stakeholders, that the transition will offer a good opportunity for physicians and patients to increase their general dialogue about asthma management.

A visit to the healthcare provider, prompted by the switch to an HFA inhaler, will allow for a reassessment of the patient's condition and adjustment of treatment if deemed appropriate. It will be especially useful for those patients who may not have seen a physician for some time.

A third assurance required before removing the exemption is that an adequate supply and

production capacity of the HFA alternative will exist. FDA has stated, and you have heard several times today, that over 50 million albuterol canisters are sold or distributed in the U.S. each year. Schering currently supplies approximately 30 million units annually.

Our manufacturing partner, 3M, stands ready to expand production in its facilities to manufacture this amount of Proventil HFA and Schering and 3M both have confidence that the necessary capacity can be in place to meet our share of the expected demand.

While much of the preparatory work to expand capacity is well underway, advanced planning activities and significant resource commitments necessary to formally initiate this process require some assurance of the timing of the transition. The overall lead time to execute these steps, including scale-up to current market demand, is approximately eighteen months, again, thus, making a fixed transition date established by FDA critical for us and our partner.

In conclusion, the time to set a transition date is now. Schering is confident that we can meet our share of the demand and ensure that asthma patients who need Proventil HFA are adequately served. The focus throughout the transition from CFC to HFA inhalers must be on education and communication efforts towards patients and providers. Schering is committed to playing its part in effecting a successful transition and supports the removal of the CFC exemption.

The first step requires that a proposed final rule be published and a clear date communicated so that all asthma stakeholders can act together. Finally, Schering believes the U.S. can join the group of countries who have already undergone a successful removal of the exemption because we do have safe and effective FDA alternatives now. We will be educating patients and providers and ensure their comfort level with the transition and industry can adequately meet the supply and demand.

Thank you.

DR. CHINCHILLI: Thank you, Dr. Garutti. Do the committee members have any questions of our three open presenters this morning? Dr. Schatz?

DR. SCHATZ: I guess a question for the stakeholders. The presentation talked, actually, about two aspects of concern. One was CFC availability, itself, and then, obviously, the detrimental aspects. But I was trying to get some sense as to what the relative concerns were and if, in fact, if CFC availability were assured, would that change the thinking in terms of a time line?

MS. WEXLER: If CFC availability was--

DR. SCHATZ: A fair amount has been emphasized about the concern as to whether CFCs will continue to be available in terms of the production as a rationale for the December 2005 date. My question was to what extent that one factor is important and if CFC availability were assured, if the production were not an issue, would that affect your thinking in terms of a transition date?

MS. WEXLER: No. I think that they work together to signal that these chemicals are being eliminated. There is a reason that Honeywell has been asked to shut the manufacturing plant in the Netherlands and that is because the Dutch government does not want CFCs produced on its soil. It is a political statement about getting out of these chemicals.

To answer your question specifically, if Baton Rouge were able to produce, it is not clear that the international community would continue to authorize those quantities and that would put the stakeholders in the position of suggesting that we don't care about international commitments.

The U.S., the government, has made a commitment to comply with the Montreal Protocol and so producing in Baton Rouge is only part of the equation. It is that gets us the potential to use them. But the right to use them legally needs to be granted by the parties to the protocol. So they have to work together in order for us to be able to go forward.

I think what, in some ways, you are asking is would we support renouncing the protocol?

DR. SCHATZ: No. It is a matter of would the date, would your date, change. I was trying to get the sensitivity of your position to CFC availability versus other considerations relative to the date you suggest.

MS. WEXLER: Again, I think that they work together. Given what we know about the timeline, the U.S.--forgive me; I want to make sure it is clear. We ask to use CFCs, wherever we get them from. Regardless of where they are produced, each country must ask the international process sort of at the beginning of the year. We just put in our request and those requests are two years in advance.

So the request that the U.S. recently submitted was for 2006 quantities. That request was not welcomed completely. It was suggested that the U.S. might want to reconsider that nomination in light of this rulemaking or the rule that is go forward.

So even if supply weren't necessarily an issue, I think that it would be foolish for us to believe that the international community is going to continue to provide authorization to use those CFCs indefinitely. So we are talking about a 2005-2006 timeframe for getting out of this and not worrying about either of those conditions, of CFC supply or the international community not granting authorizations.

I think that, as we have heard, the process of transitioning, making sure that the HFA-installed capacity is there, making sure we don't do anything precipitous and have a problem and then have no CFC production capability and the stockpiles of the CFCs that are available sort of suggest that we want to kind of look towards the sooner rather than later so that we buy ourselves some time.

In other words, I don't think the protocol parties will look kindly at a nomination for 2007 or 2008 regardless of whether Baton Rouge actually ends up coming on line in a legal way.

DR. CHINCHILLI: Thank you. Dr. Atkinson?

DR. ATKINSON: I sort of get the impression that one of the big concerns among the committee members and the FDA also is the possibility that a small percentage of asthma patients might be unable to purchase the HFA units that they need. GSK has a program, or described a program, that was going to assist with that. I wanted to ask Dr. Garutti if Schering had any such program and if they were considering creating one if they don't have one now.

DR. GARUTTI: Let me say this is a patient group and a provider group that we care very deeply about. We are committed to the respiratory business. We have been in it a long time and we are going to do whatever is necessary to serve our patient population.

First and foremost there is to make sure that there is Proventil HFA available when we do transition to the HFA-only environment. Currently, as I have pointed out, that will entail a

significant ramp-up and a significant expenditure of cost to get there. And we are confident we will get there.

In fact, Schering-Plough does have a patient assistance program. It is called SP Cares. We have had it since, I believe, the mid-1990s. It has similar eligibility requirements to those of Glaxo's program, not entirely the same but similar. Last year along we provided free drug of our primary-care products including Proventil HFA to some 75,000 low-income uninsured patients.

Periodically, we review the elements of this program and criteria and we are committed to continuing this program.

DR. CHINCHILLI: Thank you. Dr. Moss; you had a question?

DR. MOSS: I was going to ask something along the same lines. Maybe the people from GSK and Schering can talk about how they are going to market those programs for the uninsured, if they have any plans for how to make physicians aware of these programs.

MS. WEXLER: I wanted to point out that, in anticipation of this move, the stakeholders, on our website which is at inhalertransition.org, has listed all of the patient-assistance programs and has link to them so that our member organizations can now start to disseminate that information. So we also will work with the companies to promote these.

DR. JONES: Yes. Bridges to Access, actually, at the moment, has 435,000 patients in its program. We have done a lot and will endeavor to meet and strive towards this end. We have put a lot of programs in place in order to be able to reach as many people as possible and we will continue to have these outreach efforts in place to allow physicians and their associates to actually be aware of these programs.

But, as I say, we have 435,000 at the moment in the Bridges to Access program.

DR. CHINCHILLI: Thank you. Dr. Garutti?

DR. GARUTTI: I am not sure there is much more we can add. As we have indicated, we are

developing many aspects of our communication program. This is one element of them, the awareness of the SP Cares program and we are going to be working with various organizations that we mentioned to make sure that it is more widely communicated now as we transfer to an HFA-only environment.

DR. CHINCHILLI: Any other questions from committee members? If not, we are going to break for lunch. I'm sorry; Dr. Meyer. I didn't see you.

DR. MEYER: Sorry; not to delay lunch. I did want to make a clarification on an issue that was left open from Ms. Wexler's talk earlier about how the CFC sources is handled by the FDA because I think she left that as kind of an open question.

Without getting into the details of the Baton Rouge situation, what I would say is that the FDA does not approve a CFC source, per se. What we have done is we set standards for the purity that is acceptable for CFCs when used in metered-dose inhalers. It is the expectation that the sponsor

of a product that uses those CFCs will provide us evidence, both from the manufacturer as well as their own testing, that the CFCs meet those specifications and, if they do, then, in fact, they can be used in that product.

DR. CHINCHILLI: Thank you for the clarification. Let me make sure nobody else has anything. Okay. We will break for lunch. We plan to start promptly at 12:30 so please return to your seats a few minutes before 12:30 so that we can start at that time.

Thank you.

(Whereupon, at 11:22 a.m., the proceedings were recessed to be resumed at 12:30 p.m.)

A F T E R N O O N P R O C E E D I N G S

(12:30 p.m.)

DR. CHINCHILLI: We are ready to resume our afternoon session.

Open Public Hearing (Session 2)

We have a number of speakers for our open public hearing this afternoon. But, before we get started, I want to read the announcement again that I read this morning for our speakers.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

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

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

Now, in addition to that, unlike this morning, we are going to time the presentations because we have a number of presentations and a short amount of time. Ms. Jain is going to be running a timer and, when the green light comes on, that means you can start with your presentation. The yellow light means that you have one minute remaining and the red light means you are finished.

Now, we don't have a hookup here to pull you, so we would appreciate if you comply with this. Please try to finish when you see the red light.

So we are ready for Speaker No. 4 for this afternoon.

MR. JAMIESON: Good afternoon. My name is Jim Jamieson and I am here today on behalf of IPAC, the International Pharmaceutical Aerosol Consortium. IPAC is an association of leading manufacturers of MDIs for the treatment of asthma and COPD. My remarks today are made on behalf of AstraZeneca, Aventis, Boehringer-Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline and IVAX.

IPAC was created in response to the mandates of the Montreal Protocol. Since its inception over fifteen years ago, IPAC has sought a smooth and efficient transition from CFC MDIs that balances public health and environmental protection. IPAC is firmly committed to the transition from CFC MDIs as evidenced by the extraordinary investments and efforts that its members have undertaken over more than a decade.

I have been personally involved in this process for twelve years and have served as IPAC's principal point of contact with the FDA, EPA, the

State Department and other U.S. Government agencies on issues related to the MDI transition. I appeared before this committee five years ago during consideration of the FDA's rule establishing the criteria for determining an MDI to be nonessential.

IPAC's position on the FDA's albuterol rulemaking may be summarized as follows. First, IPAC fully supports FDA's Final Rule on the MDI transition issued on July 24, 2002. This rule adopts a moiety by moiety approach to the transition and establishes the four criteria for determining the nonessentiality of CFC MDIs. Once these criteria are met, FDA must undertake the requisite rulemaking process to promptly remove nonessential MDIs from the marketplace.

Second, IPAC fully supports the Stakeholders' petition and has urged FDA to issue a final rule declaring these products nonessential by March, 2005 with an effective date no later than December, 2005.

Let me explain why IPAC embraces these

positions. First, and most important and as you have now heard, there are two safe and effective CFC-free albuterol products on the U.S. market and the criteria set forth in the July, 2002 Final Rule either have been or can be met by December 2005. This position has also been advanced, as you have heard, by the Stakeholders Group.

Second, numerous other developed countries--Canada, Japan, Australia and at least twelve European nations--have already successfully transitioned patients to CFC-free albuterol products. There is no reason to believe that the United States cannot do the same. While we are focused today on a domestic rulemaking process, it is critical to understand the overarching international context. The United States' ability to secure CFC supply for MDIs is based upon essential-use authorizations allocated by the parties to the Montreal Protocol.

The international community has recognized that the completion of the albuterol MDI transition is crucial since these products represent at least

half of the CFC MDI market in the United States and around the world. In light of the progress by many other developed countries and the wide availability of CFC-free albuterol products around the world, it is unclear how much longer the international community will be willing to approve CFC volumes for use in single moiety albuterol products. This uncertainty has significant implications for patient care.

In response to the clear directive from the United States and international community to reformulate MDIs and to do it as soon as possible, as soon as feasible, IPAC member companies and other MDI companies began the difficult work of developing CFC-free alternatives.

This effort was not simply a matter of switching from one available aerosol propellent to another. It was a lengthy, challenging process requiring full R&D programs including extensive clinical trials. This effort required substantial investment from reformulating MDI companies well in excess of $1 billion and the work continues.

Almost fifteen years ago, MDI companies and the United States government embarked on an extraordinary and unprecedented partnership. The goal of this partnership was and is to balance the critical environmental interest of ozone protection with the equally vital objective of ensuring patient care, something that could not be achieved absent a strong and durable collaboration.

Industry's core responsibility in this partnership is to diligently research and develop safe, effective CFC-free alternatives. For its part, the United States undertook a parallel responsibility to secure essential-use CFCs during the development process and to ensure prompt removal of nonessential CFC MDIs as soon as new and reformulated products became available.

The pharmaceutical industry has acted in good faith and made extraordinary investments to develop ozone-friendly MDIs. It is now appropriate for the United State to honor its commitments toward the phase-out of ozone-depleting substances by declaring CFC single-moiety albuterol MDIs

nonessential.

Finally, IPAC concurs with the Stakeholders that, rather than presenting a possible risk to patients, the phase-out of CFC albuterol MDIs will actually bring benefits to patients in terms of improved treatment regimens. IPAC further believes that available patient-assistance programs will promote access to adequate treatment for potential vulnerable patient subpopulations.

IPAC is pleased that the FDA has issued the Notice of Proposed Rulemaking. Based on the considerations that I have mentioned above, IPAC urges FDA to grant the Stakeholders' request and issue a final rule removing nonessential single-moiety albuterol CFC MDIs effective December 31, 2005.

In closing, IPAC is grateful for the opportunity to present its views today. We stand ready to serve as a resource throughout this rulemaking process and future ones to progress the transition to a timely and smooth conclusion

consistent with patient health.

Thank you.

DR. CHINCHILLI: Thank you, Dr. Jamieson.

Speaker No. 5?

MR. FLANZRAICH: Good afternoon. My name is Neil Flanzraich and I am here today on behalf of IVAX Corporation. I would like to thank the FDA and the Pulmonary-Allergy Drugs Advisory Committee for giving us the opportunity to comment on the regulatory issues before the committee and to register our support for the timely removal of single-moiety albuterol MDIs from the list of essential uses of ozone-depleting substances.

IVAX is a multinational company engaged in the research, development, manufacture and marketing of generic and branded pharmaceuticals and veterinary products in the U.S. and internationally. We are perhaps best known as one of the world's leading generic companies. We were the company that brought the first generic and first inhaled generic, albuterol aerosol, and the first extended-release generic, verapamil HCL ER

tablet, products to the U.S. market as well as many other important generic products; for example, paclitaxel injection.

