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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEETING
TO DISCUSS FDA ANPR ON THE CFC PHASE-OUT PROCESS

Friday, April 11, 1997

8 o'clock a.m.

Maryland Ballroom
Quality Hotel
8727 Colesville Road
Silver Spring, Maryland

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P R O C E E D I N G S

Welcome

DR. MURPHY: Good morning. I would like to welcome you to the Pulmonary-Allergy Drugs Advisory Committee meeting on this hopefully warming-up day of April. I think we are going to have a very, very interesting discussion today and I just want to point out to everybody that the law has already been written.

The United States and the whole world is in compliance with phasing out the CFCs in non-essential medical uses, and what we are doing now is that this is part of a three-step process that you are going to hear more about, and this is a preliminary phase.

The FDA is really now pausing to get input from all of us about how this should proceed. So what we are going to do today is we are here to discuss how the FDA should come into compliance with the medical uses of CFCs.

We are not going to take any votes, and this is really directed to the panel. We are not going to ask for consensus. What the FDA would like is to really hear your individual comments and recommendations. Possibly at another step there will be more voting, et cetera, but not right now.

I think we are here to discuss things, not to

debate them. I want to make sure that we include the people who are going to make public comments, and I may ask you later this afternoon to make another comment. I want to include the EPA, the FDA, and all the panel members, because I think what we want to get out of this is a very, very good discussion.

Dr. Jenkins, do you want to make any comments before we go around? No? Okay.

I would like now to go around and have everybody introduce themselves, to state their name, where they are from, and what they do at where they are from, and anything else they would like to add.

MS. HUFFORD: We are starting at this end. I will start. I am Drusilla Hufford, Acting Director of the Stratospheric Protective Division at EPA.

MS. O'DONNELL: Good morning. I am Chris O'Donnell with the Environmental Protection Agency, and I am the Essential Use Program Manager for essential uses under the Clean Air Act and the Montreal Protocol.

DR. BILSTAD: Jim Bilstad, FDA. I am Director, Office of Drug Evaluation II.

DR. OTULANA: Good morning. I am Babatunde Otulana. I am a medical reviewer in the Pulmonary Drug Division of the FDA.

DR. JENKINS: I am John Jenkins. I am the Director of the Division of Pulmonary Drug Products at FDA, and, Dr. Murphy, I do have a couple of comments I want to make after we make introductions.

DR. SZEFLER: I am Stan Szefler from Denver, Colorado, panel member.

DR. HENDELES: Leslie Hendeles, University of Florida. I am a consultant to FDA.

DR. OSBORNE: Molly Osborne, Oregon Health Sciences University, VA. I am a pulmonologist.

DR. CRIM: Courtney Crim, St. Louis University Health Sciences Center, a pulmonologist.

DR. LIU: I am Mark Liu from Johns Hopkins Asthma and Allergy Center, in allergy and pulmonary.

DR. JENNE: I am John Jenne, adult pulmonology until recently Loyola and VA Hospital.

MR. MADOO: Leander Madoo. I provide administrative coordination to this committee.

DR. MURPHY: I am Shirley Murphy. I am a pediatric pulmonologist and allergist for the University of New Mexico.

DR. CROSS: I am Carroll Cross. I am an adult pulmonologist, University of California, Davis.

DR. LI: James Li, Allergy, Mayo Clinic.

DR. AHRENS: Richard Ahrens, pediatric allergy and pulmonology at the University of Iowa.

DR. BARANIUK: Jim Baraniuk. I am an allergist at Georgetown University.

DR. CHINCHILLI: I am Vern Chinchilli, biostatistics, Penn State, Hershey Medical Center.

DR. SESSLER: Curtis Sessler, pulmonary and critical care at the Medical College of Virginia.

MS. MITCHELL: Berri Mitchell, clinical nurse specialist in Overland Park, Kansas, consumer advocate.

DR. MURPHY: Thank you.

Dr. Jenkins.

DR. JENKINS: I just wanted to take a second to thank all the members of the committee for taking time from your very busy schedule to attend today's meeting. I think it should be a very interesting discussion and we are looking forward to hearing your comments.

I also wanted to thank our two consultants who are former members of our advisory committee, Dr. Ahrens and Dr. Hendeles, for joining us today also.

On a little bit of a sadder note, today is probably the last advisory committee meeting for a couple of our current members, and I would just like to take a moment to recognize those two members for their outstanding

services to the committee over the past several years.

The first is Berri Mitchell, who has been our consumer representative now I think for four years. She has done an outstanding job, and we will miss her when she leaves the committee.

The second person is Dr. Murphy, who is our current Chair, and has been also an outstanding member of the committee for the past four years.

Again, we have appreciated the services that you both have provided. You have been very dedicated and loyal members of the committee. You have attended almost every meeting that we have had during your tenure, and you have offered some very sage and wise counsel.

So, thanks again for your service on the committee, and as you know, we frequently invite former committee members back as consultants. We hope we can count on you to come see us again in the future.

Thanks.

[Applause.]

DR. MURPHY: Dr. Madoo, would you like to read the conflict of interest statement.

MR. MADOO: Certainly. I would also prior to that like to note that we are very pleased to have Brenda Conner, LPN in the audience as a guest. Brenda, would you like to

raise your hand, please. She will be succeeding Berri Mitchell, and I second Dr. Jenkins' comments. Berri Mitchell did an outstanding job as consumer rep and we are pleased to have another outstanding candidate rotating in.

Some administrative notes. You may note that you have been deluged by a lot of handouts. These handouts represent either slides or hard copies of the presenters' testimonials. They may deviate somewhat from the hard copies you have in front of you. The transcript will constitute the official record of the meeting.

There was one individual who, in lieu of public comment, sent in their comments, and this was a Dr. Paul D. Scalon, M.D., Pulmonary and Critical Care, Mayo Clinic, and a copy of his remarks have been provided to all committee members and are in your folders.

I will note that all this information will be part of the public record and go to docket, so after the meeting, people can, in fact, refer to this material.

Another aside, I appreciate your bearing with me here, you will note as mentioned before that there are no questions per se in a formal sense appended to your agenda. There is one page provided, and it is simply the first page of the Advanced Notice of Proposed Rulemaking.

You will note that what is boxed relates to FDA's

happy intent to receive written comments up to the date of May 5th, 1997, and the point of contact for the information is also noted relative to those comments.

That about encompasses my general comments. Now on to the conflict of interest statement.

Conflict of Interest Statement

The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. 208(b)(3), full waivers have been granted to Dr. Stanley Szeffler and Dr. Mark C. Liu.

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

We would also like to disclose for the record that

several of the committee participants have current or past involvements which we believe should be made part of the record.

Dr. Li's employer, the Mayo Clinic, is negotiating with Glaxo Wellcome for a contract for a study, which he believes will concern the development of replacements for CFCs. Dr. Li will have no involvement whatsoever in the study.

Dr. Richard Ahrens' employer, the University of Iowa, is the recipient of two grants, sponsored by 3M Pharmaceuticals, which concerns the development of replacements for CFCs.

Dr. Courtney Crim's employer, the St. Louis Health Science Center, in the past was involved in two Glaxo sponsored studies which concerned the development of replacements for CFCs. Dr. Crim has no personal role in either study.

In accordance with 5 CFR Part 2640.202(a), Interpretation, Exemptions, and Waiver Guidance Concerning 18 U.S.C., Drs. Li, Ahrens, and Crim will be allowed to participate fully in today's discussions.

With respect to FDA's invited guest, Ms. Brenda Conner has reported interests which we believe should be made public to allow the participants to objectively

ajh

evaluate her comments. Ms. Conner would like to disclose that she serves on Speakers Bureaus (non-drug specific) for Schering and Rhone Poulenc Rorer.

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 involvements, 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 involvements with any firms whose products they may wish to comment upon.

One other note. We have a very long list of public speakers who contacted me relative to a opportunity to address the panel and Dr. Murphy.

Please try to keep, as previously informed, your remarks to five minutes. Also, when you come to the podium, it is important to share with us an conflicts of interest you may have relative to your participation as a speaker at this meeting, i.e., if you were conveyed under a sponsorship and things of that nature.

Thank you so much for your interest.

I will turn the meeting back over to Dr. Murphy.

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DR. MURPHY: Thank you.

Dr. Jenkins.

Dr. Jenkins is the Director, as he said, of the Division of Pulmonary Drug Products, FDA, and he is going to lead off the discussion from the FDA.

Introduction

DR. JENKINS: Good morning.

[Slide.]

As I think you all know, the topic for today's meeting is the FDA's Advanced Notice of Proposed Rulemaking, or ANPR for short, on the CFC phaseout process that was published in the Federal Register on March the 6th, 1997.

The CFC phaseout strategy that is outlined in the ANPR represents the agency's current thinking on how the CFC phaseout and the transition to alternative products should occur.

In developing the proposed transition strategy, the overarching goal of the agency has been to develop a strategy that adequately protects the health and safety of the patients who rely on these CFC-based MDI products as these products are being phased out as mandated under U.S. and international law and treaty.

As I am sure you all recognize, the development of such a complex strategy is not an easy one since it affects

such a wide variety of interest groups, many of whom may have competing priorities and interests.

With publication of the ANPR, we have entered into the first phase of the public comment period on development of the CFC phaseout strategy for the United States. We look forward to hearing comments from the committee members and from those members of the audience today on how our proposal can be improved as we move forward in developing the final strategy.

As a final note, I would like to remind everyone that the public comment period for the ANPR closes on May 5th, 1997, and as Leander Madoo pointed out the instructions on how to submit comments are included in the ANPR.

Again, participation at today's meeting in no way precludes you from submitting formal written comments to the docket for the ANPR.

[Slide.]

This slide outlines the FDA's objectives for today's meeting. First, this meeting provides the agency with a public forum to describe how we went about developing the proposed transition strategy and to provide some insights into the rationale behind our thinking and our decisions in putting together the proposed strategy.

Second, it allows us a chance to provide an

overview of how the agency's proposed transition strategy integrates with the global phaseout of CFCs under the Montreal Protocol.

Third, we would like to describe in some detail the notice and comment rulemaking procedures that will be followed by the agency in developing and implementing the final transition strategy.

Finally, we view this as an important milestone in the development of the strategy to receive comments and feedback and recommendations from not only the members of the advisory committee, but also the public, as we move forward in our development of the final strategy.

[Slide.]

The agenda for today's meeting is as follows. I will giving an overview of the FDA regulatory history regarding CFCs.

Chris O'Donnell, representing the Environmental Protection Agency, will give an overview of the environmental issues related to CFCs, as well as the Montreal Protocol process.

Dr. Otulana will then provide an overview of the proposed transition strategy, as well as some of the rationale behind the agency's proposals.

Following that, we will move on to the open public

hearing and finish up this afternoon with a block of time for committee discussion of the proposed strategy.

As Dr. Murphy mentioned earlier, the proposed questions for discussion provided by the agency are designed to outline some of the areas that we would like to hear comments on during today's meeting, however, they are not intended to be comprehensive. The agency is not asking the committee to take any formal votes today or to try to develop any consensus opinions on these proposed questions. Rather we are interested in hearing the committee's comments on the proposed transition strategy and any recommendations you may have on how the strategy can be improved as we move forward.

[Slide.]

With that brief introduction to the agenda, and the objectives for today's meeting, let me move on to an overview of the FDA regulatory history regarding CFCs.

[Slide.]

First, I would like to summarize the statutory and regulatory basis for the CFC phaseout. The first regulations that restricted the use of CFCs in medical products were promulgated by the agency in 1978, and that was done in response to mounting evidence of the impact of chlorofluorocarbons on the earth's protective stratospheric

ozone layer./

These regulations are found in Title 21 of the Code of Federal Regulations at subsection 2.125, which I will subsequently abbreviate as either 2.125 or as the FDA essential use regulations.

Let me apologize for the need to refer to subsections of the regulations. I know that may cause some eyes to glaze over, but there is really no way to explain and for you understand the basis for the regulatory procedures we are proposing and our proposed actions without discussing 2.125, since that is the fundamental core of our proposal.

Each of the committee members has received a copy of 2.125 in your briefing package, so you can refer to that through today's meeting as needed.

2.125 as written in 1978 banned the use of CFCs in self-pressurized containers, such as MDIs, however, the regulation provided for exemptions to that ban for essential uses. The criteria for establishing that a use of CFCs for a medical product was essential are listed on the slide, and include, number one, that there are not technically feasible alternatives to the use of CFCs in the product; number two, that the product provides a substantial health benefit, environmental benefit, or other public benefit that could

not be obtained without the use of CFCs; and number three, that the release of CFCs into the environment should be insignificant or should be justified based on the benefit obtained.

Products that FDA has determined to be essential uses of CFCs over the years since 1987 are listed under subsection (e) of the regulation. Dr. Otulana will be going into more detail on the topic of these essential use listings later this morning.

[Slide.]

Now, let's look at how EPA regulations affect the use of CFCs and MDIs. The EPA regulations implementing the Clean Air Act Amendments of 1990, which were promulgated in 1993, also provide for a general ban on the use of CFCs in pressurized dispensers, such as metered dose inhalers.

Again, the EPA ban provides or the EPA regulations provide for the exemption from the general ban for medical devices that FDA considers to be essential and that are listed under the FDA's regulations at 2.125(e).

So, as you can see, the EPA and FDA regulations are actually directly linked to one another with regard to use of CFCs and MDIs.

[Slide.]

On the international front, the Montreal Protocol

on substances that deplete the ozone layer was signed in 1987. The U.S. is a signatory party to that treat, as are 159 other nations around the world.

The provisions of the Montreal Protocol were incorporated into the U.S. law by Congress when they passed the 1990 Amendments to the Clean Air Act. Under the Montreal Protocol and the U.S. Clean Air Act, the production and importation of CFCs were banned in the United States and other developed nations as of January 1st, 1996.

The Montreal Protocol also provides a mechanism for countries to receive year exemptions from the ban for certain essential uses including essential medical uses. The only medical uses for which essential use exemptions have been consistently granted by the parties to the Montreal Protocol are for metered dose inhalers for the treatment of asthma and chronic obstructive pulmonary disease or COPD.

I think it is important to note that while the FDA regulations in 1.125 restrict the use of CFCs and MDIs, it is actually the Montreal Protocol and the Clean Air Act that mandate the phaseout of the use of CFCs in all products.

[Slide.]

During the course of today's meeting, you will hear the term "essential use" used both in reference to the

listing to drugs under the FDA's regulations and also under the Montreal Protocol. The actual criteria for determination of essentiality differ between the Montreal Protocol and the FDA regulations, therefore, the listing of drugs in 2.125 does not coincide with those drug products that the Montreal Protocol has deemed to be essential.

As I said earlier, the Montreal Protocol has only recognized drugs for the treatment of asthma and COPD as being essential uses of CFCs. Those same drugs are listed under the FDA regulations, however, in addition, other drugs are also listed including such products as the nasal corticosteroids.

This disparity in the listing is the result of the application of a much more rigorous criteria for essentiality under the Montreal Protocol, and it is also due to the fact that the FDA listing has been constructed over the past 20 years, and some of the products that are listed, the essential use listing, have not been removed as those products have no longer been essential or alternatives have been developed.

As you will see during today's meeting, most, if not all, of the current essential use listings under FDA regulations for non-asthma and COPD drugs will be eliminated or are proposed to be eliminated once the proposed

transition strategy that we are discussing today is finalized.

[Slide.]

I would like now to spend a few minutes giving you an overview of the FDA's efforts to lay the groundwork in cooperation with the pharmaceutical industry for the transition to non-CFC alternative inhalation products.

Let me start on the chemistry and manufacturing area. The Division's chemistry staff provided feedback to the pharmaceutical industry in the selection of potential alternative propellants. The chemistry staff also, in cooperation with the pharmaceutical industry, developed quality control specifications for CFCs used in MDIs, the so-called universal specifications for CFCs.

These specifications are intended to maintain the purity, and therefore the safety, of CFCs used in metered dose inhalers during the transition process, and this is necessary since established producers of CFCs may be scaling back on their production capacity or may be leaving the CFC marketplace entirely. This may result in MDI manufacturers being forced to seek alternative producers or to consider stockpiling CFCs for future use.

Finally, the chemistry staff has worked very proactively with individual sponsors to assist in the

development of alternative products. This proactive approach to the development of alternatives is a theme I think that applies to each of the scientific review disciplines within the Pulmonary Division at FDA.

[Slide.]

Moving on now to the area of pharmacology/toxicology testing. The agency worked very closely with the international consortium of aerosol manufacturers, or IPAC, to ensure that a full pre-clinical safety testing battery, similar to that required for the development of a new chemical entity in the United States, was completed for HFA-134a and HFA-227. These are the most promising of the alternative propellants under development.

The agency felt that such an extensive pre-clinical safety evaluation program was necessary for these propellants due to the relative large amount of the propellant in the formulation as compared to the active drug substance, as well as the inhalation route of administration and the likely chronic and even life-long use of these products in patients.

A more limited or bridging approach was developed for the pre-clinical safety testing of the new formulations which would contain propellant, drug substance, and inactive ingredients, and this approach was possible due to the

extensive knowledge base that was developed for the propellants themselves, as well as the extensive clinical and pre-clinical knowledge base for the active drug substances which have been marketed in the United States.

In an effort to further expedite the development of these products, and to provide the pharmaceutical industry with feedback on the agency's views of the pre-clinical safety of the alternative propellants, the Division agreed to review the data for the alternative propellants under drug master files, and these were submitted by IPAC in advance of the submission of any NDAs containing alternative propellants.

Again, the Pharmacology and Toxicology review staff have worked very proactively with individual sponsors to assist in their development of alternative products.

[Slide.]

Turning to clinical issues, the Division issued a document, which we titled a Points to Consider document, in September of 1994, which was designed to detail the Division's recommendations for the clinical development of metered dose inhalers containing alternative propellants, as well as dry powder inhalers.

Similar to the preclinical safety battery given the extensive clinical safety and efficacy database

available on the drug substances already approved in the United States, the recommended clinical development programs for the most part represent a bridging approach.

In addition to demonstrating that these new products are safe and effective, the bridging approach is designed to establish that the new products are comparably safe and effective as the currently marketed CFC MDIs.

The Division has placed great emphasis on this demonstration of comparability to the currently marketed CFC MDIs, and it is part of our overall goal of ensuring that the transition to these alternative products will be as seamless as possible, in other words, the new products will be assayed and as effective as the products they are replacing.

Using the Points to Consider document as a guidepost, the Division's clinical staff have interacted very proactively with individual sponsors to tailor the recommendations to fit the numerous variables that we have encountered in each of the new clinical development programs, always with the idea of not compromising on the document's basic principles.

[Slide.]

Now, let me give you an overview of how the agency went about developing the CFC transition strategy. Over a

year ago, the Center for Drug Evaluation and Research created a CFC Workgroup as a subcommittee of the Center's Medical Policy Coordinating Committee or MPCC.

The MPCC is charged with coordinating medical policy development and implementation throughout the Center for Drugs. CFC Workgroup membership was drawn from those areas of the center with expertise in the development and regulation of metered dose inhalers and other inhalational dosage forms, as well as experts on legal and regulatory matters.

[Slide.]

The CFC Workgroup went about its task of developing a transition strategy by first conducting a comprehensive review of the relevant scientific, technical, regulatory, clinical, chemistry issues, et cetera. The group also interacted very regularly and closely with the staff of the EPA Stratospheric Protection Division.

As the CFC Workgroup developed draft proposals, these were then presented to the full membership of the MPCC for clearance and signoff, as well as feedback.

The Workgroup decided that the best way to solicit public input from the numerous interest group who have a stake in the phaseout of CFCs was for the agency to initially develop a proposed policy internally that could

then be published in an ANPR for public comment.

The Workgroup is also responsible for drafting the ANPR through its numerous iterations, and they shepherded it through the approval process within the agency, as well as gaining concurrent clearance from the Environmental Protection Agency and final clearance from the Office of Management and Budget prior to publication.

This CFC Workgroup will be continuing their activities as we move forward toward developing a final transition strategy.

[Slide.]

Let me take a moment to highlight some of the reasons the CFC Workgroup adopted the ANPR approach for the publication of the proposed transition strategy.

First, the Workgroup recognized that the phaseout of MDIs containing CFCs is a very unique situation, and there no agency precedents for how to go about developing such a transition strategy.

Given the lack of agency precedent in this area, the Workgroup recognized that the initial FDA proposal in this area should be reviewed as preliminary pending agency review of public comments

The preliminary nature of the proposed transition strategy is just the type of situation for which an ANPR is

most appropriate. The ANPR approach is also advantageous since it allows groups interested in the development of the proposed phaseout strategy a fair and equal opportunity to comment on the FDA's proposal prior to the development of a proposed rule.

Finally, the ANPR approach allowed for a more rapid publication of the proposed transition strategy. Being the first developed nation to propose a national transition strategy may allow the United States to lead the development of international transition strategies rather than place us in a position to follow the lead of other countries.

We felt that this was particularly important since it allow the FDA to develop a transition strategy that correctly matches all the unique characteristics of our regulatory health care and marketing environment rather than trying to adapt an international strategy to the U.S. environment.

[Slide.]

The FDA has also played an active role in the Montreal Protocol process. While the EPA and the State Department are the primary official representatives of the United States to the Montreal Protocol process, we have developed a very close working relationship with the staff

at both of those agencies on CFC-related issues.

Our interactions with the EPA particularly include consultation on the yearly nomination to the parties of the Montreal Protocol for essential use exemptions for the United States. In addition, Dr. Otulana, who is the chair of the CFC Workgroup, also serves as a member of the Aerosol Technical Options Committee of the Montreal Protocol governing organization.

This is an important technical subcommittee which makes recommendations to the parties to the Montreal Protocol on issues related to MDIs, and finally, FDA staff regularly attend meetings of the parties of the Montreal Protocol to serve as consultants and advisers to the representatives from the EPA and State Department on drug-related issues.

[Slide.]

The FDA also recognizes that for the transition to non-CFC products to occur in as seamless a way as is possible, it is necessary to educate patients, physicians, nurses, pharmacists, and other health care providers and interested parties about the phaseout. This is part of the reason we are here today.

To that end the FDA has also initiated a series of presentations on CFC phaseout issues at national scientific

and professional society meetings. We have also begun consultations with various interest groups including the National Asthma Education and Prevention Program to develop educational materials and programs.

To ensure that the ANPR received its broadest public input, it was placed on the FDA's Internet home page and the Division actively notified numerous professional organizations and patient advocacy groups of its availability as soon as it was published.

Finally, the FDA has published, or will be publishing in the near future, articles on the CFC phaseout process in FDA Consumer, JAMA, and the FDA Medical bulletin.

Overall, the agency has attempted to approach the challenge of the CFC phaseout in an organized comprehensive manner to facilitate our stated goal that the transition to non-CFC alternative products occur as seamlessly as possible. We remain committed to that goal and look forward to the committee's input to help us better achieve that goal.

[Slide.]

Let me take just a couple of moments to discuss the status of development of potential alternatives to CFC-based MDIs. As you all are aware, the FDA approved Proventil HFA, the first non-CFC metered dose inhaler, in

August of last year, and that product has now been on the market in the United States since January.

While I cannot comment on specific products, I can tell you that there are numerous other potential alternative products that are currently under development, many of these products are undergoing Phase III clinical testing or have completed Phase III clinical testing and are expected to be approved in the United States over the next several years.