IVAX also has a formidable commitment to proprietary medicine with an extensive proprietary pipeline that addresses important therapeutic categories including oncology, central nervous system, urological and endocrinologic disorders. We also have a strong focus on developing proprietary products for respiratory conditions.

Our position, as both a generic and propriety company, gives us a clear and sympathetic understanding of both sides of this issue. Indeed, our experience with the issues facing this committee goes much deeper. IVAX received a final approval from the FDA for a CFC albuterol and metered-dose inhaler, the generic equivalent of Glaxo-Wellcome's CFC Ventolin, and was the first company in the U.S. to market a generic albuterol aerosol product.

Prior to the approval of this generic, IVAX worked with the FDA for five years to

establish a sensitive pharmacodynamic bioequivalence study which paved the way for the approval of other generic albuterol inhalation aerosol products in the U.S. market. This resulted in significant extended use of albuterol inhalers.

IVAX' entry into the market, as well as the other companies that followed, significantly decreased the cost of albuterol to U.S. consumers. Importantly, this significant reduction in albuterol's price was a result of competition in a free-market economy. We sell, we continue to sell, this generic CFC albuterol product in both the U.S. and abroad and it has been and continues to be a contributor to our companies revenues and profits.

From the time seventeen years ago that the FDA and the EPA first encouraged U.S. companies to develop CFC-free aerosol products, IVAX has been a leader in developing and introducing environmentally friendly CFC-free respiratory products. In 1997, in France and Ireland, we became the first company in the world to win approval for, and to market, CFC-free

beclomethasone in a metered-dose inhaler.

Our CFC-free beclomethasone, QVAR, was the first HFA corticosteroid for asthma on the U.S. market. We have also developed another CFC-free product, our patented dry-powder inhaler, Airmax, which has recently been approved in several countries in Europe and which is presently being studied in a clinical trial in the U.S. with one of our innovative proprietary compounds for the treatment of asthma.

IVAX as also become a major supplier in the U.S. and around the world of inhalation solution products for nebulization which are also CFC-free products. Most pertinent to the matters concerning this committee, in January of 2003, we submitted a new drug application for an HFA formulation of albuterol in a metered-dose inhaler and it received an approvable letter from the FDA on this application on November 28, 2003.

In August, 2003, we submitted another new drug application for an HFA formulation of albuterol in our patented breath-activated

Easi-Breathe inhaler.

IVAX has, therefore, not only been a participant but a pioneer and leader in both the generic CFC albuterol and CFC-free branded albuterol markets. Our company is committed to supplying safe, affordable and environmentally responsible products and we don't believe that these goals are in conflict with each other.

As has been stated by the U.S. Stakeholders Group on MDI transition in its citizens petition, the impact of CFC emissions in accelerating depletion of ozone in the earth's stratosphere and, thus, increasing our exposure to ultraviolet radiation is scientifically well established.

Presently, CFC emissions from metered-dose inhalers are the dominant dose of CFC emissions produced by the United States. While the significant impact of these emissions are better addressed by the scientists and environmentalists appearing before this committee, given the current status of the weakened stratospheric ozone layer,

these CFC emissions remain a public-health concern. We believe their continued use remains a breach of faith with the international accords to which the U.S. is a party and to the international community that views these emissions as serious hazards.

Additionally, removing the albuterol CFC products from the U.S. market will also strengthen the hand of the governments and agencies seeking to encourage other countries to discontinue activities that release even greater volumes of CFCs into the atmosphere.

In response to the U.S. laws and international agreements calling for the phase-out of ozone-depleting substances, the leadership of other nations on this issue and the FDA's instructing the pharmaceutical industry that the Montreal Protocol and the Clean Air Act mandate an eventual complete ban on the production of ozone-depleting substances.

IVAX has invested many millions of dollars over the past seventeen years to bring CFC-free products to the U.S. and European markets. We

fully concur with GlaxoSmithKline's argument that, having urged the MDI industry for over a decade to reformulate their products to CFC-free formulations, it would be manifestly inconsistent for the U.S. government to punish the companies that have invested so much and to reward other companies which have made no effort to phaseout CFC use by proposing an inappropriate delay in albuterol nonessentiality.

As previously mentioned, we currently sell QVAR, the only CFC-free aerosol corticosteroid for asthma on U.S. market and have filed new drug applications for an HFA formulation of albuterol in a metered-dose inhaler in our patented breath-activated Easi-Breathe inhaler.

The FDA is well aware of the status of these NDAs and, hopefully, the products covered by them will join GlaxoSmithKline's Ventolin HFA and Schering-Plough's Proventil HFA on the market in the near future. Both of our HFA albuterol products will meet the FDA's final rule in regard to same active moiety, same route of

administration, same indications, approximately the same level of convenience of use as the CFC albuterol products presently on the market.

IVAX would be willing to supply to FDA with at least one-year postmarketing surveillance data for our HFA formulation of albuterol that we sell in Europe which is the equivalent to the HFA formulation of albuterol that we have filed NDAs on in the U.S.

Our HFA formulation in an MDI and in our Easi-Breathe inhaler will be manufactured in our FDA-approved plant in Waterford, Ireland. We expect our capacity for HFA products to be 50 to 60 million units a year in the near term. Given what we have heard this morning about GlaxoSmithKline's and Schering-Plough's capacities for manufacturing CFC-free albuterol units, the combined manufacturing capability of these three companies will be more than enough to satisfy the needs of the U.S. market.

For IVAX, there is also an issue of availability of CFC propellants. Whatever the

availability will be for U.S. manufacturers, it may be even more problematic for IVAX. Since we manufacture our products in Ireland, European Community approval is needed to obtain supplies. Since CFC availability is decreasing rapidly in Europe, such approval may not be forthcoming.

The effect of an interruption of IVAX's supply would be to decrease competition in the U.S. and increase prices of the CFC products still on the market. This is particularly likely since IVAX is the major supplier of true generic CFC albuterol MDIs in the U.S.

We believe that IVAX is well credentialed to discuss the issue of pricing. We are one of the world's leading generic companies and have demonstrated during our entire seventeen-year existence a commitment to provide affordable medicine to the public.

We have also demonstrated this commitment with our two main branded respiratory products in the United States, both QVAR, our CFC-free corticosteroid for asthma, and Nasarel, our

intranasal steroid for rhinitis, are the lowest-cost medicines in their categories. QVAR, our branded asthma medicine costs approximately 50 percent less and Nasarel approximately 20 percent less than the average price of the other products in its category.

We appreciate that there is a concern that the prices of these new branded CFC-free albuterol products will exceed those of the four CFC generic albuterol products currently on the market one of which is an IVAX product. We believe that the best way to control the costs of these new branded CFC-free albuterol products is the traditional American way, through the dynamics of competition in a free-market economy.

Presently, there are two competitors on the market, Schering-Plough's Proventil HFA and GlaxoSmithKline's Ventolin HFA. We expect that IVAX will be joining them in the near future with our two HFA albuterol products. These products are not presently approved and we have not yet set our pricing, but we reiterate that IVAX has an

historical commitment to providing the public with affordable medicine.

We are also committed to pursuing a substantial free sampling program as well as a patient-assistance program. In due course, we will provide the agency with additional information concerning these proposed programs. The agency's proposed rulemaking, which we have just received, sees the future entry of generics as the way to lower the current pricing of HFA albuterol. We respectively suggest that the entry of generics is still a long way off and that the agency has not properly taken into account in this regard the entry of IVAX's new HFA albuterol products that are currently pending at the agency.

It was IVAX's entry as the third competitor into the CFC albuterol market years ago that dramatically impacted these prices. It is our understanding that Sepracor may also have a CFC-free short-acting beta-agonist molecule closely related to albuterol on the market a well. The competition from these products will create

downward pricing pressure and there could certainly be additional CFC-free albuterol products, brand and generic, entering the market in the future.

It has been alleged by an opponent of the removal of CFC albuterol from the essential-use list that the FDA's removal of CFC albuterol products from the list would be inconsistent with the stated priority of carrying out its mandate under the Hatch-Waxman Amendments to promote affordability of prescription drugs by increasing the availability of generic drugs.

As a company deeply involved with the Hatch-Waxman Act selling over 8 billion generic tablets and capsules in the U.S. a year with a clear understanding of both the letter and the spirit of those amendments, we see no mandate to sell affordable drugs that put the environment and the public's health at risk.

There is no inconsistency in recognizing and abiding by what has always been true, that in the pyramid of healthcare values, "Do no harm," has always come first. The primacy of this principle

is universally accepted and, at present, twelve European countries, as well as Canada, Australia and Japan, have eliminated the use of CFCs in albuterol MDIs.

Because we believe that the removal of CFC albuterol products is important, because we believe that the FDA's conditions and criteria for removing CFC albuterol products from the essential-use list have been met, because we believe that the enormous investment we and other pharmaceutical companies have made to reformulate our MDI products in reliance on the urgings of the FDA was correct and responsible corporate behavior that should not be ignored nor published, because we believe that the United States has pledged its support for removal of these products to the citizens of the United States and the international community through the Clean Air Act and Montreal Protocol, and because we believe that leading the CFC albuterol products on the U.S. market for an extended period will have a considerable, if difficult to calculate, cost on the environment, on public health, on the U.S.

government's relationship with the international community and on its future success with volunteer collaborative pharmaceutical-industry action and because we believe that the cost of HFA albuterol products can be effectively dealt with by various mechanisms including, among others, free sampling and patient assistance programs and, of course, IVAX's entry into this market, we respectfully request that the FDA promptly issue a final rule removing the albuterol MDI products from its list of essential uses no later than December 31, 2005.

Thank you.

DR. CHINCHILLI: Thank you, Mr. Franzraich.

Speaker No. 6.

DR. ROZEK: Good afternoon. I appreciate the opportunity to appear before this committee today. My name is Richard Rozek. I am an economist and a Senior Vice President of National Economic Research Associates, a firm that has been providing research on business and public policy issues for a variety of industries since 1961.

Personally, I have been involved in the pharmaceutical industry for over twenty-five years in various academic, government--federal government, I should say--and private-sector positions.

In 2003, GlaxoSmithKline, or GSK, asked NERA to assess whether patients will be adequately served if the FDA designates albuterol CFC MDIs nonessential products. To address this issue, my colleague, Emily Bishko, and I performed an economic analysis of the cost impact on patients and third-party payers in the first year after the FDA would implement this policy change.

Our initial results, which were submitted to the docket in response to the Citizens Petition, as well as my comments today, represent the results of our own independent research on these issues related to the current and projected market environments for selling albuterol.

Now, as we have heard this morning, the FDA established criteria that it was considering designation albuterol a nonessential. Given these

criteria, which I have summarized on this slide, they really fall into two categories; the product issues and then the patient issues, I think. We focused on the economic factors surrounding whether patients would be adequately served. Specifically, our concern was whether patients will have access to albuterol MDIs after the FDA policy change.

To begin our analysis, we examined public data on the pharmaceutical industry generally and albuterol specifically. My experience in the pharmaceutical industry suggests that looking at general industry trends does not constitute a sufficient basis to analyze the effects of an FDA policy change as that proposed here.

Detailed information on the specific uses of albuterol in the U.S. is required. But two important characteristics emerged from our review of the data on the pharmaceutical industry in general and on albuterol.

First, there is a complex vertical structure in the pharmaceutical industry by which products flow, generally, from manufacturers, both

brand and generic, to patients. This is a schematic to look at that structure and we have noted the data in percentages is albuterol-specific data. As we saw this morning, approximately 84 percent of the albuterol MDIs--these are units as opposed to dollars--flows through the retail sector to patients. The remaining 16 percent flows through either clinics, universities or HMOs as a group, non-federal hospitals or federal facilities. The retail sector, obviously, is very important in this regard.

Our second result has to do with the usage of albuterol over time. We examined data from IMS covering the period 1992 to 2002, which was the last year for which we had data, although, subsequent to our submitting our report, 2003 data are available.

We noticed stability of the demand for albuterol over time. Albuterol demand stayed constant at approximately 50 million MDIs per year and that was even in the face of increasing population which is the red line at the top of the

chart, and also in the face of generic entry which occurred in approximately 1996. The first generic sales for albuterol appeared in the data that we looked at in January, 1996. So stable demand was an important factor in our subsequent analysis of these issues.

To facilitate our analysis, we made several simplifying assumptions, as economists like to do, in order to make the analysis tractable. We assumed that there is a minimal, if any, market response to the FDA policy change. What this meant for our analysis is that we assumed no additional samples, no manufacturer rebates to government programs above those legally mandated, no market entry beyond the two existing HFA MDI products and no discounts to other payers above current levels for the HFA MDI products. That is really a manifestation of the last point which is that there was no additional price competition for the HFD MDI products than what had existed before or what exists currently.

Under these assumptions, we looked at

several different perspectives. But I think, since our concern was the patient, we will focus on that first. Under these assumptions, we calculate the increase in cost to patient per MDI for each of the six channels of distribution that we noted on the vertical flow chart earlier.

Specifically, patients obtaining albuterol through the retail cash and the retail private-insurance channels would experience an increase, in our analysis, of $8.61 per MDI in the first year after the policy change and those people going through the retail private-insurance channel would pay an increase of $10.57 per MDI, respectively.

In the private-insurance channel, the effect was due to the increase in copayment that a patient would have to incur for a branded product versus a generic products. We had data on average copayments. Generic product through the private-insurance channel has a copayment of $10.00 and a branded product has an average copayment of $22.00. Shifting to only branded HFA products

available, we assume the patient would shift to the higher copayment amount, hence the increase in that channel.

Now, going a step above to a broader perspective, looking at patients and third-party payers, assuming, again, that the volume stays constant at 50 million units, we estimate that the first-year increase in the price of albuterol MDIs for all payers, whether it be the patient or a third-party payer, and in all forms of the product prior to the policy change, there is HFA, CFC, brand and generic, so that is included in our pre-policy-change analysis.

The price would increase, in our calculation, from $18.38 prior to the policy change per MDI to $28.25 after the policy change. That is the top line in this chart. That is a cost increase, overall, of $9.87 per MDI. The patient incurs $7.33 of that increase of $9.87 and the third-party payer incurs an increase of $2.54.