One potential side benefit of the CFC phaseout process is that all of the efforts of the pharmaceutical industry to reformulate the CFC-based MDIs is probably going to result in us having a much wider range of drug delivery devices available to patients and physicians when we are through with this process than we had when we started.

By that I mean we are going to have dry powder inhalers, which we don't have much of now in the United States, as well as other unique technology that is being developed.

[Slide.]

Let me now walk through the process of how we plan to finalize the development of a proposed transition strategy and the how we will go about implementing the transition strategy.

FDA will be following the notice and comment

rulemaking procedures as we codify the criteria for the phaseout of central uses under 2.125, and I will walk through the steps of that notice and comment rulemaking procedure with you as it relates to the ANPR.

We are now at the first step of this notice and comment rulemaking procedure meaning that we have published the Advanced Notice of Proposed Rulemaking. Currently, we are the middle of the 60-day public comment period for the ANPR.

After the close of the comment period, the FDA will review the comments received to the docket and will develop a proposed rule for the publication in the Federal Register. In the preamble to that proposed rule, the FDA will respond to the comments received to the ANPR docket, and the proposed rule will incorporate any modifications in the proposed transition strategy made by FDA in response to those comments. Let me again point out that the proposed rule will also be open for public comment.

[Slide.]

Once the comment for the proposed rule is closed, FDA again will review the comments received and will develop a final rule for publication in the Federal Register. Again, the preamble to the final rule will respond to the comments received to the proposed rule docket, and the final

rule will incorporate any modifications that the FDA has made in response to the comments.

[Slide.]

As currently envisioned, the final rule will codify the criteria for phaseout of the essential use listings in 2.125(e). We also expect that the final rule will eliminate the essential use listing from 2.125(e) for any drugs that are no longer considered to be essential uses of CFCs.

As you are probably aware, in the ANPR, the FDA has proposed that such drugs may include the nasal corticosteroids and those drugs currently listed under 2.125 that are no longer marketed.

[Slide.]

Once the essential use phaseout criteria are incorporated into 2.125, FDA will then monitor the availability and acceptability of non-CFC alternatives to those drugs listed as the central uses of CFCs under 2.125(e).

When we feel that the availability and acceptability of non-CFC alternatives appear to meet the phaseout criteria listed in the regulations, FDA will then develop a proposed rule which will be published in the Federal Register.

Such proposed rule will propose to eliminate the essential use listing for that drug or that class of drugs from 2.125. Again, there will be a public comment period and then FDA will develop and publish a final rule. The final rule will then eliminate that drug or therapeutic class from 2.125, therefore, meaning that the drug can no longer be marketed in the United States with CFCs.

Let me emphasize that we are only at the first stage of the process of developing the phaseout criteria, and once those phaseout criteria are developed and finalized, it will still be necessary for the FDA to go through the notice and comment rulemaking procedure again each time we propose to eliminate a drug or a class of drugs from the essential use listing.

All of these processes will include opportunities for public comment. While I cannot predict or state in an exact time frame for the completion of the various steps in this process that I have outlined, I think it should be clear that it will be some time in the future, and possibly several years, before FDA will even be proposing to eliminate the CFC essential use status for any of the currently marketed asthma and COPD metered dose inhalers.

What we are trying to do today and over the next few months and years is to lay the regulatory groundwork

that will allow the FDA to act when, and only when, alternatives to the currently CFC-based MDIs are approved and accepted by patients and physicians in the United States.

[Slide.]

In summary, the CFC phaseout process is mandated by U.S. law, regulations, and international treaty. As Dr. Murphy said, the FDA's role is to implement the mandated phaseout process in a safe and responsible manner.

The essential use exemptions for medical uses under the Montreal Protocol are temporary pending development of alternatives. These exemptions have to be renewed each year, and it is anticipated that the parties to the Montreal Protocol will become more strict in granting these criteria as the years progress, and as I have tried to point out, the transition process to non-CFC products has already started in the United States and around the world.

[Slide.]

Finally, FDA is committed to developing a transition strategy to the United States that: number one, protects the health of patients who rely on the current CFC-based metered dose inhalers during the transition process, and again, that is our primary focus.

We are also interested in meeting our domestic and

international obligations for the CFC phaseout. We want to develop a strategy that strikes an appropriate balance between the public health and the environment, and as I have said earlier, the Division's overall goal is for this transition to be as seamless as possible.

[Slide.]

In closing, let me emphasize that a successful transition to non-CFC-based products in the United States must occur as a partnership between regulators and drug developers, and must appropriately balance patient and environmental concerns.

The agency looks forward to hearing constructive comments from the committee and the speakers during the open public hearing on how we can achieve our common goal of a seamless transition.

Our next speaker will be Ms. Chris O'Donnell from the Environmental Protection Agency.

MR. MADOO: I would like to interject now for those sitting in the back, feel free to come forward and sit in the galleries flanking the table. Additional rows of chairs will be brought in during the break, so if you find yourself standing up, please feel free to come forward and take a seat. There are also chairs up in the front.

[Slide.]

MS. O'DONNELL: Good morning. I am Chris O'Donnell with the Environment Protection Agency, and I would like to thank both the FDA and the advisory committee for the opportunity to speak to the committee on what EPA believes is a significant public health issue, that is, protection of the ozone layer.

I would like to spend some time this morning just briefly discussing ozone depletion, international and U.S. efforts to reverse ozone depletion, and FDA and EPA's efforts to facilitate the transition to medical devices which use ozone depleting substances to those which do not.

I would also like to acknowledge my colleagues that are here with me today, Drusilla Hufford, who you met this morning, who is the Acting Director of the Stratospheric Protection Division, and Tom Land, who is over here, both who have worked hard many years on the issues of ozone depletion and our U.S. and international efforts to reverse ozone depletion.

[Slide.]

As I said, some of the key points is ozone depletion, what we are doing internationally and domestically, and the transition.

[Slide.]

I would like to spend a little bit of time, just

very briefly, going over ozone depletion science, just to give you some kind of framework to think about these issues. Ozone was discovered in 1839. Isolated ozone observations were made in the beginning of the 1920s, and then systematic measurements begun in the 1950s with the agreement among the world meteorological organization on how to measure ozone.

Ninety percent of the earth's ozone resides in the lower stratosphere, forming a layer that extends 6 to 25 miles above our planet's surface. This is the troposphere that is closest to us in the stratosphere, which is what we will talk about today, which is where ozone depletion occurs.

This layer, that is, the stratosphere absorbs all UVC radiation and most UV-B while allowing the longer beneficial wavelengths of sunlight to penetrate down to the land and the ocean.

The ozone layer normally exists in a state of dynamic balance. Gas is continually being formed and destroyed at equal rates. This balance maintains ozone concentrations at relatively constant levels over time.

When chlorine and bromine-containing compounds drift up into the stratosphere, the breakdown from these products, these chemicals upset the ozone balance, tipping it towards destruction.

World attention was focused on the problem of ozone depletion when two University of California scientists in 1974, Mario Molina and F. Sherwood Rowland, published their Nobel Prizewinning paper linking CFCs to ozone depletion.

At that time, in 1974, over 5 million tons of CFCs were being produced worldwide each year.

[Slide.]

What are ozone depleting chemicals or substances, ODSs as we generally refer to them? They are long lasting, water insoluble compounds containing chlorine and bromine. We find them in chlorofluorocarbons or CFCs, which is largely what we will be discussing today, hydrochlorofluorocarbons, methyl chloroform and halons.

As I said, most of today's discussion will focus on one of these ozone depleting substances, that is, CFCs. CFCs were invented in 1928. Although they were produced and used large scale around the 1950s, at that time they were considered the wonder chemical, they were low in toxicity, low in flammability, and they were inexpensive to produce.

At one time, American were literally surrounded by CFCs. We used them to cool our cars, our offices, and our homes, to preserve and package our foods, manufacture high-tech computer and electronic gear, and propeller or

medical devices as we have with metered dose inhalers.

CFCs don't dissolve in water, so they don't rain out before reaching the stratosphere. These human-made chemicals are responsible for the observed depletion in the earth's ozone layer. One chlorine atom can destroy over 100,000 ozone molecules before becoming inert.

[Slide.]

This is a very elementary sketch here of what happens with regard to ozone depletion. When CFCs are released by all types of equipment, they take generally two to five years to reach the stratosphere. As I said, CFCs are very stable, they are not water soluble, they don't rain out. Only strong UV radiation destroys CFCs, which releases chlorine. CFCs don't deplete the ozone layer, the chlorine released from them does.

In the upper atmosphere, UV light breaks off chlorine atom from the CFC molecule, the chlorine reacts rapidly with ozone, destroying it. The reactive chemical formed is chlorine oxide. Chlorine oxide undergoes further processes and regenerates the original chlorine, allowing the sequence to be repeated over and over again.

It is helpful to think about this constant natural dynamic state of ozone production-destruction that takes place as similar to the streams normally constant depth.

When we think about a stream, natural creation provides water from upstream and natural destruction removed it downstream. CFCs are like a pump downstream. They accelerate depletion, reducing the stream's depths beyond natural destruction processes.

What happens when ozone layer is destroyed? Well, it results in more UV-B radiation reaching the earth, and as we all know, UV-B radiation leads to significant public health effects, such as cancer, cataracts, and immune suppression.

[Slide.]

What do we know about what is going on in the ozone layer today? Ozone depleting substances have been measured at ground base sites since 1978, by aircraft, balloons, satellites, space shuttle missions, and most of these measurements have been undertaken by NASA and the National Oceanic and Atmospheric Administration, NOAA.

Over much of the period between 1978 and 1994, the growth rate of ozone depleting substances or gases in the atmosphere has been positive. Since 1979, annual ozone levels of the Northern Hemisphere have declined by roughly 8 percent with record lows measured in late 1994 and early 1996.

The seasonal Antarctic ozone hole, the one that we

most hear about, was first detected in the 1980s, and has grown out, and it covers a 9.5 million square miles, an area that is larger than North America.

Ozone losses have also been measured over the mid latitudes, as well as the poles, so this is not just a phenomenon that happens at the extremes. Over the Western United States, in March 1996, ozone levels were 2 to 4 percent lower than those for March 1979 to 1986.

In fact, this week NASA, in addition to some other events, released a press release that told us that the NASA satellites have measured the lowest ozone levels ever recorded over the Arctic. This is the Arctic which, as we see, is in addition to the Antarctic. The 1997 levels over the Arctic were 40 percent lower than the amounts observed between 1979 and 1982, which is the baseline year from which measurements are taken or assessed against.

[Slide.]

Some of the good news we have with regard to the ozone layer and its thinning is that recent data shows that annual growths of CFC-11 and 12, which are the CFCs that are used in metered dose inhalers, are slowing down, and these observed trends are consistent with our EPA monitoring and reporting data, so we do have some good news although we have a lot of work that remains in terms of repairing the

ozone layer.

[Slide.]

Why do we care about ozone depletion or the thinning of the ozone layer? We care about it because it has significant public health effects. One of the most significant, of course, is skin cancer.

The risk of malignant melanoma developing in an American in the U.S. has now reached 1 in 87, one American dies of skin cancer every hour, and we have seen an 1800 percent rise in malignant melanoma since the 1930s. Some of this is related to ozone depletion.

Ozone depletion, as you know, also has significant detrimental effects on plants and animals, as well. So this is significant public health concern.

[Slide.]

What has been the worldwide response to ozone depletion, what have we been doing internationally as well as domestically? In 1978, 10 years before the Montreal Protocol, which Dr. Jenkins spoke about briefly, the U.S. banned the use of CFCs as propellants in most aerosol products after three years of scientific research. I mentioned the research begun in 1974 by Molina and Rowland, and that research was followed up in 1975 by research done at the University of Michigan and Harvard predicting

significant ozone depletion based on the connection that Molina and Rowland had made in the connection of CFCs to ozone depletion.

In 1978, the Montreal Protocol on substances that deplete the ozone layer established a mechanism for international scientific cooperation for stratospheric protection. The Montreal Protocol was the first global environmental risk management treaty that recognized that atmosphere knows no national boundaries.

This landmark treaty, which at the time was signed by 26 countries, limited and eventually phased out the production of ozone depleting substances or chemicals. The original phaseout date that was scheduled for ozone depleting substance was for 1998, however, this was accelerated to 1992 based on the World Meteorological Organization's ozone trend report telling us that depletion was occurring over the mid latitudes.

There was, however, an exemption place in the Montreal Protocol for essential uses, which Dr. Jenkins also spoke to briefly, and those essential uses would be for medical devices only. So, essential uses under the protocol as they are today, as originally amended under the Montreal Protocol, are for medical uses, and those essential uses are based on there not being any alternative available or

economic alternatives.

In granting the essential uses part, parties must take every mechanism available to mitigate emissions from those essential uses. I should tell you that the parties to the Montreal Protocol considered many uses in terms of exemptions, and most other exemptions were rejected including many other medical exemptions.

[Slide.]

The Clean Air Act is our U.S. statute implementing the Montreal Protocol. It is our domestic statute for implementing the terms and agreements of the Montreal Protocol, although I should also tell you that the Clean Air Act establishes a range of regulatory programs to deal with the range of air pollution problems.

Title VI of the Act, which is stratospheric protection, deals ozone depletion, and Title VI bans the consumption of ozone depleting substances beginning January 1, 1996, except for essential uses.

Title VI also contains a use ban. As I spoke about before, in 1978, we outlawed or we banned the use of CFCs of aerosol products as a use ban. The production ban or consumption ban rather in the Clean Air Act, the way that we define it is consumption equals production plus imports minus exports.

What is important to understand here is that the ban is for the production of new CFCs. MDIs are the only remaining commercial product made in the U.S. and other developed countries with newly produced CFCs. Some products, air conditioners, for example, still use CFCs, however, these are recycled CFCs which were produced before the 1996 production ban.

MDIs are significant emission. It takes annually 6 million pounds of CFCs to produce MDIs compared to 40 million pounds to service air conditioners. Substitutes have been found in all other applications, that is, all other industrial applications, substitutes for CFCs or ozone depleting substances often in the process improving the technology and at lower cost.

As Dr. Jenkins mentioned, EPA is responsible for overseeing and implementing the essential use process. In the process, we consult with FDA and the State Department on essential use nominations. The State Department is the official representative of the U.S. to the parties on the Montreal Protocol, and FDA and EPA serve in a consultation role with the State Department.

The exemption for essential uses under the Montreal Protocol and the Clean Air Act was never intended by the parties to be a permanent exemption, as Dr. Jenkins

mentioned.

[Slide.]

Transition to CFC-free medical devices. With full compliance with the Montreal Protocol, the ozone won't recover until the middle of the next century. Full recovery of the ozone layer truly depends on full phaseout of ozone depleting substances.

We have not tacked the whole problem we acknowledge. Worldwide use of CFCs still remains large, as I mentioned. Essential uses, however, were not meant to be indefinite. The parties to the Protocol are becoming increasingly stringent with regard to essential uses, their review of essential uses, and developing criteria by which we should assess the need for essential uses.

In the future, only countries and companies with plans for active pursuit of alternative products, that is, CFC-free products, will be considered for essential uses under the Montreal Protocol.

Companies presently by the parties to the Protocol are required to conduct education on transition, they are required to differentiate packaging on CFC and non-CFC-free products.

Beginning in 1998, parties are requiring detailed reporting on production and consumption of CFCs, stockpiles,

and inventories in an effort to make the transition effort as transparent as possible, that is, to make those efforts that countries are taking transparent to the parties, and as Dr. Jenkins mentioned before, the U.S. has always demonstrated leadership in this area and we hope to continue to do so.

[Slide.]

I just want to speak briefly about the FDA's ANPRM. We believe that the ANPRM is a critical component of the U.S. strategy for meeting our obligations both under the Montreal Protocol and the Clean Air Act.

The U.S. has consistently demonstrated leadership in environmental protection and ozone depletion with early phaseout dates and being one of the first countries to ban the use of CFCs in aerosols.

The ANPRM, we believe, balances the public's need with regard to public health protection in that it balances ozone protection with the need to make certain that asthma patients and COPD have access to the medications that they need. The ANPRM does provide encouragement to developers of new technology, and ultimately we believe that the transition needs to move as expeditiously as possible without compromising patients' needs.

We also believe that it is important to recognize

investment in technologies which help protect the ozone layer.

[Slide.]

What is EPA doing in particular with regard to the transition strategy and the essential use process?

Presently, EPA is working with pharmaceutical companies and FDA to accurately determine essential use needs. It is critical that we can fully support the nominations that we send to the parties.

We are working with pharmaceuticals to match patients' needs with nominations and allocations. We will be getting a process over the next two months to meet with individual pharmaceuticals to discuss products, to discuss a number of issues with regard to the transition strategy.

It is critical, as I said, to develop the most defensible nominations as possible since our negotiators, the State Department and EPA, must go to the parties, the other countries, and be the representatives for the pharmaceutical industries for essential uses.

We will also be meeting with companies to talk about their transition to CFC-free products and to discuss market penetration and any product launches.

[Slide.]

Some of the final things that we need to do is we

need to raise patient and health care providers' comfort level around the new CFC-free products. In the past, we have been working with FDA on this issue, and we need to work with FDA to increase the momentum for new technology development, increase it and encourage it.

We respect FDA's leadership in the area of patient care. We, along with FDA and other public health organizations, are working with industry and patient advocacy organizations on outreach for patients, to discuss with patients the fact that the transition is coming and try to get patients comfortable with the idea of alternative products or, that is, products that no longer contain CFCs.

[Slide.]

Let me say that, in summary, protection of the ozone layer is a significant public health concern both domestic and globally. FDA's ANPRM is a critical part of our effort to meet our obligations under the Montreal Protocol and the Clean Air Act, and the transition and new technological developments for patients really represents an opportunity to improve technology, and as I said, we would like to see it move as expeditiously as possible.

Again, I would like to thank the committee for the opportunity, and will be available to answer any questions.

DR. JENKINS: Thank you, Chris.

Our next speaker on the program is Dr. Babatunde Otulana, who is a medical officer in the Pulmonary Division. As I mentioned earlier, he is also the Chair of the CFC Workgroup that put together this proposed transition strategy. He is also the leading representative, I think, of the FDA in this whole process, and I would just like to thank Tunde for his outstanding efforts that he has been involved in this process for the last several years.

DR. OTULANA: Thank you, John.

[Slide.]

Dr. Murphy, committee members, my task this morning is to walk the committee through the proposal that we have put out and which you have heard a lot about already. This slide shows how I propose to do this in the limited time that I have.

I will start by talking about the current regulations on the use of CFCs in self-pressurized containers, and the ones we are interested in today mostly will be the metered dose inhalers or the MDIs, as we call them.

Dr. Jenkins has talked extensively about 2.125, and I will be talking quite a bit about that regulation again this morning.

I will then proceed to talk about the strategy

itself and the thought process that guided the development of that document within the CFC Workgroup, as well as the other contributors to the development of the ANPR.

One of the things that we are proposing as the committee members will have seen from the document is that Section 2.125 may have to be reorganized in order to achieve the seamless transition that we have been talking about.

So, I will spend a few minutes showing you what this proposal for reorganizing the regulation will be. The bulk of my talk this morning will probably focus on the criteria that we are proposing to facilitate the phaseout of the CFC-MDIs, and we will spend some time on that.

Finally, I will gain reiterate the rulemaking procedures that we anticipate will take us from the ANPR stage that we are now to hopefully a final rule that will incorporate the phaseout process into the FDA regulations.

[Slide.]

Let me start now by talking about 2.125 as it currently stands in the FDA regulations. As you have heard, the section we call 2.125 is a response by the FDA back in 1978 to mounting data that suggests that ozone depletion was occurring due to emission of CFCs into the stratosphere.

The way the FDA handled this was to put in place this regulation that provided a general ban on the use of

CFC. In addition, though, they recognized that there was a need for products that will continue to be used, and may not be formulated in other media.

Therefore, the section of our regulation contains a provision for an exemption process that will allow these products to be sold legally in the United States. What Section 2.125 does is to define criteria that will have to be met by these products in order to be listed in our regulation and therefore be available for use for patients.

Section 2.125 also lists the products and drug classes that have met this criteria and are therefore recognized on that FDA law as being acceptable for being sold in the United States.

It is important to point out that our regulation states that products that are non-exempted because they have not met this essentiality criteria are taken as adulterated and misbranded. In simple language, what this means is that these products cannot be legally sold in the United States.

Finally, that regulation describes a procedure that was put in place in 1978 to allow manufacturers to petition the FDA, asking for their products to be listed. Dr. Jenkins went through the criteria that has been written into the regulation, and once a manufacturer can prove that their product meets this criteria, they will be listed as

essential.

[Slide.]

I thought I would show you some listing of the products that are currently in our regulation. This slide shows a number of products that have met those criteria over the last 20 years and have therefore been listed on that 2.125. We do have the steroid nasal sprays, the steroid MDIs and of course the adrenergic bronchodilators. These represent classes of products that are recognized together as having met the essentiality criteria.

You will note that as the regulation currently stands, no individual products are listed under these classes, and this is one of the issues that I will be talking about subsequently.

In the regulations, we also have individual active ingredients that are listed in their own right as having met the essentiality criteria. While most of the products that we currently have exempted used in the treatment of airway diseases, we have a small number of products that are actually used to treat other conditions - the contraceptive vaginal foam is still listed on the 2.125 as essential, and we have products like ergotamine titrate that over the years have been deemed essential under that regulation.

I just want to point out that in the process that

we are talking about today, as we are proposing all these products will be affected by the transition, and we hope that alternatives will be available to the majority of them.

[Slide.]

Over the next four or five slides, I just want to walk the committee through the thought process that guided the development of the ANPR that we are discussing today.

[Slide.]

After reviewing the FDA regulations and other regulations that guide the use of CFCs in the United States, we recognized that one of the first things we needed to do was to define what products will constitute acceptable alternatives to the CFC-MDIs that we proposing to phase out.

It was very helpful that at the FDA, we do have knowledge of products that have been developed in the pharmaceutical industry towards this end, and we did put that knowledge to use in coming up with products that we deem will be satisfactory in replacing the alternatives.

So one of the things we did at the beginning of the process therefore was to list out criteria that these products need to meet in order to substitute for the CFC-based MDIs.

Next, we recognized the need to have an orderly process. We recognized that in order for the transition to

proceed smoothly and seamlessly, there needs to be some criteria that will apply to all products and all manufacturing entities.

We therefore came up with this list of criteria, the details of which I will be discussing with you that we proposing in the ANPR today. In developing the criteria, we took into consideration the public health needs both in terms of treatment of patients with asthma and COPD in the United States as of today, and also the concerns that have been expressed in terms of the danger of the CFC to the ozone layer and the diseases that are associated with that.

Our approach was to attempt to balance these two public health areas of needs. Of course, the development of the criteria was also guided by the international mandate, as well as relevant parts of the U.S. law that govern the use of CFC.

[Slide.]

Section 2.125 is a very critical part of the transition that we are proposing. As you have heard, that section of our regulations is the one that allows CFC products to be sold in the United States today.

However, in developing the phaseout criteria, we recognized that things have moved on since 1978, and just as the regulation proposes that products can be listed when

there are not alternatives, we do recognize that as alternatives become available, we will need to revisit this regulation.

So, one of the important elements of our proposal is that Section 2.125 will need to be reorganized to allow phaseout of these individual products or classes for which alternatives become available. I will go into details of the proposal for the reorganization in a moment.

[Slide.]

As these CFC-free alternatives become available, then, and become accepted to patients and physician, we propose that we will phase the CFC equivalent out by amending that regulation.

Apart from the regulatory processes that I have discussed over the last two or three slides, we do recognize that while we attempt to minimize the impact of the phaseout on patients who use these products, we also need to get input from many interest groups that will be affected by the transition.

We have therefore built into the ANPR and some of the rulemaking procedures that we will be proposing, the opportunity for patient groups, health care providers, pharmaceutical industries, and other government agencies that are involved in the global phaseout of CFC to be able

to have input into whatever policies we develop.

Such opportunity includes what we are doing today, where we are providing patient group, physicians, and other interest groups to be able to come forward and give us input into our proposal.

As Dr. Jenkins said, we have also explored other opportunities to interact with physicians, scientists, and industry. We recognize that the transition policy itself is going to be a dynamic process. Therefore, we are proposing that periodically we will reassess the effectiveness of the policy and we will look at how the alternatives come into the market in terms of the due diligence being demonstrated by sponsors to produce these alternatives.

We realize that it may be necessary at some point to revisit the criteria that we are proposing based on how the transition is proceeding in the United States.

[Slide.]

I said earlier that one of the initial things we did in formulating this policy was to develop the definition of a technically feasible alternative. Again, as I mentioned, we did look at products that are in development. We look at the activity in the aerosol industry and tried to fit this product into what we will consider as meeting technically feasible alternative definition to the CFC-MDIs.

This slide shows the main elements that we think should be fulfilled before a CFC-free product is considered as an accepted alternative to the CFC equivalent. We are proposing that such a product should be delivered through the same group. Since most of the products or virtually all of the products we are talking about today are by inhalation, a technically feasible alternative to a CFC-MDI would have to be an inhalation drug product.

We are also proposing that such a product should be indicated for treating the same diseases. Again, most of the items currently listed in our regulation are for treatment of asthma and COPD, and so the alternatives should be indicated for the same diseases.

We have this condition in there that the product will have to offer the patient the same level of convenience, so that patients feel comfortable with them and are able to use them as easily as they can use the CFC equivalent.

[Slide.]

Based on those definitions, then, this slide shows the products that we think, and we are proposing, will meet the technically feasible alternative definition to the CFC-MDIs.

We are proposing that MDIs that are formulated in

alternative propellants, such as the HFAs, will be considered as a potential alternative. We are also proposing that dry powder inhalers or the multidose variety will also qualify as an alternative.

We are aware of the number of devices, miniature nebulizers, mechanical metered dose inhalers, many of which do not use propellants, that may also be considered as potential alternatives if they meet those criteria that I disclosed earlier.

Based on our assessment at the moment, we do not think that traditional nebulizers will qualify as alternatives. As I am sure the committee members realize, these nebulizers are bulky and they do not offer the same level of convenience as patients currently obtain from CFC-MDIs.

Similarly, we do not consider single-dose DPIs as technically feasible alternative because these devices are not as patient-friendly as the CFC-MDIs that we currently have.

[Slide.]

Let me now move on to our proposal for reorganizing 2.125.

[Slide.]

We are proposing that when we revise 2.125 under

our current CFC transition policy, we should create two therapeutic classes. The first therapeutic class will be the short-acting adrenergic bronchodilators, what we commonly call beta agonists, and we will have a second therapeutic class consisting of the inhaled corticosteroids.

[Slide.]

We are proposing that in that first therapeutic class consisting of beta agonists, we will have the commonly used bronchodilators. I am sure you recognize albuterol, bitolterol, pirbuterol, and others.

In this category, then, we will have all the approved short-acting beta agonists. We are also proposing that as opposed to the current 2.125, we will actually list these products by name in our regulation. This is important because part of our transition strategy is to consider phasing out individual products, so unlike the current regulation that allows manufacturers to be considered essential because the class is listed, our proposal is that individual products will have to be recognized as essential under our regulation.

[Slide.]

The second therapeutic class will consist of inhaled corticosteroids, and again you recognize the currently approved steroids on this list. Just as I said

with the first class, we also are proposing that we will list individual members of this class in the revised 2.125 in order to allow us to treat each product as an individual active ingredient.

[Slide.]

We are also proposing that when we revise 2.125, all products that do not fit into those two categories that I showed earlier will be listed as individual active moiety. We are proposing that salmeterol, epinephrine, ipratropium and with albuterol in combination, ipratropium, cromolyn, nedocromil will be considered under this category.

Salmeterol, as you know, is a adrenergic agent which is currently in our regulation considered under the beta agonist category. However, we are suggesting that we move this into individual active moiety group because its long acting nature and because we do not think it should be phased out when other beta agonists are phased out.

Epinephrine we also are pulling out or proposing to pull out of the beta agonist group because of its over-the-counter status, which other products do not currently have.

[Slide.]

Now, I will spend some time going through the criteria that we are proposing and how we arrived at some of

the recommendations in the ANPR.

As I am sure the committee members are aware, we are proposing four criteria that will have to be made for us to consider that products in the therapeutic class should be phased out.

[Slide.]

The first of the criteria is that there should be three distinct alternative products in that therapeutic class for us to consider phasing all the products in that class out.

[Slide.]

We selected the number 3 as the figure that will have to be made, the number of products that will have to be available before we phase out the entire class. After looking at a number of alternatives that we could select, to us we feel that 3 is a number that will provide adequate choice for patients and for physicians, while at the same time it will be achievable, it will not be burdensome to the regulation, and it is a number that can be made while still fulfilling the public health needs under the transition policy.

We are also recommending that the products should be distinctly different. What we mean here is that two products, one, an innovative product, and a generic product,

will not be considered distinctly different enough to be counted as two products.

So here we are looking at products that are very different, again to preserve the choice for patient and physicians, so that if a patient cannot tolerate one product, the physician will have the opportunity to prescribe another one.

These three products that we will consider under an entire therapeutic class phaseout will also have to meet the criteria that I described earlier in terms of being technically feasible, that is, they will have to be given by inhalation, they will have to be indicated for the same diseases, and they should offer the patients the same level of convenience approximately.

In addition, under this criterion, we are proposing that at least two of the three alternatives should come from different active moieties, and at least two of the alternatives should be MDIs because the MDIs are the most commonly used devices in this country.

Let me just take a moment to define an active moiety for the committee. Under our regulations, an active moiety is the molecule or the ion that contributes to the pharmacological or physiological action of the drug substance.

To give an example to clarify this, we will consider albuterol base or albuterol sulfate as the same active moiety even though one has a salt, the other doesn't have, so when we are talking about different active moieties then we will not consider an albuterol base and albuterol sulfate as different active moieties.

[Slide.]

The second of the criteria that we are proposing is that there should be adequate supply and production capacity for the United States.

[Slide.]

What we are looking for under this criterion is that the products that will be replacing the CFC-MDIs should show evidence that it could meet the needs of the projected patient population that will be using these alternatives.

One of the conditions that we have recommended in the ANPR, that it be may be useful if the three products in this case are from different production sites, again to allow for the comfort level that there will always be a steady supply in case of any unforeseen event at one of the production sites.

[Slide.]

The third criterion for the therapeutic class is that there should be at least one year of postmarketing data

in the United States for these products. As I am sure the committee members are aware, when we approve products in the United States, these products will have demonstrated evidence of safety and efficacy in the limited population that have been enrolled in the clinical trials.

In any event, when we do put these products out, we are saying that they have been proven to be safe and effective, however, under this transition we realize the importance to look closely at these products in terms of patient acceptance and the use of the products and the safety data that will come from that after the product is exposed to millions or hundreds of thousands of asthmatics and COPD that will potentially use the product.

So, when we are talking about postmarketing data, we are not really looking at data just to show that the drug is safe and effective in a limited population, we are looking at evidence of acceptance, the broad safety in a wide population.

[Slide.]

We do have in place already a postmarketing surveillance system both at the FDA and individual pharmaceutical industry that attempts to capture safety data after a drug is approved. We are proposing that in the CFC transition, such a database would be invaluable in

collecting the data.

We are also suggesting the possibility of a postmarketing study that individual pharmaceutical industry or groups of pharmaceutical industries pulling back to collect the data of the type that are described.

Again, just to emphasize, as part of the postmarketing use of these drugs, we are interested in looking at how physicians are prescribing these drugs and how patients are accepting them. Acceptability in this case will also include tolerability of the product, the presence of compliance when the products are prescribed for patients, as well as the number of factors that we generally look for in terms of drug safety.

[Slide.]

Still talking about the two therapeutic classes, we are proposing that when the first three criteria that are described are met, we will consider that the drug production and therapeutic class could successfully be phased out without creating much problem unless there is evidence, significant and credible evidence that shows that certain sub-population of patients would not be served by the alternatives that are then available.

[Slide.]

What we are talking about here is that there

should be evidence that will clearly demonstrate what the significant sub-population is, what groups of patients the alternatives will not serve, and the reason why this population will not be served by the alternatives.

What we are saying is that such an evidence cannot just be anecdotal, it has to be clearly defined scientific data relating to that sub-population. We are proposing that when these three criteria are met, it is very likely in the absence of such an evidence that a therapeutic class could be phased out.

[Slide.]

Let me now turn to those drugs that are listed on that individual active moiety, and just to you remind you committee members I am providing the list again, so that you will be aware of the products that will be phased out under the criteria that I will be discussing shortly.

I also want to draw your attention on this slide to the fact that these products as we currently have them in the United States exists as only one drug product per item, so we have only one salmeterol, one ipratropium, and so on.

[Slide.]

Based on that fact that we have only one product for each of the drug substances that I showed earlier, we are proposing that an individual active moiety will be

phased out when there is one alternative CFC-free product for that drug substance.

We think that there is really no need to have more than one product to replace one product. In addition, that product will have to meet all the criteria for a technically feasible alternative that I discussed earlier, that is, it will have to be given by the same route of delivery, it has to be indicated for the same disease, and it should offer the patient approximately the same level of convenience as the CFC product it is replacing.

The other three criteria that I discussed for the therapeutic class will also have to be in place for the CFC-free product to be accepted as substituting for the CFC product, and therefore for that product to be phased out.

[Slide.]

We do have an additional approach that you will have noticed in the ANPR, and I want to spend a moment discussing that. In addition to the therapeutic class approach that I discussed, we recognized that that proposal for requiring three alternatives, two of which must be two different active moieties and two MDIs, may result in the delay of phasing out some products that are in the therapeutic class.

Let me give an example. Take beclomethasone, for

instance. We have beclomethasone included in the inhaled steroid therapeutic class. It may develop where we have two, three, or four CFC-free beclomethasone products. Under that particular class criteria, we will not be able to remove beclomethasone even through there are three or four alternatives because we may not have the other two products that will allow the entire class to be phased out.

We therefore proposed this additional approach to the therapeutic class phaseout, and that it is shown on this slide. Under that scenario, we will consider phasing out an individual member of the therapeutic class ahead of removing the entire therapeutic class if there is one alternative product for that member of the therapeutic class.

So, under the scenario that I just talked about, when there is one alternative product to beclomethasone, even though the entire steroid class would not be phased out, we will consider phasing out beclomethasone.

Again, that alternative product will have to meet all the criteria that I discussed earlier, it will have to be given by the same route of delivery, it will have to be indicated for the same disease, and it will have to meet approximately the same level of convenience as the product, the CFC product it is replacing.

In addition to that, we still have the other

criteria that will apply to the that active moiety. This approach will complement the therapeutic class, it will not replace the therapeutic class if it makes it finally into our regulation.

What it means is that the active moiety in the therapeutic class that is phased out will contribute to the three requirements for phasing out the therapeutic class. So, again, going back to the example that I gave, if we phase out beclomethasone under that scenario, the entire therapeutic class will still be removed when we have two other active moieties to meet the criteria for the therapeutic class.

[Slide.]

Finally, let me talk about some rulemaking procedures that we will embark on by the ANPR that we are discussing today. The ANPR, as we currently have it, proposes the phaseout criteria, details of which we have talked about, and it also proposes some general transition strategies, such as the reorganization of essential use regulation 2.125.

After the public comment period and incorporation of whatever recommendations we obtain during this period, we will develop a proposed rule which will codify the phaseout criteria at that time, and in addition, will propose

eliminating non-essential uses.

The proposed rule will have a comment period also and the comments we obtain at that time will be reflected in the final rule that we will codify in CFC transition criteria, and also will have our regulation for eliminating non-essential uses.

[Slide.]

We talked about products that we are proposing as no longer essential, and Dr. Jenkins touched on this. Let me just return to that topic.

There are two categories of products that built on current knowledge we think may not be essential at the moment, and also we may consider removing from our regulations.

One category is products for which alternatives currently exist. We think the nasal corticosteroids will meet that definition. There are a number of CFC-free nasal sprays that are accepted by patients and are widely used. We will therefore be proposing in the proposed rule that I talked about that nasal steroids be removed from 2.125.

The second category is products that are no longer being marketed, and I think most people will readily agree that the products that are no longer being marketed in the United States, they cannot be deemed essential.

Two products will readily fall into this category and they include topical antibiotic powder and contraceptive vaginal foams.

[Slide.]

Finally, there is a separate rulemaking procedure that we have actually started, put in its place in terms of doing preliminary work on the proposed rule. This is quite separate from the ANPR track that I discussed earlier.

This proposed rule will propose to reorganize Section 2.125, as I have discussed. In addition, it will propose some new criteria for sponsors to get essential use exemption on that 2.125. The goal here is to tighten the criteria for listing new products, and what we are trying to achieve is to make it more difficult for new CFC products to be listed as essential during the transition phase.

We think that while we are phasing out products containing CFC, it does not make much sense to be listing new ones. So, this criteria will be proposed and there will be opportunity for public comment on our proposal at that point.

Again, this is going to be a separate rulemaking procedure that will follow a different track. After obtaining public comment on this proposed rule, we will move on to a final rule which will contain the 2.125 reorganized

as we have proposed and also will codify the new criteria for granting essential use exemption.

[Slide.]

Let me end my talk by acknowledging a number of people who have participated in the development of the transition policy that we are discussing today. Dr. Jenkins talked about the work that the CFC Workgroup has done. I want to acknowledge the individuals that contributed to that work.

As you will notice, the participants in the CFC Workgroup came from different disciplines and indeed from different divisions within the FDA. I want to thank all the members, many of whom are present today, for the tremendous amount of work that went into the development of the policy.

[Slide.]

In addition, I want to acknowledge a number of groups outside the CFC Workgroup that made a lot of effort to make the policy possible. We obtained a lot of help, suggestions, and reviews from many divisions within the FDA including the MPCC, that Dr. Jenkins talked about, and some higher level offices within the agency. Again, I want to express our appreciation for their help.

Outside the FDA, the document received reviews and suggestions from a number of agencies, and I want to

acknowledge in particular the EPA, who right from the beginning have been very supportive of the development of the policy.

We also received suggestions and reviews from the Council on Environmental Quality, and I want to acknowledge their contribution as well.

Thank you very much for your attention. The three of us speakers will be available to take your questions.

Thank you.

DR. MURPHY: I would like to thank you very much for those excellent presentations, and I think we can all see how much work that everyone put into developing this policy, and I just want to point out to the committee and everyone in the audience that as you can see, this has been developed by scientists, pulmonologists, and people that have a lot of concern.

Because we are running a little bit behind time, I would just like to ask the committee to just ask questions for clarification now, not for discussion, like I think I heard Dr. Jenkins say this, is that true, those kinds of questions, not discussion questions.

Committee Comments and Questions

DR. LIU: I think I have one quick one. The numbers went by pretty fast, but what is the percent of CFC

production as a proportion of the total CFC use in terms of, you know, in the country? I mean is it a large percentage, small percentage? I don't have a good feel for that. I thought I heard 6 million and 40 million.

DR. JENKINS: Chris, could you come up here to address those questions, so the audience can see you. I would like Chris O'Donnell from the EPA to address that question.

MS. O'DONNELL: There are two things I want to clarify. Production and use are very different with regard to this regulation, both the Montreal Protocol and the Clean Air Act. The production is for new production for metered dose inhalers, that is, CFCs that were produced after the ban, which was effective January 1st, 1996.

So there are other applications or other industrial applications and uses in this country, as I said before, cars, car air conditioners, homes, and the like, but they are using CFCs that were produced before 1996, and often they are recycled CFCs, and much of them are captured in terms of emissions.

The other thing -- and I do have some figures for you, but I just wanted to clarify that -- with regard to annual production of CFCs, the other thing to understand is that this is the only commercial product remaining in this

country that we produce CFCs for, and actually, CFCs are no longer produced in this country. Most of the CFCs are produced abroad.

So when we are talking about production of CFCs for an application, it is just for this use. What I mentioned before is that annually, it is approximately 6 million pounds for CFC production for MDIs.

One thing just to help to put it in perspective a little bit more, the essential use nomination that the U.S. sent forward to the parties of the Montreal Protocol for the years 1998 and actually largely 1999, was 4,000 metric tons of CFCs for the production of MDIs in the United States, and in a relative sense, what is interesting is that this number is larger than the aggregate uses in all sectors for close to 100 of the world's countries, so in that relative sense, you can see that it is fairly large.

I hope that is helpful. Is there any followup?

DR. MURPHY: Dr. Szeffler?

DR. SZEFLER: I would like to ask Dr. Otulana a question. I would like to commend him on his work, it's excellent in terms of the whole category of medications.

The one area that I had a question about was the inhaled corticosteroids. Having an interest in that area, I wondered how you felt about the five inhaled steroids, would

they be looked at as the same product when you speak of alternatives, or are they in separate categories?

DR. OTULANA: We do have, as I am sure you realize, two proposals in place. One will look at all the five products as being in that class, and therefore will be phased out if any alternatives become available, at least three alternatives.

What that means is that is a scenario could develop whereby some of those products may not be reformulated, and yet they will be removed. That is the first approach that I talked about.

The second approach is where we will substitute an active moiety for an active moiety. Beclomethasone would be replaced when beclomethasone becomes available, but if your question, what you are getting at is whether we will have all those five products available, are CFC-free, the answer may be maybe, maybe not. If the conditions on that class are met, then that particular will be phased out as we are currently proposing it.

DR. MURPHY: Dr. Hendeles.

DR. HENDELES: I may have missed it, but I didn't hear a comment about the clause on patient tolerability, what that means.

DR. JENKINS: I think that is a good point, Les,

and we have not rigidly defined what that means, and I think that is an important point, that we have left some of the decisionmaking about when these products are acceptable alternatives to judgment, and it is going to be hard to rigidly define a regulation that says the product is tolerable when X is met, but some of that is going to have to be left to judgment of the FDA, as well as public comment, which there will be opportunity for public comment to be raised once we get to the stage of proposing the elimination of the essential use of CFCs for a given product, of whether the alternatives are adequately accepted or adequately tolerable or safe, serve all the patient populations that have significant special populations.

DR. MURPHY: Dr. Baraniuk.

DR. BARANIUK: I just had one quick question. As far as individual member of a class, and phaseout of an entire therapeutic class, if I understand it properly, you are saying that you need two active moieties in at least two delivery systems.

DR. OTULANA: That is correct.

DR. BARANIUK: In the situation with the beta agonists, there are currently two non-CFC delivery systems available. Does that mean that if there is a third one introduced for either pirbuterol or for albuterol, that the

entire class will be phased out?

DR. OTULANA: There is only one CFC-free beta agonist that we may recognize as potential alternative, that is, Proventil HFA. Were you counting another one?

DR. BARANIUK: MaxAir dry powder.

DR. OTULANA: It is not available in this country.

DR. BARANIUK: But alternative methods, dry powders, for instance, are you considering those to be an alternative in terms of the metered dose inhalers?

DR. OTULANA: Yes, if they meet the definition that we are proposing as technically feasible alternative, they will be considered, the dry powder inhaler will be considered. We have proposed that two of the three alternatives should be metered dose inhalers because those are the widely used devices, so we do recognize that most patients and physicians are more familiar with metered dose inhalers in this country than with dry powder inhalers.

DR. BARANIUK: So what would be the minimum requirement to eliminate this entire therapeutic class given the current market?

DR. OTULANA: The minimum requirement would be --

DR. BARANIUK: For beta agonists.

DR. OTULANA: Right, for beta agonists it would be three alternative products.

DR. BARANIUK: No, no, no. Given what is on the market right now, what else has to be introduced in order to eliminate all of the other CFC-containing products?

DR. OTULANA: As I say, we only recognize one alternative currently that may qualify as a technically feasible alternative, Ventolin Rototabs, which is the other beta agonist. As I pointed out earlier, because of the single-dose nature, probably not as much as convenient as what we currently have, may not qualify.

So, the scenario currently is one alternative MDI. We will need at least one additional MDI, and maybe DPI or a MDI to meet the definition of feasible alternatives, therapeutic class.

DR. MURPHY: Dr. Osborne.

DR. OSBORNE: Again, just clarification, I think you have said this before, but as I understand it, for example, for the Class II drugs, once there are three alternatives, and at least two are MDIs, the others could be phased out as CFC-containing compounds, but certainly could be reintroduced with non-CFC-containing mixtures in which they could be propelled, or whatever?

DR. OTULANA: That is correct. What we are proposing the minimal criteria, if we have three alternatives, two MDIs, two different active moieties, we

will consider, we will propose to phase the class out, but that does not remove the opportunity for the other members of the class to be reformulated.

What we are proposing would be the minimum number of products that should be available, but there could be a lot more than what we are proposing in that class.

DR. JENKINS: Let me speak to that for just a second because I think we sometimes fall into the habit of talking about phaseout of the drug or phaseout of the class, what we are really referring to is phaseout of the essential use of CFC listing for that drug or that class.

It would mean that the product could no longer be marketed containing a CFC, would have no impact on other dosage forms for that drug or that therapeutic class, such as nebulizer solutions, dry powder inhalers, and I think maybe some of the confusion that was coming up with the beta agonist class, there is only currently one non-CFC delivery system, delivery product that we have approved that we consider as a potential alternative, and that is the Proventil HFA.

We are not considering the current albuterol dry power formulation to be an acceptable alternative for the metered dose inhaler. So, the minimum criteria, as Dr. Otulana outlined, would be we would need a total of three

acceptable alternative beta agonist delivery systems. At least two would have to be metered dose inhalers, although they could all be metered dose inhalers, and there would be at least two different active moieties.

So, with the current beta agonist situation, we have one albuterol metered dose inhaler, so we need another drug substance in addition to albuterol, plus we need another metered dose inhaler, and we need a total of three alternative products to meet the minimum criteria, but again, remember it is not just the criteria of numbers, it is the criteria of the other factors, such as acceptability, tolerability, production capacity, adequately serves patient needs. So, it is not just a numbers game. There are criteria that fall into play for the overall phaseout.

DR. MURPHY: Dr. Crim, did you have a question of clarification?

DR. CRIM: I will come back to it this afternoon.

DR. MURPHY: Dr. Liu, you had another?

DR. LIU: My question has been answered, but maybe just -- in other words, the way I understand it now, you wouldn't conceive of a scenario where DPIs would simply replace metered dose inhalers and qualify as adequate for eliminating the essential use exemption.

DR. JENKINS: Not for the two therapeutic classes.