That is not uniform across all third-party payers but that is the average for all third-party

payers here. If you remember the first charge, that includes federal facilities, hospitals--excuse me; it includes the federal government as well as private insurance and other programs.

Looking at these data as a daily increase in cost, we see that it was a half a cent per capita or 4.4 cents per asthma and COPD patient, per diagnosed asthma and COPD patient. Looking at it in the first-year impact collectively, this translates to $1.69 per capita or $16.02 per diagnosed asthma and COPD patient.

Based on the historical stable market demand for this product, the use of albuterol as a rescue medication and the relatively low market price for a prescription of albuterol relative to the average prescription product, in my view, the cost increases to patients and payers that we calculated are unlikely to have a material effect on the future use of albuterol MDIs.

By comparison, even with branded product only, we are talking about a prescription price of about $30.00. The average prescription price for a

branded price in 2003 was over $80.00, to put this in perspective.

Now, that was our quantitative analysis. We subsequently looked at other market factors. These other market factors, both current and expected, further ensure that no patient will have to forego albuterol MDIs. These other market factors we have heard about already, patient-assistance programs, those are both public and private. D.C. Healthcare Alliance is a public patient-assistance program. Bridges to Access is a private patient-assistance program.

There are patient discount programs such as GSK Orange Card and Together Rx. There is better information about these programs. We heard about the Stakeholders website, the PhRMA, the trade association for the research-based pharmaceutical industry has a website. GSK has promised 2 million additional samples in the first year alone.

We have heard about additional competition from IVAX, from Sepracor, from other 3M licensees.

3M is willing to license the HFA technology and albuterol, itself, is not patent-protected. We now have also heard today about Medicare drug coverage beginning in 2006 to further benefit the elderly patient.

Another factor that is very important in the pharmaceutical industry is buyer power; that is the ability of certain buyers to move market share and to create competition among sellers. If you recall the period between the mid-'80s and the mid-'90s, Glaxo and Schering competed with only branded albuterol in CFC form. These companies competed vigorously against each other. Now, it is up to the buyers to create that competition again if it is only Schering and Glaxo competing.

So, for a variety of reasons, these factors, together with our quantitative analysis, lead me to conclude that patients will continue to have access to albuterol after the FDA designates albuterol CFC MDIs nonessential.

Thank you very much.

DR. CHINCHILLI: Thank you, Mr. Rozek.

It is time for Speaker No. 7.

MR. DONIGER: Thank you very much for the opportunity to talk to this panel. I am David Doniger. I represent the Natural Resources Defense Council. We have more than a half a million members across the country dedicated to protecting public health and the earth's critical natural systems.

I, personally, worked on protecting the ozone layer, phasing out the ozone-depleting chemicals and constructing and implementing the Montreal Protocol and the Clean Air Act Provisions for more than twenty years.

The Montreal Protocol is the most successful international environmental agreement ever. Developed countries are way along the way to completing the phase-out of CFCs. Basically the use in inhalers is the last significant use of CFCs in this country. Developing countries are beginning on their scheduled phase-out of ozone-depleting chemicals, too. Many of them actually have completed the phase-out as well.

We are here because some uses have been deemed temporarily essential by the protocol parties and have not yet been eliminated. But the ozone layer continues to suffer from the remaining emissions of these substances. In 2003, the hole in the Antarctic ozone layer grew to near record size so this program is not finished yet.

For close to a decade, the protocol parties have been working to eliminate the remaining uses as they become nonessential including CFCs in albuterol MDIs. As you have heard, other developed countries with economies and patients similar to our own, including Australia, Canada, Japan and many members of the European Union have already completed the phase-out of these products.

The United States has the single greatest use of ozone-destroying CFCs still allowed. It is our view that they are no longer truly essential, unnecessarily harmful to the ozone layer and it is now of the utmost importance to complete the MDI CFC albuterol phaseout as quickly as possible.

Now, viewed individually, the amount of CFCs in these products may not appear to be significant compared to the general phase-out of CFCs, but the emissions of ozone-depleting substances from all sources, no matter how small, must be viewed in a cumulative manner. The emissions are cumulative and long lasting. The CFC 11 and 12 used in these products have atmospheric lifetimes of 50 and 100 years respectively.

Emissions of ozone-depleting chemicals anywhere in the world contribute to depletion of the ozone layer above the United States. Thus, the impact of FDA's decisions regarding the phase-out of CFC albuterol MDIs will go far beyond just the products used in the U.S. It will have a significant impact both here and abroad in protecting the ozone layer.

There is a ripple effect here. By adhering to the letter and spirit of its commitments under the protocol and eliminating these CFC uses as soon as they become nonessential, the United States sets an example for other

nations--actually, I was going to say to follow, but other nations are ahead of us in following.

But the opposite is also true. Where the U.S. drags its feet on the removal of nonessential CFC uses, it makes it easier for other countries to delay their phase-outs of other chemicals, of other uses, and we really do risk the possibility that the repair of the ozone layer will not occur on schedule if others, including our country, drag their feet.

The health effects of ozone depletion are serious. There are serious increases in skin-cancer rates, cataracts, suppression of immune systems and premature skin aging. The 2002 scientific association for ozone depletion estimated that, absent the controls implemented under the protocol, there would be nearly a half billion excess cases of skin cancer by 2040, worldwide. But we have to keep at this and complete the phase-out if we are going to eliminate the excess risk from depletion.

Somewhat ironically, ozone depletion, by

CFC emissions from the MDIs may even contribute to the very problem the MDIs are intended to treat. Higher levels of U.V. radiation result from depletion and those exacerbate there chemical reactions that produce ground-level ozone smog. Smog is one of the things which compounds the problem of asthma and COPD impacting the very patients who rely on the MDIs.

There is also a potential indirect effect of an FDA delay to consider and that is that there may not be new CFC production available after 2005 for this product. We know that the U.S.'s primary source of drug quality CFCs in the Netherlands will be closed down under that government's regulations at the end of 2005.

In response to this shutdown, Honeywell, the producer in the Netherlands, has proposed shifting CFC production to its plant in Baton Rouge, Louisiana. However, producing CFCs that are not currently produced at the Baton Rouge plant, including CFC 11 required for CFC albuterol MDIs, would violate U.S. law and the Montreal Protocol.

It should also be expected that the protocol parties will not continue to grant the U.S. essential use authorizations for CFC albuterol MDIs, certainly not in the kinds of volume which have been granted in the past. For the first time since the inception of the essential-use exemption more than a decade ago, the protocol's expert panel that reviews essential-use nominations has recommended only a conditional approval of the U.S. nomination for 2006, in large part due to the fact that 70 percent of the U.S. nomination was for CFC albuterol MDIs that other countries have been able to phase-out.

The way the Clean Air Act works, if the parties to the protocol do not authorize the production and consumption of CFCs for an essential use, then EPA may not authorize such production or consumption, and that includes import, for this use domestically.

Honeywell has stated that it believes that, by the end of 2005, the volume of pharmaceutical-grade CFCs available from the

Netherlands plan coupled with existing CFC inventories may be enough to satisfy the U.S. market until 2008, raising the question of why anything would need to be produced after 2005 with the closing of that plant anyway. We are pursuing that point with EPA.

But it is true that this stock is a limited, finite amount and, in our view, it is better directed, if used at all, at other kinds of MDIs, not albuterol MDIs, where the reformulation may be proceeding more slowly. In other words, every kilogram that is used in a nonessential albuterol MDI is one less kilogram that could be used in higher-value products for which the substitutes are coming more slowly.

So, due to the impending closure of the plant in the Netherlands and the likelihood that the protocol parties will not continue to grant these exemptions, there is a very real possibility that CFCs will not be available for albuterol inhalers as long as FDA appears to be assuming. I think this is a key point. A policy based on a

false assumption of continued CFC supply is actually the one most dangerous for patients because the false assumption is slowing the transition to CFC-free products and, if CFCs become unavailable sooner than FDA is supposing, patients may be caught short.

The solution is to proceed swiftly with the transition to CFC products declaring CFC MDIs nonessential now, CFC albuterol MDIs nonessential now, and relying on the safe and effective CFC-free products to cover the needs of patients. This can be done as early as 2006.

So, to conclude, completing the phase-out of the CFC albuterol MDIs will have a significant positive impact on the environment, on public health generally, on the well-being of asthma and COPD patients specifically and delay will have the opposite effect.

For these reasons, the committee should support a finding that the CFC albuterol MDIs are no longer essential and should be removed from the market, we think, as soon as January 1 of next

year.

Now, one final note. In nearly a quarter century that I have been engaged on working on this issue, protecting the ozone layer, I have heard over and over again from industries and certain government agencies that it is infeasible to phase-out various uses of ozone-depleting substances and that taking timely action to protect the ozone layer would destroy businesses, cause economies to collapse and even cause elderly people to die due to the lack of air conditioners.

Invariably, these dire predictions have proved unfounded and dozens of uses of ozone-depleting substances have been phased out successfully. Based on this historic perspective, and not intending to minimize at all the very real health considerations for the patients at issue here ,I am confident that the phase-out of CFC albuterol MDIs can be completed this year or next without adverse consequences.

Thank you for the opportunity to present to you.

DR. CHINCHILLI: Thank you, Mr. Doniger.

Speaker No. 8.

DR. RAU: Thank you for the opportunity to provide comments to the committee. My name is Joseph Rau. I am Chair of Cardiopulmonary Care Sciences at Georgia State University in Atlanta and I am speaking on behalf of the American Association for Respiratory Care, the AARC. I want to say at the outside I have no financial interest or conflicts of interest with any of the products that are being deliberated upon today.

The AARC is the national professional association representing over 34,000 respiratory therapists who provide care to patients with asthma, emphysema and other chronic obstructive pulmonary diseases. I have submitted a written statement which offers more detail on the brief comments that I would like to offer today.

The AARC support phasing out of the use of chlorofluorocarbon or CFC propellants for aerosolized inhaled medications and, in particular, the removal of the essential-use designation for

CFC albuterol metered-dose inhalers.

In addition, the AARC, however, wants to recommend monitoring the consequences of such a change on cost and patient compliance. There is no generic HFA albuterol and we have seen, with data presented today, that there is some price difference between the HFA formulations compared to the currently available generic CFC formulations.

The AARC, in general, recommends an approval process for new HFA formulation new drug applications that is as efficient and expeditious as possible to promote availability and competitive pricing of replacement drugs for bronchodilators as well as other drug classes. There is uncertainty over pharmaceutical manufacturers production of non-CFC MDI bronchodilators and other classes of inhaled drugs.

The AARC believes that this uncertainty can be reduced or, perhaps, even eliminated, if the phase-out and replacement of CFC MDIs is driven by a planned transparent timeframe agreed to by the FDA and pharmaceutical manufacturers rather than

dictated by the unavailability of CFCs. In particular, the AARC does support the proposed December, 2005 timeframe for the phase-out of CFC albuterol MDIs.

Thank you.

DR. CHINCHILLI: Thank you, Dr. Rau.

Speaker No. 9.

MS. FINDER: Hello. My name is Jodi Finder. I am here as special counsel to the Asthma Therapy Coalition. First, I would like to thank the agency and this committee for the opportunity to present ATC's views this afternoon.

What we are not debating here is that FDA is an agency that is charged with protecting America's health. FDA is, therefore, unequivocally obligated to make decisions about a drug's marketing status that are based on facts and economic realities.

If this transition is inevitable and CFC albuterol MDIs must lose their essential-use designation, then this transition away from access to affordable albuterol rescue inhalers cannot

ignore the dire medical needs of the population that relies on them the most.

Asthma is on the rise in this country, one of the most chronic and fastest-growing diseases in America. There were 20 million asthmatics in 2002. In that same year, there were more than 1.9 million ER visits that were attributable to this chronic condition. What is also not at issue here, in addition to FDA's role, is that bronchodilators are an integral part of asthma management.

There has been a disproportionate increase of asthma prevalence in the poorest and most cost-sensitive segments of society. I think we know who we are talking about here; the uninsured, the underinsured, the Medicaid recipients, the urban population--for example, inner-city children--the elderly patients who are on fixed incomes, and minorities.

Another population that we don't talk about very often that hasn't really been discussed in this debate thus far is the rural population. The West Virginia Education and Prevention Program

has done a study on this population that has shown that the prevalence rate in rural West Virginia is greater than the national rate and this number is growing.

For your reference, I have included to the committee an executive summary of that study.

A recent Journal of the American Medical Association study that looked at chronic conditions including asthma reveals that increasing copayments can decrease prescription drug use up to 32 percent and even more in some conditions. To give you a sense of what the study included, it look at diabetes, arthritis, asthma, depression and a few other chronic conditions.

The medical and financial cost of a premature ban on CFC albuterol metered-dose inhalers would far exceed the environmental benefit. We all know that generic CFC albuterol MDIs retail for more than $20 less than brand alternatives. The agency and the committee don't seem to be questioning this discrepancy.

The near-term removal of generic

alternatives would raise treatment costs, according to conservative estimates, by $500 million annually totalling approximately upward to $5 billion or more until the time that HFA inhalers come off-patent and generic alternatives may enter the market.

In fact, FDA, though, has actually said, in the rule that was issued, the proposed rule that was issued yesterday, that this number really is a conservative estimate. FDA is now saying that this number of $1 billion annually. Let me repeat that. $1 billion we are looking at as the increased cost of taking these products off the market prematurely.

In contrast to the cost here, the near-term environmental impacts are negligible. It will take fifty years for stratospheric chlorine loading to reach adequate levels to improve the environment. Even if all CFC albuterol MDIs were eliminated this year, the environmental benefit would be insignificant.

Let me explain this in a little greater

detail. This graph shows the cumulative ODS production. What you see here is actually over approximately a 50-year period. But if you look over approximately a 70-year period, you will see that ODS production totalled 23 million ODP tons worldwide.

If you look towards 2002, you see an extreme downward trend from the peak year in 1988. The sum of all CFCs reported in 2002 equalled a mere 3 percent of the total peak year from 1988, so what you are seeing, that small bar at the end, is 3 percent of that large bar you are seeing that represents the peak year of 1988.

Less than 1 percent of the 2002 ozone-depleting-substance production is attributable to U.S. CFC albuterol inhaler production. What that means is, you look at that little bar, less than 1 percent of that small bar--this would be an imperceptible line on this chart--is attributable to CFC albuterol MDI production in this country.

What this means is, if we look at having a

reasonable transition here, if a transition is inevitable, and we are looking into the next decade, that approximately eight to ten more years of CFC albuterol MDI production in this market would amount to less than 0.01 million ODP tons in contrast to that 23 million you see represented on this bar chart.

What does this mean? A moment ago, I said that it would take 50 years for the environment to reach a full recovery after taking ODS products off the market. So, what we are talking about in allowing this reasonable transition and in allowing these cost-effective products to stay on the market until generic alternatives can enter the market, bring competition and keep prices down, we are going to delay that 50 years that it already going to take the environment to recover by a matter of days, if that much. We are talking about days, 50 year plus days.

What is not in question here is that FDA cannot undermine the Hatch-Waxman Amendments. The Hatch-Waxman, we all know, has revolutionized the

normal life cycle of pharmaceuticals. The pharmaceutical market has come to progress from brand exclusivity, high dollars, towards generic competition, meaning affordable drugs, not the other way around.

Barring entry prematurely of generic alternatives for nearly a decade would represent a clear abrogation of FDA's clear mandate to promote affordability by promoting competition.

So what the Asthma Therapy Coalition is here to do today is ask the agency and the committee to consider some very important questions as it makes an ultimate decision here. First, given the price sensitivity to prescription drug use, what will be the ripple effect throughout the healthcare system and is this acceptable?

We are looking at increased hospitalizations, increased emergency-room visits, increased morbidity, increased mortality rates. Another question; which groups will be most likely affected and how can we prevent this adverse impact? How successful, really, will the current

proposed government and/or private-sector programs be? What direct environmental and patient benefits are gained by eliminating CFC albuterol MDIs before generic alternatives may enter the market? Shouldn't the billions of dollars we are talking about here, that FDA is already talking about, be spent in more impactful areas such as research and development and prevention.

Again, thank you to the agency and to the Pulmonary-Allergy Advisory Committee for this opportunity to participate in the rulemaking process today. The Asthma Therapy Coalition would be happy to serve as a resource throughout this rulemaking process.

DR. CHINCHILLI: Thank you very much.

Speaker No. 10.

DR. BERNHARDT: I am pleased to have the opportunity today to address this meeting and offer considerations for planning the U.S. program for CFC propellants used in metered-dose inhalers, or MDIs.

I am Dr. Steven Bernhardt, Global Director

of Regulatory Affairs for Honeywell Chemicals. Honeywell is a $23 billion diversified technology and manufacturing leader. We employ over 100,000 people and serve customers worldwide with components, engines and related products and services for commercial airlines, business and regional aircraft and spacecraft, automation and control technologies for homes, buildings, industry sites and airports, turbochargers for transportation systems and chemicals, films, advanced fibers and custom intermediates.

We are leading global producer and marketer of fluorine-based products including both CFCs and HFCs and, as such, are vitally interested in the proceedings and recommendations of the FDA regarding MDI propellants.

Honeywell is a supplier of propellants for MDIs manufacturers. We are committed to meet the needs of our customers and patients in this critical life-saving application. We support to orderly transition from the use of CFC propellants to non-ozone-depleting propellants such as HFCs.

Honeywell has manufactured CFCs for MDI propellent applications in the U.S. and in Europe. In recognition of the expected gradual decrease in demand for CFCs as propellent for products such as albuterol, we are planning to rationalize our global manufacturer to a single site located in Louisiana.

Our plan is to continue manufacturer of CFCs to meet patient demand for this choice of product until such time as a transition to HFCs has proceeded to the point that continued operation can no longer be justified. Supply to meet market needs can be from just-in-time CFC manufacturer as well as judicious use of inventory of propellent as preferred by our customers.

Our business plans call for us to be a supplier of CFCs, HFCs or both. It is vital that FDA and the Aerosol Technical Options Committee for UNEP is aware that supply of both options will be available and shortage of supply ought not to be a consideration for your recommended national transition plan.

We welcome working closely with both organizations to provide you with the necessary assurance that we will continue to be a partner who you can rely on for the years to come to support this elected phase-out schedule.

I, again, thank you for this opportunity to communicate Honeywell's position on the supply situation.

DR. CHINCHILLI: Thank you very much, Dr. Bernhardt.

Speaker No. 11.

MS. SANDER: Good afternoon. I am Nancy Sander. I am President and Founder of the Allergy and Asthma Network Mothers of Asthmatics, a nonprofit patient and family-education and advocacy organization based right in the neighborhood, actually, just a few miles away so all expenses associated with this trip are donated by me.

On behalf of the AANMA Board of Directors and more than 17 million Americans diagnosed with asthma, I want to thank you for the opportunity to be here and represent patient perspectives.

AANMA takes the position that the use of chlorofluorocarbons as propellants in albuterol metered-dose inhalers no longer meets the requirements for essential use under the criteria set for in the Code of Federal Regulations.

This is a poster that I see some of you have picked up already but it is newly published by our organization in cooperation with the American College of Allergy Asthma and Immunology with the MARC emergency-care physicians as well. This poster was developed to help patients identify the medications that they were on when they go to an emergency room and they don't remember the names of what they are taking.

But it also helps me with a presentation today where, if you will notice that in your top left-hand corner, you will see, across the top row and then the two in the middle row, that we have albuterol bronchodilators. Prior to the introduction of generic albuterol in 1996, albuterol sulfate was only sold as Ventolin and Proventil. Today, patients use albuterol sulfate

sold in generic, Ventolin HFA and Proventil HFA formulations.

So, with the phase-out, and I do mean phase-out, of CFC-propelled albuterol MDIs, albuterol does not disappear. So we are very confident about its availability. Will this represent a threat to patients who no longer have access to generic or less-expensive MDI bronchodilators? We think, actually, not, especially after hearing the presentation by IVAX and by GlaxoSmithKline and by Schering earlier today. Because, also, the transition takes place over time. Inhalers don't go away one day as a result of a calendar-day change. So, because it takes place over time, manufacturers, health insurers, patients and their physicians have time to plan accordingly.

As an organization, we have been helping patients make this planning transition for a number of years and also make them aware of various patient-assistance programs that various companies have.

Of the remaining short-acting inhaled bronchodilators up here, that would be Alupent, Maxair, Autohaler, Atrovent and Combivent. All of them contain CFC propellent. According to everyone today, they eventually go away as well. I think we can learn a lot about how transitions happen by paying close attention to what happens with albuterol.

The new drug application submitted by Sepracor for Xopenex and the discussions from IVAX earlier today are encouraging as well because they both utilize HFA propellants.

This brings me to one of my favorite subjects and that is, while the pressurized metered-dose inhaler is an absolutely elegant economic and portable device. It is also very complex and user-dependent. Even experienced users even have difficulty using the MDIs even though they have been taught numerous times.

The MDI is the only FDA-approved medication delivery system where a patient cannot reliably tell if they have medication left as they

continue to use it. There is no window. There is no mark on the side that says, "After this level, you have no medication." There is no dose counter or indicator. So there is no way to know when a patient has reached 200 doses, if that is the fill capacity. So it is not obvious at all when a patient is running low or needs to get a prescription refill.

The FDA and manufacturers say that shake, float and spray-testing techniques commonly employed by patients and their physicians when trying to determine or guess the amount of medication remaining inside of their MDI are unreliable. Float testing, where the MDI is dunked in water, may actually damage the device.

There was research that showed that clearly 82 percent of patients use empty MDIs. So when parents send children with asthma to school each day, is the MDI full or empty and no one can say for sure. That is why the organization continues to encourage manufacturers to adopt FDA guidance to industry and why we view that MDI

transition presents the best opportunity to incorporate dose counting and dose-indicator technology and into new devices and HFA devices.

Cost, access and education issues will never go away but they can be improved, particularly in the underserved population. We do not support an essential-use exemption for CFC albuterol. We do, however, support a united front with the FDA and with manufacturers and health insurers and other interested parties in making sure that patients make very smooth transition together.

Thank you very much.

DR. CHINCHILLI: Thank you, Ms. Sander.

Speaker No. 12.

DR. MARINELLI: Good afternoon. My name is Dr. Anthony Marinelli. I am a member of the American Thoracic Society Clinical Practice Committee and I am here to present the views of the American Thoracic Society, an organization of 15,000 pulmonary-physician and other health-professional members. I have no financial

relationships to disclose.

It is the position of the American Thoracic Society that the FDA should move forward quickly to delist CFC albuterol from the essential-use category and prepare the U.S. marketplace for the elimination of CFC albuterol.

There are four key reasons why the ATS supports delisting CFC albuterol from the essential-use category. First, I think it is important to keep in mind what is driving this process, the hole in the ozone layer. The fact that there is a hole in the ozone layer and that the hole is caused by human activity--namely, the release of ozone-depleting substances--is clearly established.

The good news is that the steps taken so far to reduce global use of ozone-depleting gases has helped reduce the size of the hole in the ozone layer. So, what the global community has been doing so far is working. The bad news is that the hole is still there and it will not fully repair itself until further reductions in ozone-depleting

emissions are made. Delisting CFC albuterol is an essential step for the U.S. to take in contributing to the global effort to preserve the ozone layer.

Second, the market is ready for a transition. There are two drug manufacturers who have FDA approval to sell HFA albuterol in the United States and there is a third manufacturer, as we have heard today, expected to enter the market in 2005. With three companies in the marketplace, there is appropriate competition to keep drug prices in check and appropriate manufacturing capacity to ensure that the U.S. market will be fully supplied with HFA albuterol. Delisting CFC albuterol should cause no albuterol supply disruption in the United States.

Third, the transition provides clinicians a teachable moment to review and improve asthma-care plans with their patients. I use the National Asthma Education and Prevention Program Guidelines for managing my patients with asthma and I encourage patients to know and avoid their asthma triggers, to use appropriate maintenance

medications to control asthma and to have immediately available rescue medications for acute exacerbations.

Despite my best efforts, I know many of my patients rely too much on rescue medications, underutilize their maintenance medications and don't take the simple steps to reduce exposure to their asthma triggers. The switch from CFC to HFA albuterol gives me an opportunity to, again, teach patients to know and avoid asthma triggers and to review the proper role of the many medications needed to manage their asthma.

I think our goal in the transition process is use the switch as a teachable moment to review and hopefully improve the care of patients with asthma. Delisting CFC albuterol will provide clinicians and patients alike an opportunity to review and improve their asthma-care plan.

Fourth, clinicians have experience helping patients get their medications. Several observers have suggested that the United States should not delist CFC albuterol from the essential-use

category because of the cost impact it will have on patients who use generic CFC albuterol.

It is true the price of HFA albuterol will be more than the generic CFC albuterol. So, if the FDA does delist CFC albuterol, the prices for albuterol will go up. Despite the cost proposed and the increases that are inevitable in medications and in virtually all aspects of healthcare, I am still able to provide, and my patients are still able to access, high-quality care.

The cost increase of albuterol in isolation from the rest of the healthcare sector cannot be used as justification for slowing efforts to reduce ozone-depleting gas emissions. The U.S. healthcare system will adjust. Clinicians have experience in assisting patients get the care that they need. Physicians and their office staff walk patients through the process of public and private assistance programs.

We use drug samples. We come up with alternative drug sources. We work with or around

insurers to ensure patients get the care they need. For example, if I write a prescription for a 90-day supply of medicine instead of a 30-day supply of medicine, the yearly co-pay to that patient will go down.

While there will be cost implications, the delisting of CFC albuterol will not increase access barriers to therapy for patients with asthma or other lung-related diseases.

On behalf of the American Thoracic Society, I appreciate the opportunity to present our views. Thank you.

DR. CHINCHILLI: Thank you, Dr. Marinelli.

Speaker No. 13. I want to committee to realize this is the last speaker.

DR. FINEGOLD: That is a great introduction. Thank you.

DR. CHINCHILLI: I didn't want to detract. I just wanted to get their attention.

DR. FINEGOLD: Well, thank you again for allowing me to participate in this meeting. I am Dr. Ira Finegold. I am an allergist and I practice

in New York City. I am also Chief of Allergy at St. Luke's Roosevelt Hospital in New York. I run the Allergy Clinic there and I am Director of the R.A. Cook Institute of Allergy.

I take care of asthmatic patients who are insured, pay out of pocket, and those who are covered by assistance programs. I am also a Past President of the American College of Allergy, Asthma and Immunology. This is a professional association of 4,000 allergists and immunologists dedicated to improving the quality of patient care through a research, advocacy and professional and public education.

I am also the College's representative for the last ten years to the U.S. Stakeholders Group who you are all very familiar with. I have no financial disclosures of significance.

We believe--and that is the College's position--that eliminating CFC-containing MDIs are important for the ozone-layer recovery, which you have heard so much about, improving patient outcomes. By that, we echo the previous speaker

regarding this as an opportunity to talk to patients about asthma and decrease, actually, the use of albuterol-containing rescue medication and increase appropriate therapies such as inhaled corticosteroids and, for allergic patients with asthma, allergy immunotherapy and, for some patients, anti-IgE therapy.

Also, we think outcomes do improve because some of the newer HFA products are actually superior devices and have less of the shortcomings of some of the earlier CFC-containing metered-dose inhalers. Also, we feel it is important to protect our patients to ensure a supply of rescue medication for them.

That leads to the whole question about the CFC supply and, as I come away from what I knew before and what I hear today, one thing I am certain is that I am uncertain about the supply. This becomes important to patients so that suddenly CFC-containing medication doesn't disappear without an orderly transition or that some of these other products that so far are not making the transition

to an HFA product still relying on CFCs are still available for patients such as Alupent, Maxair, and these drugs.

We think that the phase-out date of December 31, 2005 seems reasonable. From what we hear today and what we knew before, we believe the manufacturers can meet the demand and that, with the two products already on the market, that this is an acceptable alternative with the uncertainty of the CFC supply that is another imperative with it and, given the fact that sooner or later, CFCs will disappear, we think we might as well keep moving this process forward.