The criteria we propose require that at least two of the alternatives for the therapeutic class would be metered dose inhalers. On the individual active moieties that we listed, salmeterol, ipratropium, et cetera, there is only one current alternative.

Our proposal does not require that the one alternative that could deem the CFC use no longer essential be a metered dose inhaler. That may be something you want to comment on today. Our proposal would include the option that a dry powder inhaler could substitute for those products, but again, please keep in mind that all those other criteria have to be met, such as the ability to serve the patient populations that use that product.

So, if there were a particular sub-population of patients who use salmeterol metered dose inhaler, for example, they can't use a dry powder inhaler because they can't generate the inhalation force or whatever. Then, the criteria would not be met.

DR. MURPHY: Dr. Jenne.

DR. JENNE: I think my questions were answered, but what if a company had a different agent than the ones on the list, such as another antimuscarinic compound, for example. Could they go through the entire process of FDA approval using a dry power inhaler, for example, or else one

of the new HFAs?

DR. JENKINS: Companies are free to use whatever delivery system they want to propose to develop new products. As the regulation is currently written, as Dr. Otulana went over, it includes a class of adrenergic bronchodilators, it includes a class of inhaled corticosteroids without listing specifically the drug substances within that class, so as the regulation is currently written, if someone wanted to develop a new corticosteroid and new CFCs, that is possible.

The way we are proposing to write the new regulation would be that we will list the individual members that are currently approved, so in the future if you wanted to develop a new corticosteroid using CFCs, you would have to petition the agency to get your product listed as a new essential use and define why we need another corticosteroid that can only be delivered by CFCs, and can't be formulated in some other way.

DR. MURPHY: Is that clear?

DR. JENNE: Yes.

DR. MURPHY: Dr. Cross.

DR. CROSS: Yes, two quick questions. Dr.

Otulana, is your subcommittee of the Montreal Protocol Group going to be commenting on this document, or is it

appropriate that they do?

DR. OTULANA: The Aerosol Technical Options Committee, as we call it, has had an opportunity after the document was published to see it, and to hear some presentation on it. Like anybody else, during the comment period, they can -- I am not sure whether officially they will take a stand one way or the other.

DR. CROSS: My second question. Are there any countries that have already banned CFCs, and is there any experience that can be gleaned from these countries?

MS. O'DONNELL: Dr. Otulana is quite capable to answering this actually also. The signatories to the Montreal Protocol were required to ban the production of ozone depleting chemicals by -- that is, there is a different schedule for developed countries and developing countries, and the developed countries, which are a non-Article V under the Montreal Protocol, Article V(b), developing countries and countries with economies in transition, those non-Article V countries were required by January 1st, 1996, to ban the production of ozone depleting chemicals except for the one use is allowed for essential uses, which is medical devices or metered dose inhalers.

With regard to your question about reviewing the ANPRM, under the Montreal Protocol, the parties have

required that countries report to the parties on steps that they are taking for transition in this coming year, so there will be certainly a review, and as I said in my comments, that is why this ANPRM is so critical because it is a major component of the U.S.'s efforts to transition to CFC-free products.

DR. CROSS: So no countries have already banned their use for medical purposes.

MS. O'DONNELL: No.

DR. JENKINS: I think the question you are asking is has any country banned the use of CFCs for medical uses totally with no exemptions, and the answer to that is no, and I would point out that that is not what we are proposing today either. We are laying the framework for how to phase out the use as alternatives become available.

One group of countries that are getting very close to using very little CFCs for their medical products for the Scandinavian countries, and I think the figures are there that 70 or 80 or more percent of their inhalational products are dry powder inhalers.

They are actually one of the leading advocates of the phaseout of CFCs because they can't understand why the rest of the world can't use dry powder inhalers just like they do. But there are no countries that have completely

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banned or eliminated the use of CFCs in medical products.

DR. MURPHY: Dr. Li.

DR. LI: I have a question for Ms. O'Donnell, just a clarification question.

Can you give us an estimate of the magnitude of CFCs that are currently stockpiled either in the United States or around the world, and what the potential uses for those stockpiled products are?

MS. O'DONNELL: We do have information on U.S. companies, and what their stockpiles are, and we have that information because we can collect that information under our Clean Air Act. I did not happen to bring with me today those numbers, and some of that information is confidential business information, and I can't speak to the magnitude with regard to worldwide stockpiles.

One thing to note is that CFCs for metered dose inhalers are pharmaceutical grade CFCs, so there may be stockpiled CFCs available, that is, they were produced. When we say stockpiled, they were produced before the production ban, they were produced before January 1st, 1996, but some percentage of those would be used in other applications, like air conditioners, and they are not pharmaceutical grade.

I hope that answers your question. I just don't

have the figures.

DR. LI: It does. I think the issue is the same one that one of the other committee members raised, and that is for us to have a relative estimate of the importance of the metered dose inhaler CFCs relative to uses in refrigeration and other industrial capacities.

DR. JENKINS: I think again, as Dr. Murphy pointed out, and we pointed out during the presentation, the law has already been implemented for the phaseout and the ban of CFC use, and we are trying to discuss today how to implement that ban, so I recognize you would like to have information about the components, but we would really like to focus today on the how, and not the why.

DR. LI: And I appreciate that fully. It has some implication, for example, as we consider the potential time course for the phaseout, whether we might be more likely to recommend a very rapid or aggressive phaseout, or if we would consider one that prolonged over several years as was suggested.

DR. JENKINS: Drusilla Hufford from the EPA may want to try to address some of that.

MS. HUFFORD: I would like to just very briefly try to provide you a little historical context, if I could. At the outset of policy discussions for controlling the

ozone layer problem, the majority of U.S. uses of these chemicals were in the major air conditioning and refrigeration uses, that Chris O'Donnell has mentioned.

About a third of the problem, though, was made up of very small uses. CFCs were so industrially ubiquitous they found their way into things like mold release agents, dental applications, many, many small-use solvent cleaning applications, and so early on, the parties to the Protocol and certainly those in the U.S. environmental community and the regulatory community faced the question of should there be any kind of move to exempt small uses on the basis of their smallness.

Because small uses then in the aggregate represented such a large portion of the problem, the decision was made to go ahead and address the problem as a whole, because if we ended up exempting an individual use based on its smallness, it would be very difficult when the next small user came in, to say, well, no, we need to hold the line here.

DR. MURPHY: Dr. Ahrens.

DR. AHRENS: I would also like to comment the presenters and the Working Group for the very clear presentations and obviously the very clear thinking that has gone into all this.

The question I have relates to the phrase "patient convenience," in terms of the definition of that in the criteria for phaseout. Some of the terms I have heard under that are safety, tolerability, acceptability by the patient and physician. One of the words that is missing, that I was looking for, is something about efficacy or effectiveness in real world clinical use.

Is that intentional or is that really intended to be a part of it, and if so, how?

DR. OTULANA: We will be interested in looking at effectiveness of the product in the real world. By the time the product is approved, though, they have done extensive clinical studies, and they have established, as I pointed out earlier, safety and efficacy in the setting of clinical trials.

As part of the postmarketing data collection that we are proposing, and perhaps clinical trial that we are also suggesting, it will be possible to look at the use of the product in terms of effectiveness when it is exposed to a wider population. So, that point is valid, that effectiveness when used by hundreds of thousands of people, perhaps categories of patients that were not suitable for clinical trial should be looked at.

As I said, we do hope that by the time we approve

these products, we have a comfort level that they are effective and they are safe.

DR. AHRENS: Thank you.

DR. MURPHY: Dr. Baraniuk, you had a question. Dr. Chinchilli.

DR. CHINCHILLI: My question has to do with I don't understand the process of when a metered dose inhaler is released, what happens to its CFC, does it all get inside the patient, is it released from the patient, is there leakage from the canister? I know these are naive questions. I don't understand why it's a problem with MDIs, very basic.

DR. JENKINS: CFCs are very volatile compounds meaning that that is why they are used as propellants. When you release the CFCs from the metered dose inhaler by actuating it, the propellants aerosolize very rapidly, so they are very volatile. So most of the CFC that you release when you actuate the metered dose inhaler are either released into the atmosphere or they are exhaled by the patient.

Those CFCs that are absorbed by the patient are also going to be rapidly turned around and re-exhaled by the patient, so the CFCs are not absorbed and metabolized and destroyed by the body. They are inert biologically, so

anything that gets absorbed, you exhale it later, very shortly. Most of what comes out of the inhaler actually goes into the environment directly.

DR. MURPHY: Good question. Dr. Sessler.

DR. SESSLER: When we speak of three distinct alternative products, and we are referring to two different active moieties, is there consideration for relative dosage strength, and more specifically, the variable dosages that we see in some formulations of more recent inhaled corticosteroids?

DR. OTULANA: The products that we will consider as alternatives will still have to meet our standard criteria for effectiveness, safety, as well as the usual consideration for approving these products, which will include the chemistry, manufacturing control, which is really what you are getting at.

In terms of variability, that is something we regulate on the chemistry, a review of these products. That is just on the variability issue. In terms of multiple dose strengths of this product, we will still consider the multiple dose strengths of a product as part of that product, so if a steroid comes in three strengths, for instance, the three strengths will still be deemed as part of that drug product.

If it is reformulated, hopefully, to be reformulated in the dose strengths that the CFC alternative currently has.

DR. SESSLER: I guess my question revolves around equivalency and if, let's say, two of the other agents were developed in alternative MDI forms, with elimination then of the only multiple dosage formatted drug, I am assuming that that drug would then be eliminated from availability.

DR. OTULANA: Those are issues that are really complex in terms of are we going to get to the level of looking at each strength of a drug product as different or do we need that particular product to be reformulated and the different strengths available before we remove that drug product. I think those are really issues that we need to look further at.

As we currently have the proposal, though, that product will count as one, and if the criteria for the therapeutic class are made, that product will be considered or proposed for phaseout.

DR. MURPHY: I think we should save some of this for discussion.

Ms. Mitchell, do you have a question? Last question.

MS. MITCHELL: Is our younger pediatric population

going to be looked at as a specific sub-population?

DR. OTULANA: Yes. When we said that we will be wishing to look at evidence that some sub-populations are not served by an alternative, we do have in mind the possibility of the pediatric population or certain segments of asthmatics or COPD group that an alternative may not serve.

So, evidence will be looked at, that the CFC-free alternative will meet that population.

MS. MITCHELL: Secondarily --

DR. MURPHY: I think we are also getting into discussion here. I would like to save that. I think that this is really clarification. So why don't you save that very good point until the discussion time.

I would like to take a 10-minute break right. We will come back. Dr. Otulana is going to show one more slide, and then we will go into the public presentation.

Thank you again for your excellent presentations and questions.

[Recess.]

Open Public Hearing

DR. MURPHY: This is very early in the process and I would like to really thank the FDA for giving all of a chance to get input. Now we are going to get the

opportunity to hear some more input, and I would like to remind the people who are going to input us right now that we want to stick to five minutes, and I will ask Mr. Madoo to get out the crane and pull you off if you are going over five minutes, but we are very anxious to hear this important and hopefully succinct presentations.

I would like to start with Nancy Sander, who is President of the Allergy and Asthma Network and the Mothers of Asthmatics. Nancy, you are on.

MS. SANDER: Thank you, Dr. Murphy, and the panel here.

As Dr. Murphy said, I am Nancy Sander, President of the Allergy and Asthma Network and Mothers of Asthmatics, Inc. We are a membership-supported, nonprofit organization, involved in patient education worldwide.

We receive funding through educational grants both restricted and unrestricted from medical associations, as well as from pharmaceutical industry.

DR. MURPHY: Did you pay your own way here?

MS. SANDER: I sure did. I live right around the corner.

[Laughter.]

I am also the mother of four children, three of whom have asthma, and I also have asthma myself, and so I am

very aware that asthma is a disease of a thousand faces forever poised to steal life and breath from its victims like a thief in the night, and the FDA is charged with the unprecedented monumental task of escorting millions of those patients through a transition from CFC MDIs to alternative therapies, and I am sure there is a lot of people who do not envy you.

The FDA proposal is a framework for transition. However, does it address the needs and concerns of people with asthma who use these medications to breathe?

To find out, we solicited and received a grant, unrestricted grant from Glaxo Wellcome to conduct two studies. The first we conducted was a mail and phone survey, which Michael Sauter from Strategic Insights will elaborate on after I speak.

The second is a national survey, a mail-in survey of 19,000 patients. Each received a summary of the ANPRM identical to the ones that are in front of you and the panel and also some are distributed in the back.

We will provide results to the FDA by the May 5th deadline.

It is only when we understand the concerns of patients and caregivers that we can identify opportunities to build a seamless transition, and as we do, and as we look

at this information that we are collecting, we find that the one-year period for the collection of postmarketing data is likely to yield disappointing and misleading results. For this reason we say time is needed for the launch and marketing of each drug, time for educating physicians, increasing clinician awareness about and confidence in prescribing each drug, and then time for patients to learn to use the alternatives correctly.

So, therefore, we believe that the one-year period is a bit ambitious.

The FDA proposal also assumes that patients use medications in therapeutic classes when, in reality, we used them one active and inactive moiety at a time. Two active moieties within a therapeutic class, therefore, may not be enough.

The FDA proposal assumes that all drugs within a class are created equal, however, patients do not all perceive this to be true. In particular, the side effects associated with one may be alleviated by another in the same class. In addition, today's range of inhaled corticosteroids offer dosing schedules which can be tailored to the patients' needs.

The FDA proposal criteria for evaluation of patient acceptance in significant sub-populations needs

further clarification. Perhaps this is an area where our research will be most helpful.

The FDA proposal also appears to leave a wide-open door for a permanent exemption for CFC-containing OTC bronchodilators. The rationale that these medications are used only by the poor or those without access to medical care is not supported by our research. For example, Primatene Mist is the most expensive bronchodilator on the market, and they release more CFCs for a 20-minute period of effectiveness than those medications that have longer duration.

There are no OTC heart drugs for the poor or those without insurance, and asthma is not an OTC disease, therefore, we ask the FDA to bind OTC CFC containing MDIs to the same rules as prescription MDIs.

The transition presents perhaps the great opportunity to reverse the death rate of asthma and to stimulate the development of new and innovative therapies and to increase asthma research in the United States, and these provisions must be included in the final rule.

The process for phaseout is ultimately experience product by product, patient by patient, and one which requires a comprehensive, yet flexible, strategy. Just as the EPA closely monitors the health of the ozone, we propose

that the FDA establish a separate transition advisory panel to study transition proposals, recommendations, and to monitor the progress of patients and caregivers, and to assist the FDA in this historical event.

Time does not permit to complete my list of things I would like to go over, but we are prepared to work with the FDA and have enjoyed working with the FDA and the EPA in the past in developing the sensitive proposal that you currently have before you.

Thank you very much.

DR. MURPHY: Thank you, Nancy.

Michael Sauter. Please state where you are from and who funds you, and who paid your way.

MR. SAUTER: Michael Sauter. I am from Strategic Insights. We are an independent marketing research firm, and we are funded by the Asthma and Allergy Network, Nancy Sander's group, who just spoke.

Thank you very much for your time. Let me say that we gave you a handout, it should be in front of you. This is dated -- it is very hot off the presses -- we just got it on Tuesday evening, so we haven't had a real long time to live with it and understand it, but I would like to go through it very quickly with you and hit some of the high points.

DR. MURPHY: Could you hold it up, just to show us which handout it is? We have a number of them.

MR. SAUTER: Sure. It starts on the front like this. The top line says, "Patient Reaction to FDA Advance Notice of Proposed Rulemaking." I see one person has it.

DR. MURPHY: Go ahead. We will find it.

MR. SAUTER: What we did, because we had a very limited amount of time, is we used a pre-identified group of asthma patients identified by NFO Research of Toledo, Ohio. They have a panel of 500,000 households. Essentially one out of every 200 households in the United States is on their panel.

They have identified people who have asthma and we then sent these people a four-page summary, which is included in what we have given you, of all the stuff we saw this morning, hopefully, put in pretty easy to understand terms or easier to understand terms.

We also sent them the Federal Register, so they could see exactly what you published, and we didn't hold anything back. I am going to just go through the graphs that we have provided to you very quickly and hopefully hit some of the high spots.

In our sample, 12 percent of the sample said the asthma that they suffered from was severe. Of those people,

asthma is a disease that impacts their life very dramatically, 27 percent of our sample indicated that they had had a life-threatening event or attack in the past 12 months, 13 percent said they required hospitalization, and 68 percent said that they had restricted their activities.

The next graph talks about how it impacted on their quality of life. Fifty-eight percent said that asthma had caused them to limit their regular physical activities, 35, 33, and 28 percent said that it interfered with their normal social life, it caused a financial burden, and it made them more dependent upon others, 14 percent even said that it caused them to relocate where they live.

One of the things that is in the announcement talks about Med Watch. We wanted to see if anybody had heard of Med Watch. Forty-eight percent of people indicated that they had had an adverse reaction to a drug. Of those people, 87 percent said they had never heard of Med Watch, and of the 13 percent who said they have heard of Med Watch, only 1 percent had called. So, it doesn't appear at this time to be a very effective way of getting patients to report problems that they have had.

Inhalers are used by virtually every asthma sufferer out there. Eighty-nine percent said that they had ever used a short-acting bronchodilator, 62 percent said

they had ever used an inhaled corticosteroid, and 26 percent said they had used one or the other individual drugs that are talked about at the end.

Seventy percent have a current prescription for a short-acting bronchodilator, so you can see that we are talking about drugs that impact on virtually every asthma sufferer, and it is not just that they have an inhaler. Twenty-three percent of asthma sufferers have three or more inhalers.

Now, when we talk about three or more inhalers, that means a short-acting bronchodilator, a steroid. They may have multiple steroids, so they may have multiple bronchodilators, but we are just counting those each as one, and they have one other drug. So, there are a lot of inhalers used by a lot of people.

We looked at the penetration of these various drugs, an idea of market share. The FDA proposal does not take into account market shares, and treats all the drugs as if they are of equal -- that they are trade-offable for one another.

We see that the top five drugs that are being used by patients out there are albuterols and that we have to get down into sixth and seventh place to find Alupent or MaxAir, so they are very small drugs.

DR. MURPHY: I just want to say you have a lot of graphs there. We are not going to be able to go through all of them.

MR. SAUTER: We will cut off whenever you want.

DR. MURPHY: Why don't you point out to the panel the ones that you think are the most pertinent.

MR. SAUTER: Let me go to one that is labeled Q32A in the lower lefthand corner. It is about six more graphs into the pile. We exposed people as best we could to what is going on and what is being discussed here today.

We asked them if they agree with the proposal as it was described in the Federal Register relating to short-acting bronchodilators. Sixty-six percent of the people indicated that that was an acceptable proposal to them, 26 percent said no, it was not acceptable to them, and 8 percent said they did not know.

These numbers increased in terms of it not being acceptable when we talked to people who had been on the same inhaler for more than six years, who had another drug that they felt they were not willing to switch to, or who suffered from severe asthma.

One of the questions that came up earlier is what is the minimum for the proposal to kick in, and we proposed that to people in scenario A and scenario B. Scenario A

talks about a situation where only Proventil HFA and Ventolin are available as two of the inhalers, and MaxAir is the third one.

If we give people the option of just those three, then, 55 percent of the asthma sufferers find this an unacceptable situation.

DR. MURPHY: Why don't you make one more point. I think all this will be taken under consideration in written form by the FDA.

MR. SAUTER: Right. There is an awful lot here.

The last point I would like to make is that the majority of patients are saying that FDA proposal did not guarantee them adequate choices. Even among Proventil HFA users, they are not satisfied with having only two other choices. They are indicating, the majority of those people are indicating that they want more choices than just two other drugs.

A multidose dry powder inhaler is not acceptable to three and five patients as a replacement for a single moiety drug right now.

Okay.

DR. MURPHY: Thank you very much for all that work, and the FDA will take it all under consideration.

Ian Penn is here from the Friends of the Earth to

talk to us.

MR. MADOO: The committee might note that a handout has been provided by Friends of the Earth. It is on 100 percent post-consumer recycled paper, no chlorine used.

MR. PENN: Good morning. My name is Ian Penn. I am with Friends of the Earth, Ozone Protection Campaign.

Friends of the Earth is an environmental advocacy organization dedicated to protecting the planet from environmental degradation and empowering citizens to have a influential voice in the decisions affecting the quality of their environment and the lives.

For over a decade, Friends of the Earth's Ozone Protection Campaign has worked on the international, national, and local level to raise public awareness about the environmental and health threats posed by ozone depletion.

Friends of the Earth realizes that there is a need to strike a balance between preventing ozone depletion and increases in UV radiation and meeting the needs of patients. We agree that the transition away from CFC-containing MDIs must fully protect human health.

However, we don't believe that FDA's proposed policy adequately reflects the most current scientific evidence pointing to the need to rapidly eliminate the use

of all ozone depleting chemicals. Last year's ozone hole was the longest lasting on record. The hole measured twice the size of Europe from the Atlantic Ocean to the Ural Mountains.

As a public health agency, FDA must not ignore the health effects posed by UV radiation due to ozone depletion. Last year, NASA concluded that the amount of radiation reaching major population areas had been increasing over the last 15 years.

The largest increases have been seen in the middle and high latitudes, where population concentrations exist. With peak ozone losses expected to occur over the next decade, quickly moving away from CFC-based MDIs will help limit further ozone destruction and prevent increased UV radiation exposure.

With alternatives to CFCs already on the market, FDA must develop a transition strategy that involves and considers the needs of all stakeholders in this issue. Ultimately, FDA must move forward with action to end the essential use classification. The elimination of CFCs is a global and national effort. It is incumbent upon the FDA to eliminate CFCs in medical devices.

The essential-use exemption will not last indefinitely. This has been made clear by international

agreement and confirmed as official U.S. policy. FDA's time is best spent on developing a policy that quickly and effectively phases out CFC-MDIs.

FDA must also encourage the introduction and acceptance of alternatives. While this ANPRM is a first step in this process, we believe that more is needed to achieve a timely transition strategy that helps protect the ozone layer and addresses patient needs.

On the ANPRM, Friends of the Earth has the following recommendations.

DR. MURPHY: And you may just want to read the bold type on these in the interests of time.

MR. PENN: Okay.

In developing a policy to eliminate the essential-use status of the designated therapeutic classes, individual members within a class should be able to be removed in advance of elimination of the entire class.

The Friends of the Earth strongly believes that once there are one or more technically feasible alternatives for a member, the essential-use status of that member should be eliminated, granted, of course, that all other elements regarding the classes would apply to this elimination.

This strategy of member first and class second is the only strategy that will effectively address ozone

depletion and reduce UV-related impacts.

The FDA needs to clearly define and establish criteria for implementing due diligence in developing alternatives. We do not agree with FDA's assumption that drug manufacturers will be aggressively developing alternatives to CFC-based MDIs. We believe that FDA needs to establish a benchmark against which the actions of pharmaceutical manufacturers will be measured. This will ensure that these companies are undertaking concrete steps towards the research and development of alternatives.

FDA must suspend approval of all new CFC-containing MDIs. Friends of the Earth is concerned about the potential for continued approval of generic CFC-MDIs even as a transition strategy is put in place.

As was stated in the ANPRM, "FDA believes that as the agency will soon be eliminating essential uses, it would be a waste of scarce agency resources, as well as inconsistent with general policy, to create new essential uses, unless an extraordinary showing of public benefit can be made."

While research and development of alternatives is ongoing, FDA should suspend approval of all new generic CFC propellants. Given that FDA is looking to transition away from these substances, new CFC products will serve only to

delay recovery of the ozone layer.

It is critical to link the issue of approval of new CFC-MDIs with this proposal. Continued approval directly contradicts U.S. policy and undermines the proposed FDA transition policy. It provides disincentive to drug manufacturers to invest in the research and development of alternatives. Continued approval also fails to answer the environmental imperative of ozone depletion and its impacts on human health and the environment.

This rulemaking is a critical opportunity for the FDA to remove itself from the business of CFC use and approval. Friends of the Earth hopes that FDA will seize this opportunity and take action towards a timely transition away from CFC-based MDIs, and this allow protection of human health and the environment.

I would like to thank the advisory committee for giving Friends of the Earth the opportunity to speak on this very important issue.

Thank you.

DR. MURPHY: Thank you for your concise presentation, and your way was paid by Friends of the Earth, is that correct?

MR. PENN: Yes.

DR. MURPHY: Benjamin DeAngelo, Research

Associate, with Natural Resources Defense Council.

Would you please state your affiliation, who paid your way.

MR. MADOO: And any conflicts of interest you might have relating to this meeting.

MR. DeANGELO: I am sorry.

DR. MURPHY: Any conflict of interest that you might have?

MR. DeANGELO: No.

DR. MURPHY: Who paid your way?

MR. DeANGELO: Natural Resources Defense Council, who I represent, and I took the Metro here.

DR. MURPHY: Could you just tell us what that is briefly -- the Metro, 5.95 -- could you tell us what that is, the Natural Resources Defense Council?

MR. DeANGELO: Yes, this is in my statement here. It is a nonprofit environmental organization. We get most of our funding from private contributions, foundation money, project-related funds.

NRDC, the Natural Resources Defense Council, has been involved in shaping policy for ozone-depleting substances since 1974, less that six months after scientists first warned of human-induced stratospheric ozone depletion.

Since that time, NRDC's efforts have contributed

to many important milestones: the rules promulgated by FDA and EPA to phase out CFCs in aerosol propellants in the late 1970s; more rigorous controls and an enforce timetable for CFC reductions in other applications under the Clean Air Act; and agreement on the 1987 Montreal Protocol and its subsequent strengthening, which was spurred on by scientific data that warranted accelerated action to eliminate ozone depleting substances.

I would also like to mention that NRDC is currently engaged in strengthening our nation's air quality standards, which we hope will ultimately reduce the need for many metered dose inhalers.

Because of NRDC's involvement in these matters, I will largely focus my comments on the importance of advancing to the fullest extent the aims of the Montreal Protocol.

To date, the Montreal Protocol and its Amendments and Adjustments are showing their effect. Observations of the lower atmosphere indicate a decrease in growth rates of manufactured ozone depleting substances and an increase in their substitutes.

But there are delays in transport of ozone depleting substances from the lower to the upper atmosphere; these substances have long atmospheric lifetimes; and, once

transported to the ozone layer, a single chlorine atom from a CFC molecule can destroy several thousand ozone molecules.

Thus, despite initial signs of the Montreal Protocol's success, the 1990s has been and continues to be a time of record-level stratospheric ozone depletion, not only over polar regions, but over highly populated areas, as well.

Regarding FDA's intention to "assess the potential benefits of reducing CFC emissions from drug products," it not clear how such an assessment would be carried out. It is a well-established fact that observed trends in stratospheric ozone depletion are human-induced. Yet many factors make it extremely difficult to project what the effects on the ozone layer would be -- especially over a specific geographic area -- for a given amount of CFC release.

The science does allow us to say, though, that prolonged CFC use will only exacerbate current and near-term stratospheric ozone depletion; will only impair the eventual recovery of stratospheric ozone, which is not expected to occur until mid-21st century; can only aggravate alarming trends in skin cancer frequency; add an additional stress to both terrestrial and aquatic ecosystems; and lead to potential crop damage, which the U.S. Department of

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Agriculture, for instance, is taking quite seriously with its UV-B monitoring program.

Regarding MDI-related CFCs, the current amount of CFCs contained in MDIs do represent a small portion of total existing uses of CFCs. However, there are also many nations who are Party to the Montreal Protocol and thus subject to its commitments, despite the fact that their contribution to the total atmospheric burden of ozone depleting substances is equally small or even smaller as pointed out by the EPA earlier.

Furthermore, the current share of MDI-related CFCs under current essential use exemptions will certainly increase. The production of MDI is projected to grow rapidly, keeping pace with the increase in frequency in asthma.

It may also be worth noting here that future increases in asthma and chronic obstructive pulmonary disease in the developing world are potentially large, as can be expected with growing urbanization and, in some regions, increase tobacco consumption.

And the medical management of these diseases is increasingly --

DR. MURPHY: We need you to start summarizing. You have about 30 seconds left.

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MR. DeANGELO: Regarding the replacement of CFC-driven MDIs, FDA has already approved a CFC-alternative for an albuterol MDI, and the essential use clause of the Clean Air Act was intended to be temporary. Therefore, as a matter of policy and law, the prolonged use of CFCs in albuterol MDIs, beyond that deemed necessary to ensure patient safety, can no longer be justified. MDIs containing albuterol as their active ingredient make up a large share of total MDIs. This presents the FDA with an opportunity to expedite the phaseout of a large of share of MDI-related CFCs.

I will end my comments there, but I have more to say.

DR. MURPHY: Thank you very much. Be sure to write it in by May 1st.

MR. MADOO: Well, actually, your hand out will be part of the record, and we will send them over to docket, so thanks for your efforts.

MR. DeANGELO: I will also be submitting written comments.

DR. MURPHY: Good. Great. Thank you.

Malcolm Ko from the Atmospheric and Environmental Research, Inc.

Please tell us any conflicts and what that

organization is.

For the panel, there is a handbook.

DR. KO: The committee has a handout which should be identified by that figure showing up on the last page.

My name is Malcolm Ko. I am the Principal Scientist and Director of the Atmospheric, Chemistry, and Dynamics Program at Atmospheric and Environmental Research in Cambridge, Massachusetts.

Over the past 15 years, my group has been actively involved in research on stratospheric ozone depletion, including the development of an advanced two-dimensional numerical model of the atmosphere to assess the effects from emissions of CFCs, halons, and CFC alternatives.

Our work has been jointly funded by NASA's Mission to Planet Earth and by industry groups. For disclosure purpose, I should mention that although my company is paying for this trip, my client list include Glaxo Wellcome.

I would like to make a statement on the utility of chlorine loading calculations as a tool to measure the effect of CFC emissions on ozone and how this information can be used to assess the relative impact of usage of CFC and the alternative associated with pulmonary drugs. I hope my presentation will provide information to answering some of the questions that were raised by the committee this

morning.

The chlorine loading calculation combines the emission rates of each CFC with its atmospheric properties to obtain a measure of its impacts in the decades following the emissions. It has been used in the WMO/UNEP Ozone Assessment Reports to characterize the ozone impact from CFC emissions. An example of a chlorine loading calculation is shown in the attached figure, which shows how the equivalent chlorine loading changes from year to year.

The total height of the curve at any one year represents the total amount of equivalent chlorine in the atmosphere, which can be shown to be proportional to the expected ozone depletion that occurs during the year.

The height of each color-coded band represents the relative contribution by the particular species from cumulative emissions during prior years to the ozone depletion during that year.

Now, although only results from after 1990 are shown in the figure here, the calculation covers the period from 1930 to the year 2100. Prior to 1996, the emission rates of the species are taken from historical data, and after 1996, the calculation assumes an emission scenario in compliance with the amendments to the Montreal Protocol.

As can be seen from the figure up there, CFC-11

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and CFC-12 continue to contribute to ozone depletion after the year 2000 and beyond despite the fact that their emission to the atmosphere has stopped.

This is because CFC-11 and CFC-12 that were emitted before 1996 persist in the atmosphere and continue to release degradation products that affect ozone. With a lifetime of 50 years, the effect of this "leftover" CFC in the atmosphere is expected to continue through most of the next century.

Thus, the relative contribution of a CFC that will be emitted in the future can best be calculated by comparing it to the chlorine loading currently in the atmosphere rather than by just comparing to the amount of CFC being used for other purposes.

As an example, a typical CFC used in pulmonary drugs has a gram-molecular weight of 180 grams, contains three chlorine atoms, and has an ozone depleting potential of 1. An emission of 1,000 metric tons will add about 0.1 pptv of equivalent chlorine initially. This can be compared with the value of about 3,000 pptv in the present atmosphere at this point which by the way, come from cumulative emission of over 20 million metric tons of CFC over the years.

DR. MURPHY: We need you to start summarizing.

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You have a minute left.

DR. KO: Thank you.

Clearly, it is necessary to take into account the lifetime of the CFC to assess how long the 0.1 pptv impact from a single year emission will persist and to determine the cumulative effect from the emissions that take place in different years and from CFC used for other purposes, as well. This can be accomplished by integrating the effects in time and then comparing the integrated values.

I think the committee for giving me this opportunity to make my statement.

DR. MURPHY: Thank you. Thank you for your nice diagram.

Next, we have John Craighead, M.D., from the University of Vermont School of Medicine. Dr. Craighead, and could you tell us any conflicts you have and who paid your way.

DR. CRAIGHEAD: Madam Chairperson, members of the committee, ladies and gentlemen, I come here as a concerned physician and scientist. My way is paid by the 3M Corporation, but I speak as a scientist and physician with training in pathology.

I would like to recommend with great importance that the Environmental Protection Agency and the Federal

Food and Drug Administration work with deliberate haste and effort to facilitate the swift removal of CFCs from all therapeutic agents. Therefore, I believe it is of critical importance that we work to eliminate MDIs as essential agents when and if they contain CFCs.

Now, first, with regard to my background. I am a Professor of Pathology working actively in the field of pathology and as a scholar. I have contributed extensively to the medical literature and have published in over 30 different books with chapters in scientific contributions.

I have been a consultant to the FDA, to the Environmental Protection Agency, to the Armed Forces Institute of Pathology. I have worked with most of the Institutes of the National Institutes of Health, and I am a recent member of the National Advisory Council of the National Institute for Environmental Health Sciences.

I recently published a book on the Pathology of Environmental and Occupational Disease. I would first like to address the issue of the environment with regard to CFCs and emphasize that the contribution to the environment with regard to CFCs in therapeutic agents and MDIs is substantial, substantial in comparison to other components of our environment that we would consider as contributing to the burden of CFCs in the atmosphere.

Secondly, I would like to emphasize that the ozone barrier, the envelope that surrounds us and protects us from UV-B rays is fragile. All of the scientific information would strongly indicate that the CFC impact is reducing the ozone barrier and increasing UV irradiation.

The biologic implications of this are substantial, although difficult to quantitate and to qualitatively evaluate. The effects on plants, the genetic impact on lesser species, and then the impact on human health is potentially enormous.

Skin cancer is the most common cancer of humankind. It is directly correlated with the intensity of UV irradiation, with the increasing irradiation in the B band that is occurring today and which we would project in the future, we can project that there will be an increasing prevalence of skin cancer occurring as we turn into the new century.

It may reach crisis proportions with regard to human health. Similarly, cataracts are the most common cause of blindness in the aging population. Yet, UV light in the B spectrum is an important contributing factor to the development of cataracts.

These are factors that we cannot ignore, and they implore that we work deliberately, with haste and with

considerable effort to facilitate the introduction of new therapeutic agents with MDIs that do not contain CFCs.

Now, I am a pulmonary physician, I am a pulmonary pathologist. I am very well acquainted with the health effects of chronic obstructive pulmonary disease and asthma. It is apparent to me, though, in reviewing the pharmacological literature and the information that has accumulated on alternate forms of administration of the important agents which protect patients with asthma and COPD from the complications of their disease, that alternates exist or soon will exist.

Therefore, in summary, I would like to implore the FDA to encourage, to facilitate, and to accelerate the introduction of alternatives to the CFC-containing propellants in MDIs.

This is not an issue to be handled in a casual fashion, but in a deliberate fashion. It is important that we apply our efforts to meeting the requirements of the Montreal Protocol, and we do so with our own best interests in mind and with the interests of the health of our citizenry. It is not only a matter of pulmonary health, but it is a matter of --

DR. MURPHY: Fifteen seconds.

DR. CRAIGHEAD: -- it is a matter of the health of

the skin of our population and their eyes.

Thank you for your attention. I would be happy to answer any questions.

DR. MURPHY: Thank you very much for your presentation.

Nancy Ostrum, M.D., Allergy and Asthma Medical Group and Research Center. Dr. Ostrum, if you would like to state and conflicts and who paid your way.

DR. OSTRUM: Dr. Murphy, members of the committee, ladies and gentlemen, thank you for the opportunity to speak today. I am a practicing board-certified allergist who has had experience with CFC-free metered dose inhalers both in clinical patient care and as a clinical trial investigator.

As a matter of disclosure, my trip was sponsored by the 3M Company in light of this experience. My comments reflect my independent opinions regarding the medical issues at hand, and most importantly, the perceived concerns of the patients that I serve.

My clinical experience has been in prescribing CFC-free albuterol to patients with asthma of differing severity. This has been met with good patient acceptance and no noticeable changes in clinical stability.

I have also been involved as a clinical investigator with CFC-free metered dose inhalers containing

different agents including the beta agonist albuterol and the corticosteroids beclomethasone and triamcinolone. Although some of these trials are ongoing, and the results confidential, I am aware of no consistent adverse events or problems with patient acceptance of these study medications.

Based on my experience and the proposed framework for transition over the next few years, I am confident that these agents, once carefully reviewed by the FDA, will be scientifically and medically acceptable alternatives to CFC-containing products.

I would like to briefly offer my opinion in two areas of concern during this transition, the medically appropriate procedure for transition from CFC-containing to CFC-free products, and appropriate measures of patient acceptability.

In my clinical experience, which is corroborated by the patient survey conducted by the American Lung Association, patients trust their physician's guidance in selection of appropriate therapeutic agents, and are very hesitant to change a successful treatment program.

Clinicians often prescribe one product over another for particular patients because a certain medical regimen seems to offer superior clinical stability and patient acceptability.

Thus, the therapeutic class approach to transition is less than ideal in that it potentially deprives clinicians and patients of meaningful therapeutic choices. However, some drug categories, such as beta agonists, bronchodilators may lend themselves to this approach. Beta agonist agents with comparable beta-2 selectivity can generally be substituted for one another without significant medical concern regarding variability and efficacy and safety.

Conversely, I feel that this approach would not be ideal in the category of inhaled corticosteroids. The differences in potency per inhalation and the potential enhancement of drug deposition with alternatives propellants requires scrutiny of each active moiety rather than generalization as a class.

Thus, in the transition to CFC-free corticosteroids, I favor the active moiety by active moiety approach. This will preserve therapeutic choices and allow the careful evaluation of different agents in a timely but thorough manner.

This is also an area where I would propose significant Phase III and Phase IV trials in the pediatric population, which I feel is at greatest risk for long-term adverse effects.

I would also favor the active moiety approach to preserve the availability of agents which have a Category B rating for use during pregnancy. In addition, I would propose following adverse drug experience reports for a significant number of MDI units used in the postmarketing setting over a period of at least a year.

The information combined with the formal postmarketing studies as directed by the FDA would provide an acceptable database to support transition to the new moieties.

The issue of postmarketing surveillance of patient acceptability needs to be contrasted with that of patient popularity. This reminds me of a very popular chocolate diet that I heard about. During your period of dieting, you are required to eat a large piece of Belgian chocolate after each meal. I understand that weight loss is minimal, but compliance with the diet is superior to any plan previously studied.

DR. MURPHY: One minute to summarize.

DR. OSTRUM: Clearly, patient acceptability should be monitored through objective medical parameters to distill issues of clinical stability and patient compliance.

Finally, a comprehensive educational program for clinicians and patients regarding the CFC transition should

be put forward immediately through the NHLBI. I believe that the interests of patients and physicians in maintaining a selection of medically safe and effective medications for disease management are not at odds with a reasonable and timely transition to more environmentally safe products.

Thank you.

DR. MURPHY: Thank you very much for your comments.

Janet Remetta. Dr. Remetta, Chairperson of the International Pharmaceutical Aerosol Consortium. This is the handout from that group.

DR. REMETTA: My expenses were paid by RPR as a member of IPAC this morning.

Good morning. I am Dr. Janet Remetta, the Executive Director of Pharmaceutical Policy Planning at Rhone Poulenc Rorer Pharmaceuticals, but this morning I am speaking to you as Chairperson of the International Pharmaceutical Aerosol Consortium, also known as IPAC.

IPAC was created over seven years ago in response to the mandate of the Montreal Protocol. As an organization, it works with government, medical, and public health organizations to facilitate a smooth and efficient MDI transition.

IPAC represents the world's leading manufacturers

of MDIs. Our members include Abbott Laboratories, Astemetica, Boehringer Ingelheim, Glaxo Wellcome, Mediver Americas, Norton Health Care, Rhone Poulenc Rorer, Schering Corporation, and 3M Pharmaceuticals.

As you well know, the FDA Advanced Notice of Proposed Rulemaking affects the vital interests of each of our member companies. Some of our members are here today to express their own corporate views.

As this process continues, IPAC itself will assess the ANPR from the vantage of the entire industry. In comments to the FDA next month, we will offer our perspective on the critical goals of patient care and environmental protection.

In the meantime, I would like to provide you with some background information on the MDI industry and its program for an MDI transition. First, I will describe for you the commitment the pharmaceutical industry has made to the development of CFC-free MDIs. Secondly, there will be a report on the reformulation progress that has been made. Lastly, I will explain the measures that will be taken to protect patients and the environment as the transition proceeds.

While your committee is very familiar with the metered dose inhaler, it is worth recalling just how

remarkable this device is. The MDI has revolutionized the treatment of asthma and given a new lease on life to patients who suffer from difficulty in breathing.

Today, an estimated 70 million patients rely on these devices in 100 countries around the world. In the U.S. alone, over 14 million asthma sufferers use MDIs. As we speak, more people are being diagnosed with asthma and more people are dying from it than ever before. For example, between 1982 and 1994, there was a 61 percent increase in the estimated total number of asthma cases in the U.S.

As you know, the reformulation of MDIs has proven far more difficult than initially anticipated. We assumed at the outset that it would be possible to substitute new propellants for the old without significant change to either the medicinal formulation or the mechanical device itself, but experience has taught us otherwise.

We now know that instead of simply dropping in a new propellant, we must instead create an entirely new delivery system. An MDI is made up of numerous physical components including a canister, elastomers, a valve, and an actuator. Some of these components are themselves extremely complex. A single valve, for example, may consist of over 25 separate parts.

In the early stages of redeveloping replacement parts, we learned that many of these components interact with the next propellants in ways never previously imagined, yet, creating a new device is only part of the battle. New formulations must also be developed. Unfortunately, the surfactants and co-solvents that worked so well with CFCs, have in many instances proven incompatible with the new propellants.

We are actually redeveloping almost every element in this mix, only the active ingredients remain unchanged. The rigor and extent of regulatory review is also steadily increasing. Today's requirements for demonstrating safety and efficacy, dosing, stability, and purity are more stringent than ever. As a result, the process of pharmaceutical development and approval are far more time consuming than it was just a few years ago.

Recognizing these many variables, in 1990, the pharmaceutical industry undertook an unprecedented joint testing program to demonstrate the safety of propellants that would ultimately replace CFCs. More than 1,400 scientists, at 90 laboratories, in 10 countries all around the world, are currently at work on the development of replacement products.

The industry has already spent one billion dollars

in this effort and anticipates spending several billion more to complete it.

Finally, these efforts are bearing fruit. The first CFC-MDI has been introduced in the U.S. In addition, IPAC members have projected that by the year 2000, as many as 30, and no fewer than 11, new products will have been launched in the U.S. depending on the extent of developmental, testing, and regulatory delay companies encounter along the way.

By the year 2005, a total of 35 new products are projected for launch in the U.S. As the transition proceeds, we also want to assure the world community of our commitment to patients and the environment. Toward this end, IPAC has developed a policy to guide the transition from CFC-driven to CFC-free MDIs. This proposal was unanimously adopted last November in Costa Rica by the 140 nations which are party to the Montreal Protocol.

DR. MURPHY: One minute to summarize.

DR. REMETTA: Under this proposal, MDI manufacturers must first provide regular reports to health and environmental regulators on our progress in reformulating MDI products.

Secondly, we will undertake educational efforts that prepare health care professionals and patients for the

transition to CFC-MDIs. Our goal is to maintain an ongoing dialogue with patients, physicians, and regulatory authorities throughout the process of transition to CFC-free MDIs.

Toward that end, we have launched a joint physician and patient educational initiative with the National Asthma Education and Prevention Program. Our first fact sheet on the MDI transition is currently being prepared and will be published later this spring.

Third, we will encourage the acceptance of new products through product labeling and other appropriate marketing strategies.

Fourth, we are minimizing CFC emissions during the transition period. Emissions for manufacturing continue to be tightly controlled.

The proposal also provides for the cooperation of government officials in assuring a smooth and efficient MDI transition.

DR. MURPHY: Time.

DR. REMETTA: This is a very important point, if I could just conclude?

DR. MURPHY: Just one more point.

DR. REMETTA: At the FDA, that would mean expediting the review of alternatives to the CFC-MDI. We

envision an uncompromised priority focus on CFC-free MDI applications as the single most important step that government can take to speed the introduction of new products.

Thank you.

DR. MURPHY: Thank you very much.

Dr. Wilson from Boehringer Ingelheim.

DR. WILSON: Thank you. I represent medicine for Boehringer Ingelheim. My way here has been paid, not by Glaxo or 3M, but it has, in fact, been paid by Boehringer Ingelheim.

The position that we wish to take here before we came was that the concern for our company related to the ANPR's implications for the individual active moieties, and here we have two that are represented in the description, ipratropium and ipratropium plus albuterol.

As a company, we are strongly supportive of the objective of the Montreal Protocol, and to that end we have been an active member of IPAC and have spent some hundreds of millions of dollars in developing alternatives.

Our initial reading of the ANPR raised some concerns for its impact on the health of the individual COPD and asthma patients of an accelerated phaseout, and some potential obstacles to the development of innovative

alternatives, particularly such as non-HFA delivery systems.

For example, with only 12 months of in-use experience after the introduction of a first alternative for the individual active moiety class before triggering a phaseout, we were concerned for the practicality of then converting over 1 to 2 million COPD patients, who tend to be older patients, from ipratropium to an alternative without problems. We were concerned that the regulatory strategy for the approval of these drugs, which we strongly support, has been to show that they are comparable to the CFC version, not equivalent, and not substitutable, and to that extent the regulatory process has not required that they are examined in all sub-populations, and clearly we agree with that except that the real use over the course of that 12-month period, although we would prefer a longer period, is required to get experience with the various sub-populations who may or may not respond as effectively as alternative agents.

We have seen little evidence, and certainly in a COPD population, that a multidose powder system is equivalent to a metered aerosol under these circumstances.

With one alternatives in the individual active moiety class, there is no opportunity for patient choice, and consequently it might be that no all sub-populations

might respond, and we were concerned that with the accelerated phaseout, the opportunity for major substantive contributions and advancements into other alternatives might be crimped by virtue of this rapid phaseout.