However, even though we are in agreement with this process and have been since its inception, we thoroughly recognize the cost of the transition cannot be ignored and, to some extent, it would seem that costs can be addressed by the competitive market by a certainty that this will occur with a given date so people will move things forward, and communication, informing our patients that rescue medication is not the whole treatment

for asthma and that we need to use controlling medication.

In effect, what we want to see is patients who use one or two canisters per year as opposed to the patients who use one canister of a metered-dose inhaler of a fast-acting agent once a month.

Thank you so much for allowing me to make these comments.

DR. CHINCHILLI: Thank you, Dr. Finegold. And thank you to all the speakers during the open public hearing session.

Committee members, I would ask that you indulge me a little bit. I would like to deviate from the agenda as we have it here. We are scheduled for a break at 2:30. I would suggest that we see if there are any questions of the speakers, if the committee members have any questions because I think we will need some uninterrupted time to have our discussion.

Before we do that, though, Ms. Jain has a statement that she needs to read.

MS. JAIN: I have a statement from the

Joint Council of Allergy, Asthma and Immunology. They submitted a written statement. However, they were unable to send a representative. So I am going to read that to you. Each of you have a copy in your folders as well.

"On behalf of the Joint Council of Allergy, Asthma and Immunology, JCAAI, whose mission is to act on behalf of the specialty of allergy-immunology and the patients it serves, we are writing to express our views on the pending issue regarding the possible removal of the essential-use designation of albuterol.

"While we support the removal of CFC products from the U.S. market, we are very concerned about the adverse impact that removal of CFC-propellent albuterol products from the current market would have on some of our patients due to cost issues.

"Currently, CFC-propellent albuterol products cost much less than the non-CFC albuterol products. By our analysis, the CFC-containing albuterol products cost, on average, about $22

while, at the same time, the non-CFC albuterol costs almost double at about $44 per inhaler.

"Removal of the CFC albuterol will double the costs of treatment for our patients. The consequences of such action will more than likely mean that some patients will forego their prescribed drug-treatment plan that will eventually lead to increased overall health costs through increased asthma attacks, increased emergency-room visits and, perhaps, death.

"According to a new study by the Agency for Healthcare Research Quality, AHRQ, May 18, 2004, increases in copayments for prescription drugs can lead to much costlier medical programs as asthma patients and others forego drugs and see their conditions worsen. This study found doubling the out-of-pocket copayments patients are required to pay resulted in a decline in the use of key drugs used to control asthma.

"We hope that these factors will be considered as the committee deliberates over this important issue.

"Sincerely, Spenser Atwater, M.D., President, JCAAI."

Thank you.

DR. CHINCHILLI: So, committee members, do any of you have questions of our speakers that we have had, the ten speakers we have seen this afternoon? Dr. Schatz?

DR. SCHATZ: I had a question for Mr. Rozek. There has definitely been the concern raised about cost but your analysis actually tried to present some data on that. I wanted to make sure I understand what you were saying that, given your simplifying assumptions and assuming no mitigating factors, you estimated 50 million canisters would increase in cost by $10 a canister--that is, the total cost to the healthcare system, approximately, leading to an increased cost during that first year of $500 million.

I wanted to clarify if that is, in fact, what your findings showed.

DR. ROZEK: Yes. We actually presented, in our comments to the docket, that total number.

I think it was $493 million, exactly. But that is to the entire healthcare system and that was the first-year impact.

DR. CHINCHILLI: Thank you. Committee members, any other questions? Okay; I have that it is 1:55. Let's take a fifteen-minute break. Please be back at your seats by 2:10 and then we will have our discussion for the committee members.

(Break.)

Committee Discussion

DR. CHINCHILLI: Committee members, you have been asked to sit through lots of presentations. You have absorbed lots of information. Now it going to be your opportunity to talk and discuss.

I would ask that you turn to the last page that is attached to your agenda because that is going to help us focus our discussion. So I will give everybody a minute until they are with me.

MS. JAIN: It is attached to your agendas, if you look on the last page of your agenda, after the rosters.

DR. CHINCHILLI: The FDA has listed three issues for discussion. We will take them in order. The first one, and I will read it for everyone's benefit, "Please discuss the extent to which you believe the criteria established in 21 CFR 2.125 for removal of a drug substance from the list of essential uses for CFCs have been met for albuterol."

There are the four bullets with the four criteria, so let us discuss them. We will take them one at a time. The first criterion is as follows: "At least two non-ozone-depleting substances, non-ODS, that contain the same active moiety are being marketed with the same route of delivery for the same indication and with approximately the same level of convenience of use as the ozone-depleting products."

So, is there any discussion. Do any committee members have any questions, comments, points of discussion, that they want to make about this particular criterion?

Dr. Moss.

DR. MOSS: I had a question for anybody here from the open public hearing part of it. It says at least two, but it was raised today that there might be more than that. I think that would be an important issue in terms of cost. So I was wondering if anybody from the IVAX people or some of the other companies here that can talk about where the other new drugs, not the SmithKline or Schering, are in terms of things and when they expect them to come to market? Or not?

DR. CHINCHILLI: Please identify yourself and your affiliation.

MR. FLANZRAICH: Hello. Once again, my name is Neil Flanzraich. I am the Vice Chairman and President of IVAX. Just to repeat, in terms of, in addition to the two present products on the market, IVAX has two NDAs currently pending at the FDA. One is for an HFA formulation of albuterol in a standard inhaler. The other is for an HFA formulation of albuterol in our patented breath-activated Easi-Breathe inhaler.

With respect to the standard inhaler,

which we filed in January of '03, in November of '03, we had an approvable letter from the FDA and we have responded to it. So it is in the hands of the agency. We filed our application, our NDA, for Easi-Breathe in August of '03 and that is also pending at the FDA.

So we hope, within some reasonable timeframe, both those applications can be approved and we will have two HFA albuterol products on the market. We are also informed, just having heard what was said publicly by another opportunity, Sepracor, that they are also developing an HFA formulation of a closely related molecule to albuterol, another short-acting beta-agonist.

So, presumably, that product--I think it is called Xopenex--in an MDI with an HFA formulation will, at some point, be approaching the market. I did make the point in my presentation that one can wait for an indefinite period of time for a generic to come. IVAX is one of the leading generic companies in the world. We chose to address this market and we thought it would

actually be a quicker route to the marketplace with an NDA, a new drug application. But that does not mean that we will not be responsive to the costs and the issues in this marketplace.

We said, for example, that the current asthma product that we have on the U.S. market, it is an HFA formulation of a corticosteroid. It is a maintenance medicine called QVAR. It is the only CFC-free corticosteroid, aerosol corticosteroid, on the U.S. market. We sell it at 50 percent of the average prices of the other products on the market in that category.

We certainly would expect to sell this at a competitive price and something that would benefit the marketplace. Really, IVAX has had a long history. I think we have a proven record of being committed to making medicine affordable. We were the first generic of the very product we are talking about removing from the market now, the CFC albuterols. In that case, and in many others which I could list, we like to think we have contributed to reducing billions of dollars from the costs that

American consumers have to pay for medicine.

We will certainly bring that same tradition and commitment to the HFA albuterol marketplace

DR. CHINCHILLI: Thank you.

MR. McVICKER: Hi. My name is William McVicker and I am from Sepracor. I just wanted to confirm that our company has, indeed, submitted an NDA for Leave Albuterol, an HFD MDI, within the recent pass. The availability of that on the market will obviously depend on the review to go forward from here.

DR. CHINCHILLI: Thank you very much.

Committee members, before we start talking more about the marketplace, that is actually going to be related to one of the other bullet points. Any further discussion or questions or comments about the first criterion, that at least two non-ozone-depleting substances, et cetera, have are available. Comments? Questions? Yes; Dr. Schatz.

DR. SCHATZ: I think I would just make the comment that no comments are probably interpreted

to mean that we believe that those criteria are fulfilled. But I think maybe we better clarify that.

DR. CHINCHILLI: Okay.

DR. SCHATZ: That we be my interpretation of the "no comments."

DR. CHINCHILLI: Since our committee members are so shy, are there any committee members who disagree with that statement? It doesn't appear so. Now, we are not really voting; okay? We are really just discussing and making recommendations to the FDA. So, unlike other advisory-committee meetings, we really are not taking person-by-person votes today.

So it looks like we can move on from that particular criterion. The second criterion was that supplies and production capacity for the non-ODS products exists or will exist at levels sufficient to meet patient need. We heard this morning and some this afternoon from different pharmaceutical representatives that they can ratchet up their production and think that they can

meet the need for non-ODS MDIs in the United States.

Any comments, discussion, questions from the committee members about this issue? Dr. Moss?

DR. MOSS: I will just reiterate what I said before. It seems to me that it has been well-explained that the companies could, within an 18-month period of time, increase their production to fulfill the marketplace.

DR. CHINCHILLI: Dr. Atkinson, you had a question?

DR. ATKINSON: Yes. I was just going to add that if the FDA acts expeditiously to set a deadline for judging CFC-containing albuterol MDIs as nonessential, then that will presumably set in motion the events that these companies need to ramp up their production. So it is really kind of dependent on what happens in the next several weeks or months.

DR. CHINCHILLI: Dr. Schatz?

DR. SCHATZ: I think that does bring up the question that I probably would like to hear

from the companies involved. In terms of the timing of this, before we were led to believe that, from the final rule, essentially, until implementation, companies would need 12 to 18 months. I wonder whether that is still the concept and is it closer to 18? I just sort of wanted to be sure, I guess, I understood that timeframe.

DR. CHINCHILLI: Any comments from one of the company representatives?

DR. GARUTTI: Ron Garutti, Schering-Plough. We did say that if the date were somehow magically to be announced tomorrow, we could be ready as early as December 31, 2005. And we believe that. For any date further out, however, we think about an 18-month timeframe is the appropriate lead time.

Now, the industry and Schering-Plough and 3M were kind of energized around this issue right now to do it. The longer this goes on, other decisions may have to be made. Other commitments may fall into place. So we are saying eighteen months now but who knows what the environment will

be if the date is not announced for another two, three years?

DR. CHINCHILLI: Thank you. Comments from any other company representatives?

MS. FLANZRAICH: Neil Flanzraich from IVAX. I just wanted to say that IVAX will be ready on December 31 of 2005 to supply--as we said, we have a capacity that will be 50 to 60 million units and we will be ready at that time. So, whether you tell us now or you tell us a year before or six months before, we will be ready then.

DR. SCHATZ: Based on an approval of your medication.

MR. FLANZRAICH: Currently, the products are not approved but we would have the capacity if the products are approved.

DR. JONES: Elaine Jones, Vice President of Glaxo. It would take us six to twelve months to ramp up to manufacture 15 billion MDIs. It would take us approximately twelve to eighteen months to ramp up to the total of 30 million MDIs. So, within eighteen months, starting from now, we could

manufacture 30 million MDIs of the HFA formulation.

DR. MARTINEZ: May I add another question? That would also be true if, at any time in the next year, the decision is made. There is no other alternative decision that the company needs to make that could change that?

DR. JONES: That's correct. We only would make the decision point--it would take us, say, six to twelve for the 15 and twelve to eighteen for the 30 million depending on, actually, when that decision point was made.

DR. CHINCHILLI: Thank you. Yes; Dr. Mitchell.

MR. MITCHELL: We have announced in the Unified Agenda, which is a publicly available document published in the Federal Register, that currently we are planning to publish the final rule sometime in March of next year. That takes into account the 60-day comment period, the complexity and sensitivity of the issue and the need to consult with our sister agencies on these very important issues.

DR. CHINCHILLI: Thank you. Any other comments on this particular criterion? Are the committee members satisfied with this? Okay.

Let's move on to the third criterion--oh; sorry.

DR. SCHATZ: I'm sorry. I guess the only thing I would say in response to that last comment is that if, in fact, the final rule is published in March and it calls for December of 2005, which is a nine-month lead, then I am a little concerned from what I have heard because that won't be the twelve to eighteen months.

Now, I realize maybe something could start now, but I guess I would question whether that--is that correct, that a final rule--do the companies think, or do other people believe, from what you are hearing, that if a final rule is published in March of 2005, that a December 2005 date is too early to have adequate supply?

DR. CHINCHILLI: Does the FDA want to respond to that?

DR. MEYER: I think that is something that

we would like to hear a discussion on. We have heard the statements from the industry as to what their lead time needs to be. As Mr. Mitchell had pointed out, we are talking today about a situation where we have just published a proposed rule. We will not be to the final rule until next spring, early-summer, range.

So December would be only then, perhaps, six, seven, eight, nine months at most. We are hearing from the companies that that may be faster than they could fully ramp up to produce. I think it is a difficulty at this point in time to know where in the mix the IVAX product may or may not be so that, obviously, the input from their company is a legitimate observation, perhaps, but, as of today, is speculation.

But I think it would be important, perhaps, if the committee shares your concern to hear a little bit of discussion about that issue.

DR. CHINCHILLI: Dr. Martinez?

DR. MARTINEZ: I think that, together with that, an additional issue needs to be taken into

account which is that, if there is a rule and it says that, say, December 2005, the rule will start to take effect, producers of CFC products will tend to decrease the amount of their product with time and there could be even a period which is not the period between twelve or eighteen but earlier during which there will be less CFC products and not enough HFA products.

I am concerned that, because of the issues of the market, the FDA needs to take into account issues like the one I have said so that patients with asthma are not going to be left with this product which is essential and life-saving.

DR. CHINCHILLI: Dr. Swenson.

DR. SWENSON: Just to the point of the timing of this transition. It is not written in stone that it has to be December, 2005. I think if it were pushed back one year, that wouldn't, in any large way, go against the spirit of this transition simply to make for practical applications and the ability to make the transition more smoothly. Am I correct?

DR. MEYER: I guess with the one caveat that we cannot necessarily predict what the response of the parties to the Montreal Protocol would be to, say, a December 31, 2006 timeframe. Otherwise I would agree with your statement.

With regard to what Dr. Martinez just said, I would state that the U.S. nomination for 2005, which included a substantial allotment of CFCs for the production of albuterol, has been approved by the parties. So we don't have any expectation at this point that there will be a shortage of CFCs for the production of albuterol through 2005.

So I can't definitively say that there wouldn't be some dropout in the market at this point but we at least expect that, as long as it is legal to sell these products, that the manufacturers would do so.