However, during the course of the meeting -- and this is why I have discarded by overheads -- I found many clarifications that have been very helpful from the presentations both of Dr. Jenkins and Dr. Otulana, and I would applaud the FDA for the clarity and the professionalism which they have enveloped to this process because clearly we are much more comfortable with the situation as they have proposed, and the issues that I would like to refer to are the careful assessment by physicians and patients of the response to an alternative before triggering the phaseout, and I think we agree that is imperative.

Next, we were encouraged by the product by product review before proposing the withdrawal, and then with an opportunity for comment, and that we also applaud. We think that is very positive, that the suggestions that the developers of all alternatives who are making good-faith efforts already in the pipeline would be encouraged by the agency, and the very close interaction between the agency, physicians, and patients would certainly go a long way

towards this.

So we would encourage both the committee and the agency to consider four points: that the periodic careful assessment of the success of any alternative before proposing a withdrawal -- which we applaud -- should have more definition, I think in the next phase; that we would continue to encourage the active support for innovative products that are in late-stage development, so an accelerated withdrawal does not jeopardize the final opportunity for these emerging onto the market.

We would encourage a review of the experience of introduction of alternative formulations in other countries to see how successful this has been, whether any problems have emerged, and finally, because of the new assessment of the ANPR as a result of the production at this meeting, we would encourage a prolongation of the comment period because I think the view of many of us may be a little different now from hearing the presentations rather than from reading the document.

DR. MURPHY: Thank you. Congratulations. You are a minute under.

Next, Dr. Rickard from Glaxo. Kathleen Rickard, Director of U.S. Respiratory Medical Affairs at Glaxo.

DR. RICKARD: Good morning. I am Dr. Kathy

Rickard, Director of U.S. Respiratory Medical Affairs at Glaxo Wellcome and a practicing pulmonologist on the faculty at the University of North Carolina. I am pleased to be able to provide some preliminary comments to the advisory committee from Glaxo Wellcome.

As you are aware, Glaxo Wellcome has long been a leader in the development of safe and effective respiratory medications beginning with Ventolin and Beclovent, and continuing with our new innovative products, Serevent and Flovent.

We are committed to protecting the environment with the conversion of these important products to non-CFC-containing MDIs. Currently, we have research and development staff in 12 laboratories worldwide who are actively engaged in developing alternatives to CFC-MDIs.

This has been a technically challenging, time consuming, resource-intensive and costly procedure, but we anticipate having CFC alternatives for our products on the market well within the time frame of CFC phaseout considered reasonable under the Montreal Protocol.

We believe it is very important as we progress through this transition period to ensure that a wide range of therapeutic options remain available to physicians and patients. Therefore, in any transition policy, we must be

careful that well established and accepted products are not removed from the market prematurely and thereby avoiding potentially compromising patients' health. I have been advised by environmental experts that CFC emissions from MDIs worldwide have contributed less than 0.5 percent to total atmospheric chlorine loading - the standard scientific measure of contribution to ozone depletion.

Even if the amount of CFCs used in MDIs does not decline over the next decade, the contribution of CFC emissions from MDIs would be less than 1 percent of total atmospheric chlorine loading. As you all know, asthma is a life-threatening disease that can be fatal, thus, this minimal impact upon the environment must be balanced against the impact upon patient health if currently available MDIs were to be prematurely removed from the market.

The ANPR raises a number of important medical and scientific questions that could have a direct bearing on the availability of needed medications during the transition period. I will briefly highlight three.

First, what will be the impact on patients if according to the therapeutic class provision current medications are no longer available?

The continued availability of individual class products should be a major consideration in light of this

proposal that could reduce the available medications to two active ingredients per therapeutic class.

In comments already submitted to the FDA on the ANPR, many patients have expressed grave concern and anxiety over losing the medications they have come to rely on.

As you all are aware, many patients require multiple types of inhalers to control their disease. This often includes a long trial and error period before the right medications are found to work best for that individual.

Forcing a patient to stop using the very medications that have been found to work best for them, and have developed confidence in, may lead to much consternation and, even more importantly, worsening of their disease control.

There are many reasons why different patients respond to different types of medications, taste, spray performance, lung deposition, as well as both the active ingredients and excipients found in the drug product itself. The need to have a variety of medications available to treat the many different patients we see on a daily basis must be recognized. For these reasons we believe the therapeutic class provision of the proposal would have an unfavorable impact on patients.

Second. Is the therapeutic class approach appropriate from a medical perspective?

Consider, for a moment, the therapeutic class of inhaled corticosteroids. There are profound differences between the different members of this class in potency on a microgram to microgram basis. Changing patients from a more potent compounds with which the patient has achieved good control to a less potent one could lead to a loss of control of the patient's disease or at the very least, an increase in the dosage required to maintain control.

Newer generation medications, such as fluticasone, have been shown to dramatically improve control of asthma. For example, in many patients who are oral corticosteroid dependent, the use of fluticasone has led to complete withdrawal of oral corticosteroid therapy while improving asthma control.

Even within at therapeutic class, each medication exhibits a unique therapeutic profile that proves to be important to a sub-population of patients. For this reason, we do not believe the therapeutic class approach is medically appropriate.

Third and last. Is a multidose dry powder inhaler device a suitable substitute for an MDI as assumed in the ANPR?

A key question is can a dry powder device meet the needs of all our patient types? Dry powders, though marketed for many years, have not achieved widespread market acceptance.

DR. MURPHY: One minute to summarize.

DR. RICKARD: This may be related to individual patient preferences, but in particular, you must keep in mind that various populations including very young patients or elderly or more severe patients may not be able to generate the flow needed to use these devices. Thus, dry powder devices may not meet the needs of many of our patients and MDIs will continue to be the best device for delivery of medications in certain patient populations.

In closing, I would like to reiterate: Glaxo Wellcome is committed to developing environmentally friendly reformulations of currently available medications as soon as possible and within the guidelines of the Montreal Protocol.

This has been a difficult challenge for Glaxo Wellcome and the industry as a whole. We are just beginning to see the results of the work to date. Our preliminary view, at this time, is that the regulatory mechanism proposed in the ANPR, which could result in the banning of time-tested products, would unnecessarily put patients at risk.

As a company committed to providing important asthma medications, and as health care professionals, we must ensure that that as we transition to new formulations, we do not lose sight of our most important goal: that all patients continue to have access to medications which have been instrumental in controlling their disease and helping them to live a more normal life.

Lastly, I would like to thank the committee for allowing me to present these comments.

DR. MURPHY: Thank you, Dr. Rickard. We appreciate it.

Dean Handley, Dr. Handley, Director of Scientific Affairs, for Sepracor. There is a handout, and there was handout for Dr. Rickard.

DR. HANDLEY: Good morning. I represent Sepracor Pharmaceuticals, who will assume responsibility for my transportation.

Sepracor is an emerging pharmaceutical company committed towards to the development efforts that make meaningful improvements in the safety and efficacy of widely sold existing drugs.

Reflecting this commitment, the single isomers or the beta agonists are developmental candidates within the bronchodilator class. Levalbuterol, the single R enantiomer

racemic albuterol, and in turn, R,R-formoterol, the single enantiomer of racemic formoterol, often potential advantages in safety and efficacy over existing racemates. With comparable effort, we have focused on the metabolites of second-generation antihistamines, fexofenadine, the active metabolite of terfenadine, and similarly, norastemizole, the active metabolite of astemizole, provides salient examples of candidates with enhanced therapeutic profiles.

Within the area of asthma therapeutics, our primary position is that children and adults with asthma deserve continued and timely access of new and innovative therapies. Couched within this position, we feel that the pharmaceutical advances should be encouraged as a first priority. With equal consistency, it is our position that patent and technical barriers surrounding the HFA technology impede or preclude successful formulations of therapeutic innovations.

As evidence to these concerns, the currently existing patents, as they were designed, prohibit access to HFAs. Furthermore, many in the field relate significant technical hurdles, as we have heard this morning, which will create extensive and admittedly unnecessary delays in providing asthmatics with pharmaceutical advances.

Turning to our examples with albuterol,

levalbuterol is the single isomer or enantiomer version of racemic albuterol, and by definition, racemic albuterol in all marketed forms exists as a 50-50 mixture composed of equal amounts of the two enantiomers termed S and R isomers of which levalbuterol is the single R isomer.

Clear and consistent research substantiates that the levalbuterol is sole responsible for the observed clinical bronchodilation of the racemate. The S-isomer provides no therapeutic benefit, and is, in fact, an unnecessary contaminant.

Extensive preclinical and clinical studies conducted with levalbuterol demonstrate an improved therapeutic index as compared with the conventional racemic albuterol.

Let us share with you some of the hurdles we have had with the HFA situation. With respect to HFAs, Sepracor has been denied access to HFA technology relevant to levalbuterol formulation by patent holders, specifically, patent holders that market racemic albuterol.

Despite not being able to access critical HFA technology, Sepracor is actively pursuing a parallel track strategy designed to meet the essential needs of the patients with asthma and the defined objectives of the Montreal Protocol.

The duality of our approach involves the first generation levalbuterol formulated with a CVD propellant that will ensure asthmatic patients the most timely access to this improved therapy.

The second generation alternative formulation in development will require additional years associated with the technical and patent barriers within the HFA field.

We support a rational phaseout of CFC propellants which balances the needs of both the patients and the environment. Central to this position are timely advances in pharmaceutical therapy for children and adults asthmatics which should be encouraged as the first priority.

Accordingly, innovators should not be initially encumbered by the numerous barriers associated with the HFA and DPI technologies.

Equally important, product innovators must commit to pursue a non-CFC formulation for second generation compounds.

So, in conclusion, we support a position of timely access of innovative therapies to asthmatic patients should be allowed under the essential medical use exemption. This avoid the patent and technical barriers surrounding HFA technology. In turn, innovators must be seen to pursue an HFA formulation which will be applied to subsequent second

generation compounds.

Thank you for your time.

DR. MURPHY: Thank you very much.

Mary Worstell is next as Martha White is not going to present. Mary is the Executive Director of the Asthma and Allergy Foundation of America.

MS. WORSTELL: Good morning. I am Mary Worstell. I am the Executive Director of the Asthma and Allergy Foundation of America. We are a not-for-profit, patient advocate, patient education organization. We work in public awareness, allied health education, asthma and allergy disease research. I live locally and AAFA is supporting my attendance here.

AAFA welcomes the opportunity to address this body regarding such an important health issue as the elimination of CFC essential use status. We applaud the effort of the FDA and the EPA to arrive at a transition policy which promotes the health needs of the general population without compromising the health of persons with asthma.

Asthma is a chronic disease which requires daily adherence to a medical regime. Patient compliance is directly related to the acceptability of medications in terms of taste, the ease of use, frequency of dose, and other such factors.

When medication is inconvenient or unpleasant to use, the health care community routinely witnesses patients' increased morbidity and what is more tragic, increased mortality. Therefore, postmarketing surveillance to assess patient acceptance and use of the alternative products becomes vital to protect patient interests before removing essential use status.

Internally, AAFA has embarked on a consensus process by assembling a task force with a broad representation of professionals and patients which will make final recommendations to the AAFA board of directors on the issue of CFC-free transition policy. This task force is comprised of: four physicians, three of whom provide direct patient care and one who is medical director for a health insurer; three allied health professionals, representing home health care, an allergy specialty office, and AAFA national program staff; and finally, three patient advocates who, in their professional work, represent biomedical technology, public relations, and a foundation chapter.

Eight of the task force members are asthma patients and/or are parents of children with asthma.

The final recommendation of AAFA's task force and board of directors will be presented for discussion at the stakeholders' meeting next week, and you will hear more of

that in the following presentation.

AAFA wants this council to understand that we endorse the goal of a smooth transition to CFC-free anti-asthma products. Ultimately for this to occur, health professionals, patients, and their caregivers must have a good understanding of the need for the transition and confidence in the new alternative products.

AAFA believes the relationship between the health provider and patient is key for a safe, successful transition. To this end, AAFA has over the past 18 months undertaken a variety of educational initiatives, including: informative articles regarding ozone depletion and CFC-free technology development via our membership newsletter; a press release regarding the first CFC-free product following FDA approval; and correspondence to the FDA/EPA, co-authored with the American Lung Association, stating our commitment the policy and education process.

Currently , AAFA and the American Lung Association are also co-authoring a series of informative mailings to health professionals regarding patient needs in this transition.

Finally, on an international level, AAFA is networking with asthma organizations throughout Europe and Canada to encourage and define our role in forging a smooth

transition to CFC products.

AAFA applauds the initiative of the FDA and EPA in producing this draft policy to provide a finite transition period to CFC-free metered dose inhaler technology and, concurrently, an impetus to the pharmaceutical industry to develop new products. Our task force has reviewed the draft policy. Their initial consensus opinion highlights, but is not limited, to the following concerns:

Removal of essential-use status for nasal corticosteroids via MDI at this time due to the lack of patient acceptance, particularly pediatric patient acceptance, of the aqueous products;

Second, grouping of inhaled corticosteroids and bronchodilators into classes which would require only two products of the same moiety before removal of essential-use status. This process may sacrifice patient compliance and safety, with particular regard to special needs of patient subgroups, for example, pregnant women;

Finally, cost of the new products must not result in undue financial burden to asthma patients.

AAFA will work diligently to address these concerns to its satisfaction for a consensus response to the FDA and EPA through the stakeholders early next month. We will continue our efforts to educate health professionals

and their patients regarding this issue.

We remain committed to the process of balancing asthma and allergy patients' concerns and their interests with the health and welfare of people worldwide.

Thank you.

DR. MURPHY: Thank you.

Next is Alfred Munzer, M.D., who is past president of the American Lung Association.

Dr. Munzer.

DR. MUNZER: Thank you very much.

My name is Alfred Munzer and I am a physician specializing in diseases of the lung and past president of the American Lung Association. I appear here as a volunteer for the association, and I am not being paid for my appearance.

The American Lung Association is the nation's oldest voluntary health organization and has, since its inception, viewed its mission as both the treatment and prevention of lung disease.

The American Lung Association has, for many years, viewed the transition to CFC-free metered dose inhalers as both a challenge and an opportunity. The challenge we face is to balance our role as patient advocates and our commitment to the environment with our understanding that

the transition will move forward.

We are also provided a unique opportunity to refocus attention on the proper diagnosis and management of asthma. This includes the need to revitalize the relationship between physicians and other health care professionals and their patients with asthma.

The American Lung Association's dual concern for the environment and for the patient with lung disease has led to a partnership with the pharmaceutical industry and government in seeking a seamless transition to CFC-free metered dose inhalers.

The ALA has collaborated with the IPAC on the need and structure for an "essential use" exemption under the Montreal Protocol to allow manufacturers time to develop safe and effective alternatives to the CFC inhaler.

ALA also worked with IPAC on the initial nomination of MDIs in this category. At the request of the Environmental Protection Agency, the ALA serves as the convener of a stakeholders' process to provide ongoing advice and counsel from medical professional and lay organizations in the transition.

The American Lung Association applauds the Food and Drug Administration for planning a thoughtful, deliberate and minimally disruptive transition process. We

appreciate being invited to provide input early in the decisionmaking process and pledge the support of our nationwide organization and our medical section, the American Thoracic Society.

We also recognize that by FDA's action, the United States becomes the first Party to the Protocol to address how the transition to CFC-free metered dose inhalers might be managed. Again, this leadership role deserves our praise regardless of the outcome of our comments on the proposal.

In comments to the Technology and Economic Assessment Panel, the American Lung Association with the Stakeholders Group outlined criteria for a successful transition including: mechanisms to ensure product safety and efficacy; steps to secure patient acceptance through education and monitoring activities; mechanisms to preserve the patient/physician relationship; a clearly defined time frame to allow health care providers to plan and implement patient treatment strategies and corresponding patient education efforts; mechanisms to address product withdrawal including voluntary withdrawal of products for which a CFC-free alternative does not exist.

The Advance Notice raises many questions and controversies regarding the structure and time frame for the transition. The American Lung Association and the American

Thoracic Society are reviewing the following aspects of the notice for comment:

1. Whether, in fact, the availability of an identical pharmacologic agent in a CFC-free inhaler should displace a product in the CFC formulation;
2. Whether the identical pharmacologic agent in a metered dose inhaler and in a dry powder inhaler are alternatives acceptable to patient populations;
3. Whether products not identical might nonetheless be considered equivalent;
4. Whether the placement of OTC products in a group other than their pharmacologic peers is acceptable;
5. Whether the decisionmaking structure adequately addresses the special needs of the pediatric population;
6. Whether the variety of time frames under consideration provide sufficient time for the general practitioner to appropriately transition patients to the new formulations ensuring that the patient receives a sound treatment plan, education, and followup;
7. Whether the provision for postmarketing surveillance studies are adequate to assess all the factors to determine patient acceptance of a new formulation.

The American Lung Association looks forward to an

ongoing dialogue with the Food and Drug Administration as the plan for the transition is laid out.

Thank you again for the opportunity to address this very important issue affecting the well-being of millions of people with asthma and chronic obstructive pulmonary disease, as well as the well-being of our planet.

Thank you.

DR. MURPHY: Thank you very much.

John Georgitis. Dr. Georgitis is Chair of the American College of Chest Physicians, Council on Sections, and a member of the ACCP Board of Regents.

DR. GEORGITIS: Good morning. Thank you.

DR. MURPHY: And who paid your way here?

DR. GEORGITIS: Well, I am here representing the American College of Chest Physicians, who has sponsored my trip here. I am a Professor of Pediatrics at the Bowman Gray School of Medicine and Fellow of the American College of Chest Physicians, and a member of the ACCP Board of Regents.

Also, today with me is Alvin Lever, who is the executive vice president and CEO of the college. The ACCP is a professional medical society of more than 16,000 physicians, scientists, educators, and allied health professionals who specialize in cardiopulmonary health and

critical care medicine worldwide.

Our mission is to promote the prevention and treatment of diseases of the chest through leadership, education, research and communication.

As you have known, there have been a continual increase in the incidence, morbidity, and mortality of asthma in recent years, particularly in the inner cities. As we address this issue today, we must keep this important aspect, the health of the U.S. population foremost in our concerns.

The ACCP strongly supports the Montreal Protocol to phase out substances that deplete the ozone layer. We also feel that it is important that new CFC formulations not be considered or approved.

We agree that alternatives must continue to be developed for the CFC propellants used in MDIs today, especially, for asthma and COPD. As you know, in November of 1988, signees of the protocol approved measures to accelerate production of non-CFC alternatives.

We agree with the Food and Drug Administration that it is important to strike an appropriate balance that best protects the public health while ensuring the availability of treatment alternatives for asthma and COPD.

We, however, have several serious concerns.

First, the proposal to eliminate the CFC-MDIs at least 12 months after a single, non-CFC-MDI containing the same ingredient is very limiting. Physicians and their patients should have the widest range of options possible. The current FDA proposal would severely limit the options of the physician and increase the risk to the patient further especially if only one new product is not tolerated by the patient.

Moreover, removing an entire class of medications when three new products were just recently available limits the choices to the physicians and patients. The rapid acceptance of new formulations will heighten the risks associated with unintended adverse consequences caused by new products. We are very concerned about the risk to the patient if he or she cannot tolerate or obtain satisfactory results from the new formulation.

Also, what is there is a product recall or unanticipated product difficulties based upon supply and demand? What would our patients' alternatives be? We don't see that they would have any.

The FDA recommendation that essential use of nasal CFCs be lifted is very laudable since there are now six non-CFC alternatives available, and greater than 60 percent of patients are already using them, but there is still a

sub-population that need the CFC nasal inhalers.

We are concerned that this accelerated timetable for transition to non-CFC formulations may have a serious impact on the future health costs and patient care. Many of the current medications taken off the market will be the less costly generic formulations. The proposal could be given to the patient and physician are more expensive, but fewer choices.

Also, physicians and patients need to be educated in using these new products. Without time for adequate education to assist in transitioning to the new methods, the potential of increased morbidity and mortality is a real threat.

We strongly recommend that the FDA not take any further action this year since the Protocol parties have adopted a series of measures to assist ongoing market forces in effecting a transition to non-CFC including a federally sponsored transition committee especially aimed at education and since over 140 nations, including the U.S., have just rejected the product ban proposal.

The ACCP recommends that no further action be taken by the FDA until the preliminary meeting of the Montreal Protocol, scheduled for November of 1998. The FDA strongly should take under advisement the recommendations

made at that time.

DR. MURPHY: Twenty-five seconds.

DR. GEORGITIS: We feel the FDA should wait until the broad range of CFC-free medications are available and acceptable for both patients and physicians.

Thank you.

DR. MURPHY: Thank you. Thank you very much.

Daniel Ein, who is president-elect of the Joint Council of Allergy, Asthma, and Immunology. Dr. Ein.

DR. EIN: I am Dr. Daniel Ein, president-elect of the Joint Council of Allergy, Asthma, and Immunology. I have no conflicts of interest, financial or otherwise, and since I drove here from my office downtown, I funded my own way.

The Joint Council is a professional nonprofit organization comprised of the American Academy of Allergy, Asthma, and Immunology, and the American College of Allergy, Asthma, and Immunology. On behalf of the 4,000 clinicians and researchers who are dedicated to providing care for the 10 to 15 million Americans who suffer from asthma, I thank you on behalf of my organizations for the opportunity to present comments to you today. Actually, after hearing Dr. Georgitis, I wanted to get up here and say me, too, and then finish. We have not communicated about our comments prior

to this meeting.

The Joint Council supports a timely and orderly transition to CFC-free metered dose inhalers for the management of asthma, but one which honors the patient-physician covenant of selecting appropriate therapeutic options. A seamless process must be established to facilitate the increased utilization of non-CFC products when they become available.

We have, however, significant concerns as it relates to our ability to appropriately manage our patients with this disease. We feel it is inappropriate for the FDA to remove all CFC products for an active moiety when only one non-CFC alternative is available.

This does not allow for any market competition, and it disadvantages those populations which depend on less expensive agents for the treatment of their asthma. This would have enormous financial impact for state Medicaid drug costs, Medicare patients, and uninsured or inadequately insured individuals who could not afford the new non-CFC agent.

Further, the mandatory change in medication as a result of the actions proposed would have the potential to substantially disrupt the current course of treatment for many of our patients and significantly limit our treatment

options. We do not believe that this is in the best interests of patients and could certainly lead to detrimental unintended consequences.

The Joint Council believes that U.S. policy with regards to CFC-containing MDIs must recognize the enormous changes in clinical practice and significant patient experience which will be necessary to ensure a smooth and safe transition to the new product.

We are concerned about the FDA proposal especially with regards to treating all inhaled corticosteroids or all short-acting bronchodilators as therapeutic equivalents. In fact, there are medically significant differences among individual members within these classes of drugs.

As practicing physicians, with extensive experience in the treatment of asthma, we oppose each of these components of the proposal because we believe they will unfairly punish those of lower socioeconomic status, those are the patients and populations most vulnerable to morbidity and mortality of this disease, and also to the elderly populations on fixed incomes.

The Joint Council opposes any ban or phaseout of existing CFC-containing MDIs until such time as there is a range of therapeutic options in the marketplace. We believe that the current target date established by the Montreal

Protocol of 2005 is reasonable especially since the environmental impact of CFCs used for health purposes is not great relative to the risk of inadequate treatment options for persons with asthma.