DR. CHINCHILLI: Dr. Reiss?

DR. REISS: I would just like to know what the factors are that lead to the March date why that date is March and not at an earlier possible

timeframe given the concerns that Fernando raised.

MR. MITCHELL: This is obviously a very sensitive issue. So it is something we would need time to consider. We are looking at a 60-day comment period. We need time to evaluate those comments. In response to the Advance Notice of Proposed Rulemaking which we published some years ago to set up, start the regulatory process, to allow us to use essential uses.

We received over 10,000 comments. We don't expect anything on that order of magnitude, but that is the thing that keeps me awake at night.

Then, in addition to that, to the inherent sensitivity, this is an issue which we, under the Clean Air Act, we have to consult with EPA because it implements the Montreal Protocol. We consult with the State Department. There is the Council in Environmental Quality so it is a very complicated rulemaking procedure and it does take time.

DR. MEYER: On the other hand, I did want to point out that, under the Montreal Protocol, we do have to--they have called for us to have a final

rule by the Open-Ended Working Group in the summer of 2005. That date has not been set yet but it is generally in June or July, mid-July.

DR. CHINCHILLI: Dr. Atkinson?

DR. ATKINSON: If I recall correctly, the Shareholders Group proposed a possible additional amount of CFC-containing product to be sold during 2006, I suppose, as a supplement. If there was a shortage, if there was a shortfall, how would that--if limited supplies in sort of quota fashion could be available. Would that be possible from the FDA's standpoint, I guess?

MR. MITCHELL: I mean, there are difficulties with that. If this final rule goes into place on the effective date, it will be illegal to sell, for any manufacturer to sell, any wholesaler to sell, any retailer to dispense, these drugs.

There is always the possibility of enforcement discretion by EPA but that is something I really can't comment on and, also, one wonders how many CFC MDIs would be produced when those

manufacturers are looking at an effective date. So I am not sure how viable that sort of option is.

DR. CHINCHILLI: Yes; Dr. Martinez?

DR. MARTINEZ: I expressed my concern in the face of these uncertainties that we are hearing about. I am not an economist, but I am sure that companies that are producing CFC products, in the same way that they need time to ramp up, they need time to ramp down.

I am not so sure that they can very precisely calculate until December 31. Again, I would need the help of an economist. How many of these products are going to be sold and, if they work for profit as they should, they are going to be on the safe side than producing excessively that they have to throw away if it is going to be considered later a poison that cannot be used.

So, at this point, my concern is that because needs to be done in a way that the transition occurs so that nobody is left without these products, which are life-saving, it would be very important to have guarantees that the products

are going to be available and that that transition is going to be dealt with in a way that the patients are going to be covered.

DR. CHINCHILLI: Dr. Moss?

DR. MOSS: Can we have some of the companies maybe talk about those issues. I know GSK doesn't make the CFC ones but maybe Schering can talk about how they were going to deal with the transition phase to make sure that patients are not without medications on December 25, Christmas Day.

DR. GARUTTI: Thank you. Ron Garutti, Schering-Plough. So we are the largest supplier of CFC albuterol inhalers. We are not going to walk away from this patient population. As long as the essential-use exemption remains in place, we will supply this product to the patients and providers who need them along with our HFA product. So you can be assured about that.

DR. CHINCHILLI: Dr. Meyer, did you have a comment?

DR. MEYER: I was just going to point out that I very much appreciate Dr. Martinez's

concerns. I think we certainly share those. But, to some degree, your concern is irrespective of the actual date that we are talking about. Whether it is tomorrow, whether it is ten years from now, that concern remains. I think it will entail the FDA working with the industry as well as the advocacy groups to assure that there is good communication and that the supply does remain adequate.

DR. MARTINEZ: Your point is very precise and very good.

DR. CHINCHILLI: Dr. Schatz?

DR. SCHATZ: Dr. Meyer, you raised the question as to whether, even if we or you decide that 2006 would be the better date, the Montreal Protocol decision makers may feel differently. It talks about criteria laid out by the parties for essential uses. Are those substantially different than these four, because it would seem, if they are not and we believe that the supplies won't be adequate, then the fact that would come to a different conclusion seems less likely. But maybe if you could explain what differences there might

be.

DR. MEYER: Let me answer that to the best degree I can. Up until the very recent past, and I, perhaps, didn't spend enough time on this in my slides, the Montreal Protocol very much deferred to the individual party to make the determinations within their own border, within their own use, what was essential and what was not.

Unless it seemed on its fact to be nonsensical or against the Montreal Protocol, those were approved. Obviously, over time, there has been a ratcheting up in terms of decisions, in terms of how closely the individual uses are looked at by the Protocol.

A lot of it now gets back to the decision IV/25 that we showed a few times where it basically says that if there are technically and economically feasible alternatives available, then the use is no longer essential. I think how that is interpreted perhaps has changed a little bit with as well.

So I think, depending on how rigorous you were in looking at what is a technically and

economically feasible alternative, you could say that these are sufficiently stringent or not sufficiently stringent. I think that it is just hard to predict at this point because it has been a little bit of a changing reality as far as how the Montreal Protocol has regarded the nominations.

DR. CHINCHILLI: So, Dr. Meyer, if the date were, say--went beyond December 31 of 2005, would the Montreal Protocol and the other participating countries have no real say in what happens in the United States but there could be some political fallout from delaying it much beyond December 31 of 2005.

DR. MEYER: Let me just be very clear. The reason I sort of raised this caveat before about the parties was just to make clear that we are not in control of all the variables here, but not to suggest, necessarily, that the parties would definitely find it unacceptable to go beyond December 31, 2005. I don't know, but I just wanted to say that that is really something we can't determine as an agency.

In terms of what you just asked, though, if we were to get to a point where we considered a use essential and pressed on, despite the Montreal Protocol telling us that they no longer considered that an essential use, then that might set up a scenario where we would be producing CFCs that they had not authorized us to produce. If that happened, we would be out of compliance with the Montreal Protocol, which I don't believe we want to do.

At least in principle, this is a very--as folks have said, this is a very successful treat. The United States has played an important role in the treaty and is committed to the Montreal Protocol. So, certainly, the best path forward would be one that meets our commitments to patient safety and access to important medicines but, also, meets our obligations under the Montreal Protocol.

DR. CHINCHILLI: Dr. Lutter, did you have a comment?

DR. LUTTER: No comment.

DR. CHINCHILLI: Dr. Martinez?

DR. MARTINEZ: Dr. Meyer, the decision, and looking here at your Slide No. 12, just as a point of clarification; Decision IV-25 that you showed to is that a plan could be presented in order to be in compliance with the Montreal Protocol and submitted by the Summer of 2005 for the continued use of CFCs.

So it could be that, if we all consider--and I am not saying that I am proposing that, but simply saying that if we would consider that since we cannot have the final rule before March that we could propose that this date is not December 31 but September, 2006. That could be presented as part of Decision IV-25 to the Montreal Protocol and be within the stipulations of the protocol.

Am I right.

DR. MEYER: I think that is a correct observation. Under that kind of scenario, I think it would be quite reasonable for us to point out issues of ramping up production in meeting the critical need of patients. So I think that would

still meet the spirit of what was asked for.

What is asked for in Decision IV-25 is for us to name a date-certain at which time we will no longer consider albuterol to be essential. It doesn't state to us what that date should be.

DR. MARTINEZ: I think the spirit of the committee, if I may say, is that sufficient time needs to be dedicated for us to be able to assure patients that this product will be there. Thus, I would say that a period of at least eighteen months from the moment in which a final rule comes out would need to be present for this to be fulfilled.

DR. CHINCHILLI: Mr. Mitchell?

MR. MITCHELL: In looking at dates, I think there are no finite legal limits to the dates the committee can look at or FDA can look at. Obviously, the longer in the future that we are, the more problems we might have with the Montreal Protocol. But, in the Notice of Proposed Rulemaking, our focus is basically we talked about dates between twelve months after publication of the final rule up to the end of this decade.

So that is sort of range we are focusing on. Obviously, people are free to comment, suggest any dates--in the next century, but I mean, how much consideration they will be given is another question.

DR. CHINCHILLI: Dr. Reiss?

DR. REISS: Just the comment that you just made, then, suggests that the end of 2005 data is really not possible at this point given the 12-month timeframe that you were just alluding to.

MR. MITCHELL: No; quite the contrary. Based on preliminary discussions we have had internally in FDA and externally, that is the range of dates we think are probably most likely. But if we are presented with data during the comment period, including the data that we have heard today, then there is nothing to stop us from finalizing a date that is any possible date. I mean, that was just suggested to try to help guide discussion or guide comments.

DR. CHINCHILLI: Dr. Jones, did you have a comment?

DR. JONES: Elaine Jones, GlaxoSmithKline. I just wanted to make one additional comment. We know that the data of the final rule is obviously something that would be that decision point but, in addition to that, I just wanted to say that some indication from the agency about what date they were considering, even without the publication of the final rule, would be sufficient for us to consider to ramp-up our manufacturing processes.

MR. MITCHELL: That is very difficult for us. The only way we can speak on this issue is through notice and comment rulemaking in the final rule. I could give you a date this moment, but it wouldn't be worth the paper it is not written on. So that is the way the Administrative Procedure Acts works and our hands are pretty much tied.

DR. CHINCHILLI: Yes; Dr. Reiss?

DR. REISS: Along the same lines, I would actually like to hear from my colleagues. If a date is published in March of next year and then the date that is published is the end of 2005, sort of given what you have said today, or given what

has been discussed about a year or eighteen months, how would everybody sort of deal with that issue right now? Would we start ramping up now or would you wait until March?

DR. JONES: Elaine Jones, GlaxoSmithKline. If the rule was published in March and it was December '05 timeline, as I say, we have committed to be able to produce 15 million MDIs within six to twelve months. It is not an impossibility to produce 30 and it would require considerable investment on behalf of GSK, and considerable time. So it is something that we had not discussed previously and so can't give a definitive answer.

But, obviously, if that is what the agency would like us to do, then it is certainly something that we would consider.

DR. GARUTTI: Ron Garutti, Schering-Plough. I have a proposal for you. The proposed rule, the rule that has been distributed outside today, is not yet published, as I understand it. It is theoretically possible. You will tell me why it is not practical. You could

withhold that for a day or two or three. There is a lot of information. You have already a lot of information from the major stakeholders that could lead one towards December 31, '05, as being a proposed date now subject to comment.

DR. CHINCHILLI: What is your reaction to that?

MR. MITCHELL: Complete and utter dismay. I, personally, started drafting this thing in August of last year. It will publish next week. There is absolutely no realistic possibility of us being able to make significant revisions to that document, clearing it through our sister agencies, clearing it through OMB and getting it published in any sort of meaningful timeframe that would allow us to get a final rule published in time for the Open-Ended Working Group that meets next summer.

DR. CHINCHILLI: I think we expected that response. Dr. Kercsmar?

DR. KERCSMAR: I think what we are hearing is that, in the absence of having a firm date, nothing will happen as far as increasing production

from the current manufacturers of HFA albuterol right now. So I guess I just need somebody to tell me that what I am hearing is that this date is not realistic, because I think what I am hearing, the corollary is that nothing will happen without a date and a date that is realistic.

MR. FLANZRAICH: Neil Flanzraich, again, from IVAX. Again, with the very important understanding that, of course, our products are not approved yet, I think I heard Glaxo say that it wasn't definitive that they would try to accommodate even a shorter warning period. We certainly, with the hope and expectation that our products will come to the market, are ready to supply a very substantial part of the U.S. market.

I am sure that Schering, even though they made a very good proposal just now, would also try. So I don't think you can assume that the answer is that there is no way that that date could be met.

DR. MARTINEZ: But, with all due respect, patients are not saved by trying. They are saved with the medicine available. While you try, they

may die.

MR. FLANZRAICH: But I think what you will get more definitive answers--people are saying they can't speak today, but you will hear, between now and the final proposal of the rule from the manufacturers, and they may be able to accommodate a shorter period of time. And then there will be the kind of clarity that you need for the patients. So we should not rule out the possibility of having this come into effect by the December 31, '05.

DR. CHINCHILLI: Dr. Moss?

DR. MOSS: I think it is important to reiterate what Dr. Martinez said. I mean, if we run out of these medications for patients, they will end up in the emergency room. There will be increased morbidity and potentially mortality. So I think, in this situation--I think everyone is sort of saying the same thing, but we should make sure we are playing it safe, that there is clearly going to be the supply of medications for these patients so that we don't run into that problem. That would not be a good thing.

DR. MEYER: Dr. Moss, can I just paraphrase what I think I heard you say just so I am clear for the record.

DR. MOSS: Absolutely.

DR. MEYER: To the degree that there is uncertainty in setting a date when the time comes for us to do so, what you are saying is that when we face those uncertainties, we should take a more conservative approach in setting the date that errs on the side of patient safety over sort of an aggressive timetable in terms of the environmental considerations.

DR. MOSS: What I would say is that the company said twelve to eighteen months. You know, if you thought twelve to eighteen months from July 1, it fits perfectly for the 18-month thing to think that now, all of a sudden, we are going to rush things and speed things up and hope it all works. I think there is a safety issue there. So I just wanted to note that.

DR. CHINCHILLI: Dr. Schatz?

DR. SCHATZ: Again, to be as specific as

possible, it sounds to me like the most conservative and, I think, acceptable approach would be to plan no sooner than eighteen months from the final rule because we have a lot of assurances that everybody can get ready by then. Anything else sounds like it could be just trying.

DR. CHINCHILLI: Dr. Meyer, I think you have heard the committee's feelings on this.

Any other final comment on this criterion? Okay. Thank you. Let's move on to the next one. "Adequate U.S. postmarketing-use data is available for the non-ODS products." So, were the committee members satisfied with what they heard today in terms of postmarketing data for non-ODS products? Any comments, questions? Is it related to their previous criterion? You are satisfied we have resolved this one?

Dr. Swenson?

DR. SWENSON: Just for the agency, we really didn't see any data regarding the safety and the track record. Can you give us a brief synopsis? I suspect, because they have been out as

long as they have, they are probably safe. But can you tell us so from your data monitoring?