I certainly don't need to remind this panel of the seriousness of asthma as a public health concern affecting millions of Americans as it does. Any policy to alter therapeutic options must not risk or limit these options nor the choices of physicians and patients in its management.

On behalf of the patients who we treat, we request that you reconsider the proposal and refine the proposal as published on March 6th. We believe that you, in conjunction with the EPA, should do all that is possible to encourage industry to pursue the development and approval of alternatives to existing CFC-MDIs, but without jeopardizing treatment regimes.

Further, in keeping with the commitment adopted at last year's meetings of the parties of the Protocol, the FDA should assure that pharmaceutical sponsors receiving CFC exemptions are putting forth due diligence and evidence of reasonable progress to develop non-CFC products.

We of the professional societies of Allergy stand ready to help with the transition to CFC-free MDIs in any way we can, and we thank you for consideration of our

thoughts.

DR. MURPHY: Thank you and I apologize to you for mispronouncing your name.

I believe James Limbaugh is not going to speak.

Charles Rice from the National Association of Pharmaceutical Manufacturers.

MR. RICE: My name is Charles Rice. I am president and CEO of Day Laboratories of Napa, California, and a member of the board of directors of the National Association of Pharmaceutical Manufacturers representing the independent generic drug companies in the U.S.A.

NAPM is in full support of the committee's activities and certainly of the intentions and spirit of the Montreal Protocol. However, we cannot support this proposal as it is written. We applaud your efforts at least on the dedicated goal of a seamless transition which this proposal will not effect. We also applaud your efforts at considering all relevant information.

We are a bit concerned that throughout this process none of the generic associations have been contacted for input. You must remember, although we are generic associations, many of our members are not generic companies, and we are also innovators.

In terms of your considerations as stated today,

there are no mentions of the impact on generic drugs. There is no mention of the future potential for generic alternatives. We know in past history what has happened with FDA regulations for approval of generic alternatives for this classification of drugs, and it is appalling on a world scale.

The costs of albuterol sulfate inhalation delays alone approach 3 to 4 billion dollars, not million, billion dollars. If we take this action without a consideration for generic alternatives, for the next decade, there will be no generic alternatives or versions of these products, and the costs will be in the tens of billions of dollars, potentially hundreds of billions.

We do not think this is in accordance with Executive Order 12866, which seems to have been somehow or another evaded in this initial proposal. We encourage you to go back and look at this executive order and factor in all the aspects including the economic considerations and considerations of equity which are specified in this executive order.

The FDA has been very quick to notify all of the industry, both branded and generic, that its resources are limited. Some of the provisions of this proposal might as well require a new branch of government. There is a lot of

work to be done here.

We appreciate new terms, such as credible evidence and persuasive evidence. We would like to see those moved into the generic drug provisions today. Maybe we could get moving and stop wasting time on nonproductive work.

However, we feel the agency may be setting itself up for an increase in workload that it has not yet anticipated. There are guidelines to be written, informal guidances, position papers, notices. Someone has to do this. NAPM and the other associations would very much like to know where these resources are coming from and what is going to stand by the side and be avoided or negated during this process. This is not very easy.

I think some of you have even mentioned these are highly complex issues. NAPM wants to stress the patient must be first. The Montreal Protocol is very important, but the health and public safety is the charter mission of FDA, and it must be the priority.

I would like to clear the air on one statement that does show up in this proposal. I know it is nice to think of regulations as spurring innovation, but I believe we can safely say it is false assumption. Regulations spur change. Sometimes it is change for the better, sometimes it is change for the worse, and sometimes it is change for the

sake of change, but it is not spurring innovation.

What spurs innovation is competition, and we can parade any number of economists through this advisory committee to testify to that exact fact.

In the U.S. pharmaceutical marketplace, the best means of competition happens to be generic drugs, and those data are irrefutable. Nothing in this proposal allows for a provision for generic drugs. In fact, for the next --

DR. MURPHY: Forty seconds to summarize.

MR. RICE: -- decade, there will be none.

I strongly urge you to reconsider. NAPM has a alternative proposal we would be happy to discuss with the advisory panel and any of the members of the audience. However, we need a different forum and a bit more than five minutes for that.

Thank you for your time.

DR. MURPHY: Thank you very much for your comments.

Gene Colice. If I pronounced it wrong, correct me. Dr. Colice is the Associate Director of Clinical Research for 3M. And Mark DuVal also.

MR. DuVAL: I am actually Mark DuVal. I am Division Counsel for 3M Pharmaceuticals. My attendance has been paid for by Glaxo Wellcome.

[Laughter.]

MR. DuVAL: Just seeing if you are still awake. On behalf of 3M Pharmaceuticals, I will discuss the overarching public policy issues and Dr. Colice, Associate Director for Clinical Research, will then address the postmarketing surveillance requirement.

I want to tell you a story, a story of a company that 10 years ago responded to an environmental mandate, a challenge, and spent \$125 million to do so, and 500 person years, and then launched the world's first CFC-free albuterol in Europe over two years ago. It is now approved in 36 countries.

We are also sharing our CFC-free technology which ultimately will create more competition in the marketplace and more choices for patients and physicians. We are currently today working with seven different companies on 11 different drugs, and because the ANPRM was published, four other companies came to our door commencing negotiations on contracts for seven more drugs.

The best example of how we provided our technology to these companies, who can still sell them under their own trade names, is Proventil HFA to Schering-Plough.

What has the Montreal Protocol challenged us to do? Makes of MDIs were given a temporary exemption to

develop technically feasible alternatives. Every member of our industry started with the same time frame and opportunity to do so. This does not mean we had to develop products that are bioequivalent or even substitutable in a technical sense. We sought out to develop technically feasible alternatives.

Indeed, in our development efforts on our products and those of our partners, it is not surprising that we found we can make dramatic improvements to this 40-year-old technology which we invented.

This environmental mandate has resulted in technologically improved products for patients.

Moving to the FDA's suggested transition approaches, we believe the FDA is on the right track. We feel it is best to proceed first by transitioning products on an individual active-moiety by active-moiety basis because it commences transition on a CFC-MDI as soon as an alternative becomes available.

When enough individual active moieties are reformulated and transitioned off the market, then an entire therapeutic class of drugs could be transitioned off the market. This will provide FDA with an opportunity to evaluate the success of the individual active moiety transitions, prior to removing the whole therapeutic class.

To help us visualize what a transition might look like, let's look at an example transition on this overhead. I apologize for its size, and there is not enough time to go through it as I had hoped, but the only thing I guess we heard disappointing about the FDA's remarks today was when they said that the first product may be transitioned three or more years from now.

It is disappointing because when the FDA approves a product, it is a technically feasible alternative, medically and under the law. The FDA at that point in time, if we are looking for true time compression in the regulatory process, could publish a rule stating that they now have an alternative, but that other products will not be transitioned off the market until postmarketing surveillance data is collected, however we define that, and Dr. Colice will address that.

Then, if the PMS data is satisfactory, the FDA could publish a final rule stating that the CFC-containing versions that have become nonessential will come off the marketplace.

That entire transition process could take a year to a year and a half, which is more than enough time. We have been out on the market for a long time in Europe, over two years. We are approaching four months in the U.S., and

this product have been sampled for a long time in terms of Proventil HFA.

Then, if you look at the therapeutic class approach, as you accumulate critical mass, two to five years later, you would have a therapeutic class transition.

This dual approach has many advantages, and I will only mention two.

DR. MURPHY: Your group has two more minutes.

MR. DuVAL: Proceeding first with the active moiety approach gives the patient and physician the most choices because, for example, in the beta agonist situation, beta agonists would be available until the individual active moiety transition takes place.

Second, during the transition period of the first active moiety, there will be two or more albuterols, but at the end of the transition, there may not be two albuterols, but neither are there two Seravents, Azmacorts, Flovents, or Tilades. As you know in our industry most active moieties in MDIs are sold by only one company, due to patent protection. Choice is preserved by having several active moieties, not by having several versions of a single active moiety.

Second, the therapeutic class approach has another important purpose. Under this approach, the company who

lags behind in reformulating their CFC-MDI runs the risk of losing their product. The therapeutic class approach therefore provides the incentive for companies to proceed quickly in reformulating their products.

By announcing to the world that the first product will be three to four years away, we will have people walk away from us who are currently willing to start developing CVC-free products, but with that kind of lag time, they will go back to their own lab even though they failed and try and start all over again, and that is an unnecessary delay for the environment.

DR. MURPHY: Thank you. Gene, you have a minute to tell us the message.

DR. COLICE: A minute. Okay. Thanks very much. I thought you might give me extra time because we are so far ahead. Just kidding.

DR. MURPHY: No, to be fair to everybody.

DR. COLICE: And I understand. Certainly, if there are questions that the panel might have, we would be available afterwards.

Concerning criterion 3, which relates to postmarketing safety data, let me remind you that the propellants have been extensively evaluated. IPAC has done that process. The active moieties involved in the

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transition process are well known through decades of use in millions of patient years.

The new formulations have been extensively evaluated and the committee obviously knows that, having gone through the rigor of the evaluation of Proventil HFA. Once the new formulation is approved, it should be considered a technically feasible alternative. It is reasonable to collect additional safety data after approval, and we believe that additional safety data could come in either of two ways: surveillance of spontaneously reported adverse events, if sales ensure use of the product in a large enough population, or a formal postmarketing surveillance study, if initial sales are not sufficient. Data accumulated outside the U.S. should be used in this process.

We feel it is unnecessary to incorporate criteria of patient acceptance into postmarketing surveillance studies for several reasons. Obviously, the experience with the active moiety is one very important one. Second, of course, is the rigor at which the new formulation has gone through the approval process.

The approval we believe is a very important transition point.

Thank you very much, and I will certainly be

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available to answer any questions.

DR. MURPHY: Good, and I would like to ask you to stay, and everyone if they can, to stay in case the panel wants to ask further questions.

Thank you all for your very informative and succinct summaries. What I would like to do now is ask if there are other comments or statements from the floor in this publicly open meeting. I would like to ask you, if you are coming forth from the floor, to limit your comments to two minutes.

Does anybody have any comments?

[No response.]

DR. MURPHY: I think what I would like to do now is break for lunch since this is a good breaking point. I would like everybody to be back here by 1:15.

[Whereupon, at 12:15 p.m., the proceedings were recessed, to be resumed at 1:15 p.m.]

AFTERNOON SESSION

[1:15 p.m.]

Open Committee Discussion

DR. MURPHY: What we are after here is not a consensus and not a vote. Again, the laws have been set, so we are not going to change the law about whether this has to be done or not. So, I think we are here to discuss how it should be done.

I guess before everybody leaves, as outgoing Chair and outgoing committee member, I would like to just thank all of you for the wonderful job you have done on the committee, and I would also like to thank the FDA and John and Bob for everything I have learned while I have been here and for the wonderful presentations that they have given, and for all of you from industry for the excellent job that you have done. I think this has been a really wonderful experience.

And for anybody who is coming on the panel, I would just like to say that when I was Chair of the National Asthma Guidelines we set some very strict criteria for whether you could be on it or not, and that had to be staying through the meetings, and being a West Coaster myself, I know how hard it is to get back, but the FDA is willing to pay your fare overnight, and they do bring us in

here as consultants, and they really want all of our opinions, so I think any effort that you can make to stay through the meetings is really important to the FDA.

Did everybody find their questions? Okay.

When we are discussing things, if somebody from the audience has a really important point, particularly I would say technically, if you have information from your own experience, your data, your company, your organization, that you really would like to contribute at this time, I am very willing to have you contribute because I think what we want out of this is really to hear everybody's ideas as to how to do this best.

I would say that it is always easier to critique something that has been written than to write something fresh, and I think that this is early in this process. The FDA has done a wonderful job of putting up a first draft, and that is really what it is.

I think they are anxious to hear, not just that it's not good, but how could it be better and what alternatives would you have, and that might be even submitting something in writing to them.

I am going to move a bit around with these questions. What should constitute a "technically feasible alternative" to a CFC-propelled MDI (including what are the

roles of dry powder inhalers and novel devices as alternatives)?

What comments do you have as a group on that? Do you think dry powder inhalers can substitute for MDIs, where do you think they can substitute for MDIs, what other devices might substitute for MDIs, what are your feelings as clinicians, et cetera, about this?

DR. JENNE: Well, I am a little bit disturbed by the fact that the DPIs are sort of taking a back seat simply because they haven't been introduced in this country and that the Scandinavians are quite enthused about them, and I think that one of the concerns is if we are going to focus on MDIs in this country, how long do we have to wait for the second application of the HFA to the next moiety, and I have no idea. I don't know whether anybody is willing to give us an estimate of that.

But if we, let's say hypothetically, had to wait two or three years, we certainly would want to be exploring the DPI situation and the satisfaction that people get from using the DPI.

DR. MURPHY: Berri.

MS. MITCHELL: Just another comment on that. I think, as an educator, so much of my time is spent in trying to teach and re-teach people how to use MDIs. We have had

to go to spacing devices, we have had all kinds of different options, and as we are well aware, when we add the spacers in, it doesn't necessarily mean that we are getting the same amount of medication that we think we are.

So, definitely, I think this opens up a new field of really innovative ideas for the patients, and I think if we can potentially come at it from a very positive standpoint and provide as much consumer information as possible to make this an easy transition, incorporating them into the process, it will be a positive move forward for them in terms of not just their breathing, but the rest of their health as far as that is concerned, too.

DR. MURPHY: That is a good comment.

Les.

DR. HENDELES: I wonder what would happen if the American public liked the DPIs, actually liked them better than the MDIs, you might consider in that policy where you have a requirement of at least two MDIs, you might somehow adjust that because at least the people in Europe, in the Scandinavian countries, had both MDI and DPI available, and those people elected to prefer, 80 percent of the people prefer the DPI, and that just kind of happened spontaneously. It could very well happen in this country.

We don't know because our patients haven't had

that option, and once they get that option, they may very well prefer it, so that 2 to 1 ratio that you have might need to be adjusted.

DR. MURPHY: Molly, you had a comment?

DR. OSBORNE; It is a comment and a question. The question first. My question is, how much do you want this committee to specifically address technical feasibility? In other words, we have learned a lot in the last year or two about delivery systems, canisters, elasticizers, propellants, solvents, delivery devices, and I am not clear on how much we need to define what a particle size distribution is, what the delivery time is.

It seems to me that in broad categories, we need to make sure the delivery system is basically equivalent, and I think, as Berri was getting at, that is it giving a comparable potency drug to the patient, and if not, then, we as educators and patients need to understand the difference between the new system and the old system, and other than that, I am not sure how much you want the committee to address today.

DR. MURPHY: I would ask John how much detail would you like, Dr. Jenkins, from the committee?

DR. JENKINS: I am sorry, I was distracted.
Detail on what?

DR. MURPHY: Detail on -- Molly?

DR. OSBORNE: In other words, we can certainly say that for the new devices, when you ask about technically feasible alternatives, we want them to have basically the same kind of delivery and the same kind of potency of the drug when it is deposited in the airways, but whether you want us to get into actual delivery systems, the canisters, whether the organic solvents affect the elasticizers, whether the propellants give a different delivery time, those sorts of questions, I am not sure if that is what you are looking for or whether you simply want clinical opinions.

DR. JENKINS: We are certainly not interested in your delving into the elasticizers and the excipients and all those issues. The term "technically feasible alternative" kind of comes out of the requirement under the essential use determinations where it says that the use of CFCs are essential, number one, because there is no technically feasible alternative way to deliver the drug without the CFC. So, the word "technically feasible" kind of comes out of the criteria for essentiality.

I think what we are talking about is more the broad general sense, and it kind of bridges also into patient acceptance and convenience and overall general

medical acceptability, and not -- we will take care of the issues related to elastomers and rubber gaskets and all that stuff. We are more interested in the broad clinical questions.

DR. OSBORNE: Then, I would just say we need to make sure that the drugs are either equivalent in terms of their potency or if they are not, that both educators and health care providers and patients are aware of that. There needs to be a way to define potency.

DR. MURPHY: Dick, you had a question?

DR. AHRENS: Reflecting the same issue. I do have some concerns about efficacy in this definition that you are after here. The emphasis has clearly been on tolerability and patient acceptance and safety, and so on, and I think that is appropriate, but I do have concerns about the fact that we may have, already do have products marketed that we really don't know what the relative potency is, that is, how many puffs of this new inhaler are equivalent to how many puffs of that older inhaler.

If you take the example of Proventil HFA, and then think for a second about the fact that epidemiologic studies show that fenoterol is associated with greater risk of life-threatening events than is albuterol, and at least one of the credible explanations, at least part of the credible

explanations for that, not the only one, is that it is twice as potent.

Now, suppose we have a new product like Proventil HFA replacing albuterol, that might be twice as potent, and yet we don't know that prior to marketing because in the approval process, providing that information in a clearly understandable fashion was not a requirement.

From what I have been privy to in terms of data on Proventil HFA, I think we really don't know what the relative potency is. We know that it certainly has an effect better than placebo, and it is roughly in very crude kind of bronchodilator studies in the same ballpark, but we don't know what the relative potency is, and it is entirely within the realm of possibility that it is twice as potent.

If we really don't know that before it is marketed, I guess I am not reassured by the postmarketing studies being required for one year in a situation where the product is, in fact, going to see really very little use, that we are really going to pick up on the fact that in real life circumstances, for example, when the patient wakes up in the middle of the night or has a severe enough attack that they might have to go to the emergency room or even have a life-threatening event, that we are going to know about what the relative potency is and that it isn't going

to have either potentially more significant long-term toxicity or perhaps less efficacy if it is considerably less potent.

So I guess it would be wise to have that information, and for beta agonists that is certainly very doable, for inhaled steroids it is maybe a little harder, but I think not impossible.

DR. MURPHY: Let's take that first point, and I would like to ask maybe John to comment, and you would like to comment from 3M.

DR. JENKINS: I think Dr. Ahrens' points are well taken. The clinical program that we have been recommending that sponsors follow have been focused on trying to show comparability between the new product and the old product. That doesn't mean that the dose out of the mouthpiece has to be the same. We are looking at clinical effect comparability, the safety and efficacy comparability, and as you know, for inhalational products, that is very difficult to do, because of the dose-response curves often being very shallow.

So we do have some data, and I know you have seen it for Proventil HFA, but we will hopefully have data for all the products that we are approving under this transition policy to give clinicians some idea of how comparable they

are to what they have been used to using. It won't be perfect, and it won't be the bioequivalence type of data that you would get, for example, for a generic.

One other point -- I know Dr. Colice from 3M is probably eager to speak to the point of Proventil HFA -- the 12 month of postmarketing U.S. data is considered to be the minimum amount of data. Again, that doesn't mean that once 12 months have passed we always will know enough. I mean if the product doesn't get very much penetration into the marketplace, and the manufacturer hasn't done a large postmarketing formal study, then, we may not know enough after a year to make a judgment about the widespread acceptability of the product. So that is factored in, as well.

DR. MURPHY: Do you have a comment, Dr. Colice?

DR. COLICE: Dr. Ahrens's comments about the potency of Proventil HFA, although superficially may seem reasonable, I think are really unacceptable. I think with Proventil HFA, we have an extremely well characterized molecule, and it is really very clear that it just can't be twice as potent, from everything we know about the particle size and the medication delivery, it is just scientifically and biologically not plausible.

So, to make statements like that to suggest that

this product could be twice as potent as Proventil, is just really not acceptable.

DR. MURPHY: Well, I think that you were raising that as a theoretical.

DR. AHRENS: I have spent years thinking about this sort of thing, and working on this area, and with the studies that were done, I mean the kind of confidence that it gives you in terms of knowing what the relative potency is virtually none, and with that said, you know, I have heard a lot this morning about -- and I am certainly aware that it is true -- about how all these things had to be totally reengineered. With beclomethasone, there certainly is some current evidence that more may be delivered. Now, this is a different product with albuterol, I understand that.

I think it is certainly within the realm of possibility, and to imply that I know that it is twice as potent, or in fact, in my heart of hearts I really believe that is true, would be unacceptable. To raise that at least as a possibility, I think it is actually more likely based on the data that I have seen, that it is probably between about 50 and 75 percent more potent. I think it is more potent.

Coming back to my original point, I guess, is that

I think we have got two choices. One is to really have a postmarketing surveillance program that not only addresses safety and tolerability issues, but makes sure that when a patient uses this product in the middle of the night, when they wake up with asthma or when they have a potentially life-threatening event or need to go to the emergency room, that it provides equal protection for the patient in that circumstance, and we don't need the relative potency information if we have adequate postmarketing programs that assure that that is true, and that there is no greater toxicity because it might be more potent.

On the other hand, if you knew what the relative potency was, before you launched into those programs, you would have a much better idea of how to target the postmarketing programs and achieve the maximum benefit from them by knowing what to really look for.

If it is more potent on a puff-for-puff basis, looking for less efficacy is probably not an issue, but greater toxicity might well be. And I understand that it is not a requirement for a new product that it be bioequivalent on a puff-for-puff basis to the old product, and I think that is entirely appropriate.

My only concern is not knowing what the relative efficacy is. If a product is more or less potent than what

we have all been used to using, I think we need to know what that is, and if we know what that is, we will know better what to be aware of as possible pitfalls as the transition gets made.

Now, in my heart of hearts, a disaster scenario like rising death rate because it is twice as potent, I think is really quite unlikely, but we are dealing with a whole lot of people here, and we have methodologies that are -- you know, this kind of information is not that hard to provide, and I am concerned that we are failing to take the opportunity to protect the patients in the greatest way possible.

DR. MURPHY: I just want to see if I am hearing you right. So, what you would like is to see relative potency data, so that you know where the drugs stand as they come out, be it a dry powder inhaler or an HFA, is that --

DR. AHRENS: Yes.

DR. MURPHY: And, John, what kind of requirement is there for that at all now to look at relative potency of drugs as they come out?

DR. JENKINS: Well, our recommended clinical programs include an active control in dose-ranging studies, as well as the pivotal safety and efficacy trials. Again, there is no requirement that the drug be shown to be

equivalent or even be shown to be exactly how potent it is versus the other drug, but we do try to get some general level of feeling for that.

If that were to be the standard, I would be interested in hearing how people would propose to go about doing that, particularly with the inhaled corticosteroids, and in that class of drugs, the dose-response curve for efficacy is very flat, so it is hard to get a separation of doses. It is much easier now to do the potency on the systemic absorption side, and we are recommending that companies do that.

We are looking at the systemic safety by pharmacokinetics or by adrenal axis suppression studies or both. On the bronchodilators, sometimes the pharmacokinetics for systemic safety are less easily accomplished, but we are looking at cumulative dose safety studies compared to the CFC product, but for efficacy, I would be curious to know where we go beyond what already is being done.

DR. MURPHY: Let's just take that one point. Who has some thoughts about that? Les? This is looking at efficacy. How would one look at efficacy?

DR. HENDELES: I think the issues have to be separated. You have to look at efficacy and systemic effect

perhaps separately, and then somehow determine a ratio. I would raise the issue with Dick with the Proventil HFA, that cumulative dose-ranging study that they conducted probably would have demonstrated toxicity if the drug was not comparable.

I agree that the topical efficacy part was hard to determine from that study, but you certainly would have seen, if it was delivering more drug to the alveoli, you would have seen a change in serum potassium or heart rate, right?

DR. MURPHY: Do have a comment to follow that, Dr. Colice?