DR. MEYER: I think for the purposes of the proposed rule, we really didn't contest that this was not the case. In other words, these products have substantial worldwide experience. We have some postmarketing, formal postmarketing data, available, particularly for the EM product as well as some analyses for the GSK product.

At this point, the postmarketing experience that we have seen, both from more formal data and from the informal safety reporting, is that these products do not appear to be substantially different from the CFC products in terms of how they perform. So we have not expressed any concern in that regard.

DR. CHINCHILLI: Dr. Martinez?

DR. MARTINEZ: Does the agency have information that will allow us to believe that puff-for-puff the two products are equally effective in producing bronchodilation?

DR. MEYER: The approval for these were

both based on comparisons to CFC products as well as--they stood on their own as far as safety and efficacy, showing of safety and efficacy, but they included programs where they were directly compared head-to-head with the CFC products.

Both in terms of the pharmacodynamic effect in FEV1 with one, two, four puffs, that type of consideration in sort of a short-term study as well in longer-term treatment studies, we didn't see any substantial differences. As was stated earlier by one of the manufacturers, and I forget which one--I think it was Schering-Plough--the mouth feel of these can be somewhat different. I am sure individual patients may feel some allegiance to one over the other.

But, in looking at those kinds of reports, we have a lot of reservations because I remember days when I worked for the V.A. and, depending on--back before there were generics available, the Ventolin source would shift from seemingly quarter to quarter. I know that those products were very, very similar at that time, the Proventil and the

Ventolin.

Veterans would come in saying, "You know, this one doesn't work as well as the one you gave me last month. I just doesn't." Unfortunately, both asthma and COPD are diseases where patients get better and worse irrespective of the specific medicine. But they want to tie it into something so, if their medicine happened to be changed at the time they were feeling somewhat worse, they blame it on the medicine.

So we do get those kinds of reports. But all the data in the NDAs at this point really showed very comparable results both in terms of the pharmacodynamics as well as how they looked in a 12-week study, treatment study.

DR. CHINCHILLI: Thank you. Mr. Mitchell?

MR. MITCHELL: There is a study we cite in the proposed rule. It was evaluating the vehicle Evohaler, which is the HFA inhaler marketed in the U.K., which is very similar to, but not quite identical, to the Ventolin HFA product. That study, even given the differences in the product,

does give us some assurance that we are not looking at any serious problems.

DR. CHINCHILLI: Any other comments on this particular criterion? If not, we will move on to the fourth one because I do believe we will spend some time on this. "Patients who medically require the ODS product are adequately served by the non-ODS products containing the active moiety and other available products."

Remember, the FDA is interpreting "adequately served" to include the economic issue. So who would like to start with this one? Dr. Schatz?

DR. SCHATZ: I think Dr. Garutti pointed out what I think we all believe, that this isn't a question of if, it is a question of when. But that "when," as in the proposed rule, has a lot to say in terms of the total cost of the healthcare system.

We have heard a lot of good reasons to make this transition as soon as possible, but the only thorn, as you could probably tell from my

questioning, is the extra cost, which it sounds to me is at least $500 million a year. Yes; there are some things that could raise it and some things that could lower it, but I think that that is as good an estimate as we could come to.

In a system that doesn't have unlimited resources, that is an important consideration. So that is going to be a problem, no matter what to some extent, but I just have to raise the concern. I would certainly like to spend that $500 million on something other than albuterol.

But I think the only real lesson is to make sure that however this transition occurs, we do it in a way that tries to mitigate, as much as possible. There are clearly some things that could do that, that extra cost. But that is a very disturbing number to me.

DR. CHINCHILLI: Dr. Swenson?

DR. SWENSON: I had some questions to Mr. Rozek about the NERA study, if he is here. I think he is coming to the microphone. I will go ahead and start my question. On your slide that was

entitled "Overall Impact on Patients and Third-Party Payers in the First Year," the final figure you give in the first year, increase in cost per asthma or COPD patient is $16.00 which doesn't sound that high.

But what I want to ask you is that that is a global average figure and the group that we are most concerned about is the cost-sensitive--those people that probably fall into the underserved category.

As I do my math here, I think that if there are 50 million MDIs prescribed in the United States per year and we say, for purposes of just simplicity, we have 20 million patients using those 50 million, that comes out to about two-and-a-half canisters per year. Am I right on that?

DR. ROZEK: Yes. In our calculation for the $16.00, we used 20 million asthma patients and 10 million COPD patients. So we added those together and got about 30, or slightly over 30, million, total.

DR. SWENSON: So that figure of $16.00,

then, is calculated in that fashion. But I am worried that those patients that may be most sensitive to transition here may be using probably one or maybe even more canisters per month so that the cost impact to them comes down quite heavily at maybe something around $100 per year.

Did you go into a breakdown on those costs?

DR. ROZEK: We looked at--to calculate that particular number, we used the total recalculated as a cost to the healthcare system and then the number of diagnosed asthma and COPD patients. We, then, pointed out, though, that there were other programs available to ensure access to people who might have difficulty affording one, two, three or four canisters a year such as the patient-assistance programs, Together Rx, GSK Orange Card, the public-assistance programs such as the D.C. Healthy Families, D.C. Healthcare Alliance. The additional samples would be available to people who would need additional canisters of the product as well.

So we felt that there were--certainly what we presented were average results and that there may be variation within that, some people using one canister, some people may be using three or four. For the people that couldn't afford three or four, there would be these patient-assistance programs.

DR. SWENSON: Do you, or possibly the companies, have any idea of the effectiveness of these assistance programs? Are they 80 percent effective to the target groups?

DR. ROZEK: I think we heard today from Glaxo in terms of the total number of people that have been helped with albuterol-specific programs. Glaxo has a relatively small share of the total albuterol being used today. I believe it is about 3 percent, and they were spending significant resources, or valuing the albuterol that went through their patient-assistance problem quite significantly for that 3 percent marketshare that they currently have.

Schering indicate they had a similar program. I would assume that Glaxo would expand

its program as its marketshare expanded and that there would be more people who would be aware of the Glaxo program as a result of information available about the Glaxo product.

DR. SWENSON: While I have you up here, just one more question, slightly different, and that is you made what appears to be a very conservative, maybe almost worst-case, scenario here because you simplified and didn't assume any changes in the outreach of the companies and other changes that they might do and the way prices may fluctuate.

Given that we might have maybe two more and possibly other players in this market, what number of companies competing really make a difference in price. There might be examples within the pharmaceutical industry on this issue or maybe more broadly in the business world. What number of competitors really begins to make a difference on price? When does competition really come into play?

DR. ROZEK: That is an interesting

question that economists debate all the time. Many of the answers that relate to specific industries--when I worked at the Federal Trade Commission, for example, there was a study that one of my colleagues there put out that we used to use in deciding when to bring merger investigations. It had to do with the strong third-firm effect.

When you have a strong third firm in the marketplace, that was effective at alleviating any market power that the first two firms might have. So if you were looking at a merger of two firms that would create a strong third firm, that was considered to be a beneficial effect on market competition.

But, again, this is an industry-specific issue. Interestingly enough, I did a study on competition in the pharmaceutical industry from the following perspective. I looked at all of the products that were identical chemicals. Ventolin and Proventil appeared in that list, if you looked at data from the late '80s and early '90s. Erythropoietin would be another example of that

kind of competition where they were identical chemicals--no generics--identical chemicals marketed by the branded company.

You can see, when you have only two, in that particular case, you get a lot of competition for marketshare, for getting onto formularies, for disseminating information about the product and distinguishing the product one from the other even though they are the exact, same chemical in terms of what kinds of patient-assistance programs are available, what kinds of benefits you can provide to patients other than the drug, itself, in terms of registries for use of the product and reminders and that sort of thing.

So, in the pharmaceutical industry, I did do a study of competition between two players when it was the exact identical product and there was no threat of generic competition. You can see there that marketshares move quickly back and forth and that prices do respond in a downward direction when the two are there, assuming that you have enough big buyers who can move marketshare and can extract

that kind of gain.

Now, that is not to say that the gain flows to everybody from that type of competition because it does help to have a very aggressive buyer side of the market to gain that. But I would say generally a strong third firm is very helpful. If you look at the Department of Justice-Federal Trade Committee Merger Guidelines, they like to see about five equally sized firms in a market. But sometimes they will approve mergers with four.

I think we are approaching, in the case of albuterol with Sepracor and with IVAX and with the availability of licensing opportunities from 3M, for example, to anyone who has an albuterol product they want to package in the HFA technology, that threat of competition, as well, adds to the overall competitive structure in the marketplace.

So two could be enough for competition in a pharmaceutical product, three for sure and, if you are going to four or five, you wouldn't have even any problem with the Federal Trade Commission or the Department of Justice, in my view, saying

anything was amiss in that kind of a market structure.

DR. CHINCHILLI: Thank you, Dr. Rozek, for answering those questions. Further comments, statements from the committee? Yes; Dr. Lutter?

DR. LUTTER: If I could offer one piece of data in response to one of the questions just asked, we looked, as I described, at the MEPS data, the Medical Expenditure Panel Survey. Among the people surveyed, which is the noninstitutionalized, under 65, population, if you look further at those who have family incomes less than 400 percent of the poverty line and who are either uninsured or who have non-group insurance, they had 3.8 prescription per year for albuterol MDIs.

DR. CHINCHILLI: Dr. Martinez, did you have a comment?

DR. MARTINEZ: No.

DR. CHINCHILLI: Dr. Moss?

DR. MOSS: I have a question for some of the companies. This is not the first country where we talk about transitioning so this has happened in

other countries. Realizing the healthcare systems work differently, but what happened in the prices of the Proventil and Ventolin HFA in other countries where this has been approved? Did their prices go down? If so, why?

DR. CHINCHILLI: Anybody respond to that?

DR. JONES: Elaine Jones, GlaxoSmithKline. As you said, actually, the pricing system in the European countries where we have done this and also in Australia and Canada are totally different. So the scenario can't be applied.

DR. MOSS: Good. Now that I have you up here, what is the price compared--if you convert to American dollars, how do these products compare in other countries compared to the United States. That is really what I wanted to get you to say.

DR. JONES: Actually, I don't know the price. I don't know whether any of our commercial colleagues here know the price of Ventolin HFA across Europe. I don't think we have that information here, but we could--sorry; I don't have that information.

DR. CHINCHILLI: Any other questions, comments, from the committee? Dr. Martinez.

DR. MARTINEZ: I think this is the issue. For any practicing physician, this is the issue because, particularly for the pediatrician, the main group of patients that we see with severe asthma coming to our emergency rooms are minority patients who are either in poverty or are disenfranchised or don't speak good English or have many of the other difficulties that make them particularly susceptible to severe disease.

Thus, considering this very attentively is a need because our main objective is to provide the public with the best possible medicines that we can have at prices that are affordable and that will allow them, in this case, to survive because this could be a life-threatening disease.

The main concern I have is the conflict in which, in this case, is not a conflict of interest of but a conflict of care. We all care about the earth and about the environment and we all would love for it to become better and better.

Certainly, there are many other ways, by the way, in which we could make it better, but I know that we are not discussing this here. We are discussing this issue very specifically.

What we are asking the public, and that is the first point I wanted to make, is to spend, according to the proposed document that Dr. Mitchell has so clearly written, that, in the best possible scenario if the rule comes in 2006, the public will transfer to the pharmaceutical industry $6.9 billion between 2006 and 2015.

That will happen because, as a society, we have decided that we will take care of the environment. If that were the society as a whole, the issue would be clear and simple. But my opinion is that it is not. The reason why I say that is that, although we have been given means of distributions of cost by patient, any practicing physician knows that these distributions are so tremendously skewed that, in this case, the mean has no meaning.

Most of the patients who really spend most

of the money are a small group, perhaps 10 percent of all patients with asthma, who spend probably 80 percent of the cost. That is not only for hospitalizations. It happens that those patients are primarily poor, disenfranchised, and not participating in the system, not knowing about the system, no knowing about their rights.

I was telling about an anecdote. Two or three weeks ago, I was on call. A young girl who I had followed for two years and not seen for two years came to the emergency room dying of asthma. When I asked the parents why is it that the girl was there, they said, well, we didn't have money to buy the inhalers and we didn't even have money to buy the albuterol. But you have the right. They didn't know that they had the right.

Now, this is not going to change from one day to the next. So the difficulty when we take a measure like this and when we do something like this is that we affect, or may affect, significantly the lives of a lot of people. That needs to be considered because it is part of our

everyday life in our practice.

I do understand, and I commend them for that, that industry has made significant efforts to palliate this by providing for free these products to individuals and patients who will not have access to these products. The difficulty is that, in the same way that those patients don't know of the existence of these rights that they may have in many states, even if they don't have insurance for their children to have insurance, they also don't know about these systems and, thus, cannot use them, don't have the opportunity to use them.

The greatest difficulty, then, is that I think this ruling, or this rule, inevitably, by the way in which our system is built, will significantly affect the poor and the disenfranchised and that, unless an effort is made, and I haven't heard of any systematic effort to ensure that this will be palliated in the best possible way, like it has been done with other measures that, as a society, we have taken.

For example, for persons with disabilities

now, we have a lot of things that are going well for them, certainly, they are not enough. But society, as a whole, is paying a price for that because, for example, at least in our state, businesses that put up ramps for people who need them and that are disabled can get a tax cut, or something of that sort.

I don't see any of those measures being thought about here and I am completely convinced, given my experience in my practice, that this will significantly affect the disenfranchised and the poor.

So, in the end, what we are really doing is, for the sake of the atmosphere which will be good for all of us, we are, once again, charging the disenfranchised and the poor. I don't know if there is a solution for that because of the way in which our system is made, but, for a practicing physician, this is something that cannot be denied.

It is true, as a representative of the American Thoracic Society said, and I completely agree with him, that many other costs are

increasing and that, in the end, we cannot, every time we make a decision, think about who and whom is going to be affected. But I think it is very important for us to take all these issues into consideration.

DR. CHINCHILLI: Dr. Moss.

DR. MOSS: That is why I asked the question about the marketing for these programs because I agree with you. I don't see them--you know, the companies talk about hundreds of thousands of people but I don't know about them and I don't think a lot of people know about them.

I think there are other trickle-down effects which is what I talked about before where only 6 percent of the medications are prescribed in the hospital. Everyone is worried about the retail side of it, but there are indigent-care hospitals around the United States where they are on the means of falling apart. I mean, all these hospitals--and there are huge financial strains. Maybe private practitioners outside of Chicago can deal with stuff, but those of us that care for the

indigent-care patients, it is about to fall apart. It is cracking and crumbling.

States are not giving the money back. The pharmaceutical budgets are going up. Activated protein series Agras is a good example of that. They were afraid that that one compound might destroy the entire Grady Hospital system. It is a $7,000 drug and it is very expensive. Different situation here. Not as expensive, but a much more common disease.

So I agree. I think that is the bottom line is the cost issue here and the companies need to address that. That is why I asked the question in a round about way, how much do these medications cost in other countries. If they are less, why are they less and how are the companies going to deal with this issue. I think everyone agrees that this needs to be done, but the cost issue will impact patient care.

DR. CHINCHILLI: Any response from the companies? We heard about some of your programs this morning. Okay. So committee members? Do you

have any specific recommendations to the FDA in proceeding forward with this, in terms of the economic issue, in terms of the problems that the poor and the indigent will encounter with their asthma because of this? Dr. Schatz?

DR. SCHATZ: The one thought that comes to my mind is that the longer the transition period, presumably the more certain things might happen in terms of additional competitors, additional experience with what is going to happen. I mean, again, I think the concept of thinking of some more specific ideas and things that various people, including the companies, could do to mitigate it is important, too, but it does seem like that the longer the timeframe involve, the less this impact would be, not only because it becomes a year or two or three closer to generic, but other market factors as well.

So I guess that would be my most immediate thought.

DR. CHINCHILLI: Dr. Moss?

DR. MOSS: Not to sound too wishy-washy

here, but, on the flip side, I think it is very important that companies have made the effort to come up with environmentally friendly medications and should be commended for that and receive some compensation for that. So I think that would be a bad precedent to say that this stuff is not important to go through.

So, as I just said, the price is an issue but I think this has to be looked at a little as an issue longer term, that the message should not be given to pharmaceutical companies that having environmentally friendly strategies are not felt to be important.

DR. CHINCHILLI: Any other comments, recommendations by the committee? Dr. Jones?

DR. JONES: Elaine Jones. We talked a lot about Bridges to Access as well as the other GlaxoSmithKline programs. We have endeavored to reach everyone and we have done considerable things in order to be able to reach everyone. We try. Obviously, we haven't reached everyone. You haven't heard of some of the programs that we have

done, but we are committed to actually getting our message to everyone and are willing to work with the agency in means to achieve this.

We have, currently, 435,000 patients registered in the Bridges to Access program which actually gives free medicine to the population that you are speaking about. There is no ceiling to that. Any patient who is eligible will receive medicine and they won't just receive one medicine. They will receive Ventolin or any preventative medicine as well if they are prescribed.

As I say, we will continue to strive to get the messages about GSK's programs to everyone and, as I said, we will work with the agency, if they have any ideas about how we can expand and get these messages across. We believe it is a very valuable program.

DR. CHINCHILLI: Thank you. Dr. Schatz?

DR. SCHATZ: Again, I don't want anything to think that I also don't appreciate the efforts of the pharmaceutical-company industry in trying to respond to this, but, again, the cost issue--but I

wanted to raise that there has been an emphasis on the people who would be eligible for the Bridges to Access and similar programs and that is appropriate. This is clearly an impacted group.

But I take care of the working patients in an HMO and I can tell you that these patients, who would absolutely not be eligible for this, are also impacted when their co-pay goes from $10 for a generic to $25 for a brand. We have had some changes recently that we are hearing from a lot of patients. These change make a difference also.

So, while I absolutely agree that the typically impacted may be more impacted, this is something that is going to affect, as the whole healthcare crisis is more and more, a much bigger segment of society, and I don't think we can forget that either.

DR. CHINCHILLI: That is a good point. Dr. Reiss?

DR. REISS: I just wanted to point out that, while everyone is raising really good issues, we are really not here to debate the healthcare

system and how the healthcare system works. We are here to debate the merits of making this transition and its impact. A lot of the things that have been raised really have to do with the form and structure of the healthcare system and not necessarily whether this is an appropriate or inappropriate thing to do.

DR. MARTINEZ: I respectfully disagree because, if I read correctly, it says, "Patients who medically require the ODS product are adequately served by non-ODS products containing--," and one of the issues that we have been told that needs to be considered is cost. We are not discussing the healthcare system here. We are just reading very precisely what it says here. Here it says, very precisely, "If they are going to be adequately served by non-ODS products containing the active moiety."

Well, if they can't buy them, they are not being adequately served. So it is not an issue of the healthcare system. My opinion is that a significant number of patients are not going to be

adequately served. I am not saying that what we have to recommend or our opinion should be that this is not done. It is just very important for those who make the decision to understand that.

DR. CHINCHILLI: Dr. Schatz?

DR. SCHATZ: Again, I would just add that what we are talking about is a change in our healthcare system, so we have to bring up our healthcare system. I don't think anyone that I have heard has done it to discuss the healthcare system. It is how this change makes an impact in our healthcare system.

DR. JONES: Elaine Jones, GlaxoSmithKline. I just wanted to make one additional comment to the previous comment. The current marketplace has no samples in it, professional samples, or very few for albuterol CFC. GlaxoSmithKline has committed to giving at least 2 million professional samples each year during the transition periods.

DR. CHINCHILLI: Dr. Meyer, and Dr. Sullivan, you have heard some of the discussion by the committee members. Do you have any reactions,

any comments? This is a dilemma, this particular issue, and we knew this would be the thorniest issue to deal with.

DR. MEYER: I would just say that I very much appreciate the thoughts that we have heard expressed and I actually would also like to express, again, thanks to the people who are making public statements including the regulated industry.

I think you understand our dilemma in proposing the rule and I think we will get to questions--or, not questions, but points, subsequent here whether there is anything else that you think we could ask for or other things that you would suggest that we do to help us get to a final rule.

So we very much appreciate the comments and look forward to any suggestion you might have as to ways to sort of help get through this dilemma. This is a very important issue.

DR. CHINCHILLI: Why don't we use that as a segue, then, into Items, Issues, 2 and 3. Committee members, please suggest any additional

data or information you believe would be important to consider in making a determination regarding the essential-use status of albuterol. Also, please comment on any additional issues you believe would be important to consider in making a determination regarding the essential-use status of albuterol.

Is there anything we can recommend to the FDA, to the agency, about any additional data or information that might help them proceed with this decision? Dr. Moss?

DR. MOSS: I don't know if it is possible--it sounds like a lot of this economic stuff is based on a lot of assumptions, but it might be helpful to see how the economic impact would change if there is a third or fourth drug since, if that is not going to happen right away, that might happen down the road, and it might lower the burden of the economic impact which would address the issues that everyone has raised here.

So I don't know how feasible that is, or how good the data is, but that might help give better information upon the effect of cost. If the

cost goes down, then there would be more access to patients and the negative effects of not having access to medications would be alleviated to some extent.

DR. CHINCHILLI: Dr. Swenson?

DR. SWENSON: If I could ask the agency members here, and, again, this may be beyond your powers and your charge, but, in going before the Montreal Protocol for these medical exemptions, have the issues, not so much of the availability of other products that are satisfactory and equal but, in fact, the issues of the cost implication to patients, been discussed? Do they turn a deaf ear to these discussions?

I get the sense that we are being pushed to come to full compliance here and we have such a unique situation in the United States that, in this case, has the case been made to attempt some, at least prolongation of this transition to allow for the peculiar and unique nature of our healthcare system?

DR. MEYER: I certainly don't want to

characterize the Montreal Protocol, the response of either the body as a whole or individual parties to these kinds of considerations but, yes, the issue of the unique circumstances of the United States healthcare system and the impacts that are more significant in the United States, we don't have numbers to talk about here, but I can assure you that the differential we are talking about here is greater in the United States and the overall cost of these medications is greater in the United States than the other countries that have been referred to where the phase-out has occurred for albuterol.

Those issues have been presented and argued to the meeting of the Montreal Protocol.

DR. CHINCHILLI: Dr. Lutter?

DR. LUTTER: Let me offer another insight in response to that same question. I was in Nairobi last October, November, where this most recent decision by the Montreal Protocol parties was taken. At that time, the decision on the table was what would be the date by which each party

would have to set a date-certain to delist.

But also on the table was a proposal to set a date-certain. We offered two explanations to other parties in the Montreal Protocol. One is that we have an Administrative Procedures Act. We have a very different form of government than a parliamentary system that exists in other countries. That lays forth a different process for delisting that, necessarily, is more time consuming but also, of course, the economic one.

I think the sympathies were mixed. Some countries were much more attuned to the idea that the U.S. system is unusual if not unique and others view this is a problem that we would have to solve.

So I am not sure I have clarified the understanding very much, but it was brought up, it was debated, and we had sort of a mixed reaction.

DR. CHINCHILLI: Committee members, I don't know if we are running out of steam or we just have nothing else to offer. This is complex. Any other comments, recommendations, questions?

DR. MARTINEZ: May I ask a question?

DR. CHINCHILLI: Sure. I am begging for questions.

DR. MARTINEZ: Members of Congress and state legislatures and so forth are considering the possibility of opening the U.S. market to importations of medicines from other countries with the idea that this could decrease costs of these medicines. In which way such a process would, or will, affect--I am asking the agency--issues regarding this particular medicine. This is from a person who lives 60 miles from the border and knows how much these medicines cost in Nogales, Arizona.

MR. MITCHELL: By the terms of our regulations, we are really focussing on products that are approved in the United States. We cannot really consider prices or supplies of drugs in Canada, Mexico or any off-shore sources. The answer is no, we are not really looking at those sorts of issues in this process.

DR. CHINCHILLI: Dr. Schatz?

DR. SCHATZ: I mean, again, the only other perspective or question--there are a lot of things

we have heard about that theoretically could mitigate what we are all concerned about but that is nothing that can be written into a rule, I would guess. We could all hope it happens.

So I think we do need to focus on what sorts of things this rule could do to mitigate this. That is where I said that the only thing I can think of is delaying it some. Again, I don't like the idea that that doesn't reward companies that we should feel positive toward who have taken these steps towards something we all eventually want.

But I can't think of any other way to write this rule in a way that makes a certainty less of a financial impact. I would open that up to other people because everything else, while I hope it happens and it could happen, it is actually nothing that I can think of that the rule can do anything about.

DR. CHINCHILLI: When we discussed the issue of patient safety with one of the previous criteria, it is related to that, that waiting, not

shooting for December 31, 2005 when the announcement may not appear until March of 2005, there is an issue of concern about patient safety and enough inhalers being available. So I think, yes; the two are tied together.

Yes; Ms. Schell?

MS. SCHELL: I guess I need a point of clarification probably from the companies. But if this is inevitable that this will be going to happen but the date is unclear and it may be delayed, why can't you start production eighteen months anytime and still be ready for whenever the date appears?

DR. MEYER: I was going to answer on their behalf, but I will let them answer.

DR. GARUTTI: Ron Garutti, Schering-Plough. It is not in anybody's interest for the industry to produce a great deal of HFA product that is not going to essentially really be used until the kind of behavior change that we alluded to, provider- and patient-wise, has the impact of, this is here, this is now, this is

happening and everyone is focused on it.

It would not be to any of our interests for a product to be produced and run past its expiration and have to be destroyed.

MR. MITCHELL: Also, to reiterate a point that was made earlier, the companies would be expending large amounts of capital in order to get this capacity on line. To ask them to spend that capital and then not generate any revenue with it seems, just as a personal point, to be somewhat impractical.

DR. CHINCHILLI: Committee members, last change. Final comments, questions, issues? Dr. Reiss?

DR. REISS: Just one other point to follow up on the questions about the economic analyses that we were talking about before. It might also be helpful to do a more detailed economic analysis where we are talking about mean values, and one might be hidden within those mean values and what not, to be able to really sort of understand who is the real population at risk that might be affected,

might shed and provide some additional light on the topic as a follow up.

DR. CHINCHILLI: Thank you. Dr. Meyer, it looks like the committee has exhausted itself.

DR. MEYER: I am not sure whether there were any other observations. We asked about data and so on, but I guess the other thing is you have perhaps, or hopefully, had a chance to read through the proposed rule. You have certainly heard a lot of presentations and discussion today. Is there anything else you think we are missing in this? Is there some other element that we need to consider that we, perhaps, haven't considered?

It is perfectly acceptable if you don't have any, but I just wanted to be clear on that, whether there is anything else we have missed.

DR. CHINCHILLI: I guess not.

DR. MEYER: If not, then I would like to certainly thank you all for your careful deliberations today and for your attendance, your thoughts. This, obviously, has been quite an undertaking to get to this point and I think we

will take very careful thought on our part moving forward. We appreciate your adding to the considerations that we need to take as we do move forward.

I would state that, apart from this effort with the albuterol, the transition to non-CFC products is actually, I think, by and large, going to be easier and more natural with some of the other products. We have already seen, as I have pointed out in one of my slides, a fair amount of transition occurs already.

Albuterol is the only MDI for which generics are available. To date, it appears that the HFA alternatives are priced quite comparably to the branded products that they replace. I guess in the case of QVAR, it might even be somewhat lower than the branded products.

So, where there is not generic competition, where there is sort of one-on-one replacement by the same companies and so on, a lot of these issues go away. There will still be occasions where we will come back to this committee

for products that are not being reformulated, as mentioned this morning, and I suspect epinephrine will be a particularly interesting discussion in the not-too-distant future.

But, for the purposes of today, I thank you. I thank Dr. Chinchilli for serving as our Acting Chair today and look forward to future discussions with the committee. Thank you.

MS. JAIN: Before the meeting is adjourned and the committee members leave, if anyone would like to have their background information mailed to them, please just leave them at your seats with your name tag. We are happy to do that for you.

Thanks again to all of the open public hearing participants and the time that they took to do their detailed research, present and submit written and Powerpoint presentations. Thank you.

DR. CHINCHILLI: Thank you, everyone. We are adjourned.

(Whereupon, at 3:38 p.m., the meeting was adjourned.)

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