DR. COLICE: I think there has been a little selective memory here. I think as the committee should remember, we presented information on potency ratios, comparing Proventil HFA and Ventolin. We presented that very information. From our calculations using accepted approaches, it is clearly not anywhere near 50 percent or 75 percent more potent than Ventolin. That information was presented to this committee. I would be glad to distribute it to you again if you would like, but it seems to be selective memory when you refute the information you have already had in front of you, which clearly shows that Dr. Ahrens is incorrect.

DR. MURPHY: What I am looking for here is not who is correct and everything, but really how do you look at it and how did you look at it in your studies. I just can't recall right now.

DR. COLICE: We had a cumulative dose study in which patients were given up to 16 puffs of the beta agonist over a short time period, about two hours, and we monitored bronchodilation, as well as serum potassium and heart rate, and there actually are no differences between the Proventil and Ventolin groups. So that is a dosage which is well in excess of the labeling, and we saw nothing to be concerned of in terms of adverse effects including carefully monitored potassium levels.

DR. HENDELES: Isn't that what I said?

DR. MURPHY: Yes.

DR. AHRENS: And I think that is accurate. I have no dispute with that in terms of the systemic effect. The systemic effect is, as Les said, probably related to the alveolar delivery, whereas, the efficacy is probably more related to the airway delivery, which are not necessarily the same thing.

I do actually remember the data quite well. I think the difference is not in our recollection, but in our interpretation of what that data says.

DR. HENDELES: To answer the second part of the question, I think that Soren Peterson has shown us that even though the dose-response curve for inhaled steroids may be flat for symptoms and pulmonary function, there is a marked dose-response curve for blocking of exercise-induced asthma when the drug is used for a month period, which is an indirect measure of airway reactivity, so I think that is possible by using a surrogate-like airway reactivity to maybe distinguish or at least to define what relative potency is topically, and then, as you said, there is a dose-response relationship for systemic, so one could come up with a topical systemic ratio for each new product.

DR. MURPHY: Now, you are an expert on reactivity, Dick. What do you think about that in steroids?

DR. AHRENS: I think that the technology, the methodology is not clearly as well worked out as it is for beta agonists, but I think the kind of approach that Les is talking about has a real good chance of working and being able to come up with that information.

To my knowledge, it hasn't been put to the test of has it actually been done and you come up with clear-cut topical to systemic ratios that you can show people. That hasn't been done yet, I think it probably can be, whereas, obviously, for beta agonists, coming up with very precise

potency ratios for at least efficacy has been done, and it has been used extensively in the generic development process.

DR. MURPHY: John Jenne, you are an expert in beta-2 agonists. You have given a lot of thought to how you look at relative comparability, potency, efficacy. What suggestions do you have?

DR. JENNE: Well, I think the most precise approach is the methyl choline protective ability, which we did go into at one of our recent meetings. I think that has a greater accuracy than dose-response curve or cumulative dose-response curve as far as FEV-1 response, and so forth, is concerned, and I think either of those two are acceptable as far as the FDA is concerned.

I haven't heard anything about urine levels of albuterol or serum levels which is another way of at least looking at drug delivery to the alveoli, although not necessarily not to the bronchi. But I am sympathetic to the methyl choline challenge type approach, frankly. I think that would have a little more discrimination.

DR. MURPHY: Has 3M looked at any methyl choline reactivity data and blocking compared with albuterol, the FHA versus the CFC?

DR. COLICE: As the FDA will remember, we tried to

do a study like that. The design was originally suggested by the HPB. It was an innovative design. We found it very difficult to complete that study with the acceptable quality we like to see. Actually, some of the suggestions that the committee has raised in the past, I think Dr. Cross suggested some deposition studies, and Dr. Jenne has suggested looking at serum levels, and I think those are reasonable things, and we intend to pursue those, which should provide more information.

DR. MURPHY: Stan, you have thought a lot about equivalency of the inhaled steroids. Do you want to comment on that?

DR. SZEFLER: As you know, it's a challenging issue. I think in a couple of areas, when you are talking about therapeutic equivalence or models, we have to think in terms of not only one model, but some of the subcategories that are pertinent, and by that I mean the children less than six years of age where metered dose inhalers or DPIs might even be comparable.

The challenging issue is how much change in potency that is statistically significant is really clinically significant, is a major question. I think the models are pretty well worked out where you can get numbers fixed for bronchodilators and then make that decision about

statistical difference and clinical acceptance, and we should be forced into those models about making those decisions.

With inhaled steroids, as we have talked about, the models aren't really clear-cut, and John was very clear in terms of the dose-response curves, particularly FEV-1 is very shallow, but there may be other parameters that we can look at to model, I think similar to what Dick did with bronchodilator response.

We have got to pick out clinically relevant efficacy parameters that are useful for the patient, it gives us short-term information, but reassures us about long-term efficacy.

So I think looking at FEV-1s and bronchoprotective response is satisfactory for bronchodilators, and the models are there, but for inhaled steroids, it is a little bit more challenging, and I am not sure we can look at them as one category as therapeutically equivalent.

I think the recent NIH guidelines recognized that, and broke drugs down into three categories by dose ranges, and that has to be considered in terms of these decisions about one drug being equivalent across the category. So, I think the models, if there is time that needs to be added on in terms of developing models, it is with the inhaled

steroid class. I think that is much more poorly defined than the bronchodilator class.

I think the challenges in the bronchodilator class are to separate out clinically significant differences in potency. I think that is where the two of you are having differences is in terms of statistical significance and clinical significance. So, I think that parameter needs to be ironed out. The models are there. The significance of the differences have to be sorted out.

With the inhaled steroids, there is more work needed to develop the models to do the comparisons.

DR. MURPHY: Does anybody from industry, from the inhaled steroids want to talk about any models that they think are good for looking at this?

DR. SZEFLER: I think we are taking on that as an issue with the Asthma Clinical Research Network, so we are certainly interested in inviting industry to participate in that kind of protocol. We are attempting to develop these kind of models, as Vern would mention to you, they are challenging from both the model design and the statistical analysis of that and putting it together.

DR. MURPHY: Vern, you are the coordinating center for the Asthma Network. What thoughts have you all had about this, and what are the problems statistically that the

FDA should know about ahead of time?

DR. CHINCHILLI: How much time do I have? A standing joke. To be honest, the network itself is waiting to see what happens with this particular meeting today and where the FDA is going to go in terms of these CFC-free inhalers.

We have not incorporated any of them yet in any of our studies. We started two new studies in February, and they do not involve these types of inhalers. We will be doing more studies in the future, but we are sort of just waiting to see what happens in that regard.

So, to be honest, I haven't give a lot of thought to the statistical issues involved in terms of the CFC-free inhalers. We do have challenges continually in terms of analyzing the data we get in our current studies, and I can talk about some of that, but I think we will be getting off the subject here.

DR. MURPHY: John.

DR. JENKINS: I think we started out this discussion talking about acceptable alternatives, and I think we have gotten off onto a component of that, but we haven't really heard any discussion about how the committee members feel about multiple-dose dry powder inhalers as being acceptable alternatives to metered dose inhalers, so I

am really curious if we could steer the conversation back to are they acceptable alternatives or should they not be considered acceptable alternatives.

DR. MURPHY: I was just about to ask Courtney that question. How do you feel as a practitioner about this?

DR. CRIM: Not to dodge that, but I would sort of like to include the recent discussion on this. From a clinical standpoint, I think it would be based on the clinical efficacy of it. To what degree one can say what we have been using previously to treat an acute exacerbation with a CFC propelled MDI, how would that compare either with a dry powder or what have you, in other words, what would be the clinically equivalent dose for that.

If that is the case, then, I guess I have no major problems with it. Then, again, I guess it would become a question of to what degree the practicing clinician, be it a pulmonologist, allergist, or any primary care physician in the community, would feel comfortable making that transition from what we have been using in the past to one of these particular medications.

I have heard about the Scandinavian experience with dry powder inhalers, but I guess I am somewhat old enough to recall at least the reservations that were present initially with the cromolyn spinhalers as far as the powder.

I will put it in that context, so that they have been reluctant from back then, so to what degree clinicians and/or patients in the United States would feel comfortable with that, I am not quite certain as far as least having physicians feel comfortable making that transition from a CFC to a dry powder, but as a general theme, if it is clinically efficacious, at least comparable, you know, by whatever means that one can come up with, be it methyl choline challenge, exercise-induced bronchospasm, I think that would help, but I think those would be the bigger concerns that I would have.

DR. MURPHY: John.

DR. JENKINS: I guess we are interested in maybe addressing an issue that is hard for you to address because we don't have these multiple-dose dry powder inhalers available, but the scenario is likely to be that we will have a lot of multiple-dose dry powder inhalers because they are under development, and again, the efforts that we are recommending are that they be compared to the currently marketed CFC products usually and that we will be able to assess how they compare to the CFC products, so we should be able to give you information about you may be used to using one puff twice a day for your old product, and now this is a one-puff once a day or four times a day.

We will be giving you dosing recommendations compared to the old product. I guess more the focus is how do you feel about dry powder inhalers, are there patients that you think just aren't going to be served by dry powder inhalers, is it a crazy idea to even consider dry powder inhalers as an acceptable alternative to a metered dose inhaler, some of those type of questions.

DR. MURPHY: Curtis. give us an answer to that one.

DR. SESSLER: Good luck. No, I think there is probably people in this room who can answer that better than I in terms of experience with that in clinical trials, otherwise, I think we really need to learn more about the acceptance in Sweden and places like that, where it has been out in the marketplace for a while, and see if they have identified populations that do not do well with that form of delivery.

So, I think there is two different issues there. One is calling upon our local talent for their observations and then seeing what we have go out there because there is no experience in the marketplace in the U.S. so far.

DR. MURPHY: Has anybody sitting on the panel done a trial with the multiple-dose dry powder inhalers?

DR. LI: I will try to answer this particular

question directly. I guess I would say in my opinion, that the dry powder inhaler formulations are roughly equivalent to metered dose inhalers, and that many patients are able to use either product and to use either product successfully.

That would be my general opinion, that they are roughly equivalent. Now, clearly, also, they are not identical, and that is obvious. So, it wouldn't be a stretch to guess or to surmise that there would be some individual patients who would be more comfortable with a metered dose inhaler and be less comfortable using a dry powder formulation, and vice versa.

In fact, the experience is that some patients would prefer a dry powder formulation over a metered dose inhaler. It is going to be a little bit difficult to define what those characteristics are. I mean dry powder inhalers are breath-actuated, so that is an advantage, but perhaps for some patients might be a hindrance.

The ergonomics of the metered dose inhaler and the dry powder formulations are different, so again, they are reasonable.

DR. MURPHY: What did you think in your trial, did people like the dry powder inhaler or not, did you have people throw them down and run out the door?

DR. LI: That is an important question and I will

answer that, but even beyond that, the difficulty with answering that is that the people in our trial are like professional trial patients.

DR. MURPHY: They would never throw down an inhaler.

DR. LI: I don't want to get into ethnic stereotypes, but Midwestern, upstanding, honest, hard-working --

DR. MURPHY: There you have it, the people who are going out in the floods, they are staying up all night building barricades.

DR. LI: So it is not necessarily a representative sample, and that is an important point. But I would answer that, many of the patients preferred the dry powder formulation.

DR. MURPHY: Who hasn't spoken yet that would like to speak?

DR. LIU: I basically agree with Dr. Li except in one situation where at least theoretically, in my mind, without being hindered by data, is that in the people with very severe lung function, or small children, or that sort of situation, the metered dose inhalers and the dry powders, I don't think would be equivalent because it may take a certain flow rate in order to distribute and disperse a

powder whereas a metered dose inhaler sort of comes out already that way.

So, I think for the majority of patients who have reasonably normal lung function, they probably are fairly equivalent, but I there certainly is a rather significant subgroup and perhaps are very clinically relevant -- or at least a couple of subgroups in which they would not.

DR. MURPHY: Les.

DR. HENDELES: I think the small kids that we teach to use a metered dose inhaler through an Inspir-Ease device for an inhaled steroid, you may not be able to use a DPI with them.

The other thing I want to point out is that right now the most important variable with an inhaled steroid is whether the patient takes it or not, and what studies are available indicate that we can't do any worse than what we are doing right now.

The adherence rate is 36 percent to 45 percent for inhaled steroids, so we can't do much worse than that.

DR. MURPHY: Molly.

DR. OSBORNE: I only have anecdotal evidence, unfortunately, and maybe the postmarketing surveillance evidence is really going to be important to get a representative sample as we have already said. But

anecdotally, I have several patients with quite severe asthma who have obtained DPI cortical steroids and have done very, very well with them, so at least anecdotally, even in the person with severe airflow obstruction, it can be effective and patients can be compliant.

DR. MURPHY: Does anybody else a burning comment about this issue? Jim.

DR. BARANIUK: I think if you look at the budesonide data, that is basically the turbowhaler from Europe, if you look at that, it has been very effective. I think that tells us that the dry powder will work.

Could I digress for a second?

DR. MURPHY: Let's focus on this right now. I would like to get some closure on this.

Carroll.

DR. CROSS: Jim just made my point, but also at lunchtime, it suggested our next meeting be in Stockholm or Oslo or Copenhagen where we can get direct testimony.

DR. MURPHY: As Chair of the panel, I will just say one thing about this issue. That is that I had the opportunity to work -- and which is fully disclosed to the FDA -- for Fisons Corporation from 1982 to 1985, and I must say I had never used the spinhaler before I went to work with them, and thought it was a terrible device.

Then, I worked with a pulmonologist at the University of Massachusetts, who had everybody who had everybody on cromolyn, and I saw how much of it was bias, and I think also different countries do things differently, and I noticed when I worked for Fisons that France liked all their drugs in suppository form, Sweden liked them inhaled, so there are different cultural biases.

Stan, one comment.

DR. SZEFLER: To answer John's question specifically in terms of acceptance, I think the patient populations I am most concerned about is the children under six. The DPIs are totally unacceptable until a device comes that can deliver the drug.

The false sense of security in terms of Sweden and their acceptance is that the drug was developed there, budesonide was developed there, the turbowhaler device was used there. They are accustomed to it because of teaching in clinical practice.

The other thing is they don't have a need for an MDI because they have budesonide nebulizing solution, so there is an alternative for the younger children in terms of the nebulized preparation, so there is not a pressing need for that preparation, but there would be a pressing need in our country if we only had the DPI and we didn't have an MDI

inhaled steroid that we could at least deliver under acceptable forms of administration with an MDI, and so that is the gap, particularly with the steroids. I am not that worried about the bronchodilators, but for the steroids I am worried about an acceptable delivery system.

DR. MURPHY: Well, we heard something today about new, not traditional nebulizers, but other nebulizers, devices for drugs. Can you comment on that or is that proprietary, John?

DR. JENKINS: There may be people in the audience who may want to talk about any of their new devices, but I think everyone knows that there is a lot of effort going into trying to develop very portable, very small, hand-held nebulizers, as well as maybe trying to develop metered dose inhalers that don't require a propellant, but maybe use some sort of a mechanical force to aerosolize the drug product, but I can't speak to any individual products, but if anyone in the audience would like to do that, then, I will leave it to them.

DR. MURPHY: Yes, Doug.

DR. WILSON: Doug Wilson, Boehringer Ingelheim. Yes, we have had in development for about eight years a hand-held, portable, multi-dose mini-nebulizer, which is about the same size as the metered aerosol, designed for

most of the inhaled products, and we are now at the stage of just about entering Phase III with that, and that delivers as a small puff about a 15-microliter puff of solution with the drug forced through jets in a ceramic chip which is attached to the device.

The device is discharged by a mechanical spring, and is multiloaded and will give you I think 200 doses.

DR. MURPHY: Great. That is good to hear about.

Does anybody else want to comment from the industry perspective? Thank you very much.

So I think what we are hearing, just to summarize it, is that people feel that there is a role for dry powder inhalers and that in most patients they can be substituted, but there are patients, particularly children, that there is a gap there, and there is a need for new devices such as we just heard from Dr. Wilson.

Is that a fair summary of that? Do you have enough discussion? Okay.

Let's move on to the next question. When should an alternative product be considered a medically acceptable alternative -- and I think this is what we were talking about before -- for the purposes of deeming its CFC counterpart no longer essential, including the amount of safety data that should be available n any CFC-free

alternative before the corresponding CFC drug is phased out?

So this is not just approving, this is when has it been there long enough to phase out the other drugs of the same category.

Who would like to lead off some thoughts on that?

Jim.

DR. BARANIUK: I will lead off. I think this whole debate is about devices, not drugs, and as we learned at other meetings, new devices may as well be new drugs, right? With a new device NDA application, the company will have to show safety and efficacy, going through the usual product approval.

After it is approved, I would think it is important to have side-by-side comparisons of the new device compared to the old device, and to use it in the situations where we usually use our albuterol, for instance, in mild asthmatics, in moderate asthmatics, and in severe asthmatics. I think we have to use it in special indications like exercise-induced bronchospasm.

Unless you can test a device in each of those settings, you won't know if it is an alternative, if it a satisfactory alternative, especially if you are going to overturn the use of an entire class of compounds.

DR. MURPHY: Then, what would you want to see as

outcomes in that kind of a --

DR. BARANIUK: Well, I think there would be a tendency to want to use mild patients, or instance, to show that there is a comparability in bronchodilator effects in mild populations, but from a physician's perspective, as Dick said earlier, we want to make sure that the drug will work in the middle of the night with the device, with whatever propellant or delivery system you use.

I think that is a critical thing. That may have to be FDA-mandated, industry-initiated, but I think we have to look very carefully at these indications to make sure the drug is robust enough.

DR. MURPHY: You would want to see it in acute asthma, as well as a chronic bronchodilator effect.

DR. BARANIUK: Absolutely.

DR. MURPHY: I bet Ms. Mitchell would like to see some patient satisfaction --

MS. MITCHELL: Yes.

DR. MURPHY: -- trial comparably?

MS. MITCHELL: Taking a look at that overall quality of life issue in terms of that. When I talk to my support group and ask them what it is that they want, I mean they want to make sure that whatever they are getting as a replacement is going to do for them what they are used to

having done and particularly in that acute scenario.

I think there is nothing more scary than being out there and having something not work for them. You know, too many of them have been in a situation where they have had to call 911, and the school nurse has had to do that, and that just isn't a scenario, and I think they are more concerned about it for their children than they are even in terms of themselves, because they figure as an adult, I can figure out what to do, but my child may not have that option.

DR. MURPHY: Good. Stan.

DR. SZEFLER: I would think in these postmarketing studies, I think as Richard mentioned, there should be some pointed questions, it shouldn't just be open-ended, and a lot of emphasis besides just clinical effectiveness should be placed on performance standards.

DR. MURPHY: For the device, you say, performance standards for the device?

DR. SZEFLER: For the device exactly. In talking to Les before we had our break, he mentioned to me something I wasn't aware of, and I keep up with this literature, in that the HFAs -- and maybe I can be corrected on this -- is they require cleaning every week, the actuator.

Could I have some clearance on that, because that is something that I think we need to be aware of in terms of

performance, because what we are expecting patients to do, what we are telling them to do, they don't always do, and if there are some significant flaws in terms of delivery that alter its performance, even if it's written, it may not be acceptable because they are not doing it, and there is two areas, that, and I think the other area that I have communicated with John with, that I am very concerned about, is patient's ability to determine when the canister is empty, and I think we really need some clearance issues on those things in terms of assessing performance under real life conditions. But if I could get some clearance on that cleaning, that would be helpful.

DR. MURPHY: From 3M. You make a lot of devices at 3M. Can you talk about, is that a recommendation for all MDIs?

DR. COLICE: Yes. You are speaking specifically about Proventil HFA, and in the reformulation process, it is important to recognize that the product is not the same, it is not identical to Proventil, it is different, and that we believe confers certain advantage, product improvement, performance, and also it entail a difference in taking care of the product, and we are making that very clear that, yes, the product has to be cleaned on a regular basis.

DR. SZEFLER: Yes, that is where I have concerns

about the year. You know, I have heard these different groups come up and say let's put this out as quickly as we can, and I wonder if a year is really satisfactory to get that kind of information, unless it is really detail structured, not only efficacy but performance of the product. So, you get the answers within that year.

DR. MURPHY: Good comments. Les.

DR. HENDELES: Getting back to James' comment about wanting it to work in the middle of the night, if that is an important thing, why not test if in the middle of the night?

DR. BARANIUK: Exactly correct.

DR. HENDELES: I mean I think the nocturnal asthma model is an important way of testing both efficacy and safety simultaneously in a cumulative dose fashion, and it is very easy to do if you have access to a clinical research center, and if the two products are comparable under that circumstance, meaning that it takes roughly the same number of puffs to relieve an acute attack in the middle of the night, then, I can't think of any other circumstance where they wouldn't be therapeutically equivalent.

DR. BARANIUK: The situation is that they don't need a middle-of-the-night study right now for approval, but that is where we would want the drug to work, so perhaps

this has to become a new standard that the FDA will require in order for the new device to be introduced. I mean as it is, they don't need to have a clinical research center study that would investigate that.

DR. MURPHY: Jim, you have comment?

DR. LI: I wanted to emphasize the point that has already been made, and that would be in my way of looking at this important question, I think it is helpful to separate somewhat the approval process for the new drug and the new device and with a different propellant or delivery system, and the phaseout of the older or the previous drugs.

In both areas, but particularly the latter with the phaseout, is this issue you meet, and that is why we are here today. We are really setting some precedents or the agency is in trying to determine a policy, because the situation is quite different, say, for evaluating a generic product where a phaseout of the existing product isn't going to be mandated or isn't necessarily obligatory.

I agree with what Jim said. I think with the approval process, as we have looked through various drugs that were presented here, if it is a truly new product, and often there will be a few hundred or at most a few thousand patients total who are exposed to a new drug or a new device, and that would be compared with, in this case,

existing devices that have been around for 20 years or more, that have several tens of millions, if not more, people.

So, in order to make the decision to phase out a product that has been around 10, 20 years or more, and has, you know, 50 millions users or more, in favor of a product that has been used by a few thousand patients, I think is some cause for concern, and I think there are ways to deal with it.

We have talked about more structured studies of effectiveness. I think the real world effectiveness issue is important, and we heard about some areas where that specifically can come up. I will just mention a couple of others. That would be, in the case of bronchodilators, would be, say, excess use or misuse of the drug.

Now, I supposed you could conduct a study, a clinical study to examine that, but it still wouldn't be exactly the same as having a structured postmarketing surveillance type of study, so we could get some information, gather information about what happens and what is the safety, and I suppose the efficacy of using twice, five times, 10 times the recommended dose of these new products. I think that would be very valuable information, and we kind of know that information about existing products.

DR. MURPHY: Didn't 3M do that? You went up to seven -- how many puffs did you say -- 16 puffs?

DR. COLICE: In at least three studies, we acutely went up to 16 puffs, three separate studies, within two hours.

DR. LI: That would be the sort of study that I think that would be helpful. I think I was thinking maybe along the lines of -- I won't put words in your mouth -- but I would be interested in someone with an asthma exacerbation at 4:00 a.m., who is acutely ill, and if that individual took 10 puffs, whether it would be comparable to existing products. Paradoxical bronchospasm would be another. I mean we have heard about doses and how to find -- if the canister is empty and cleaning the canister -- paradoxical bronchospasm, some patients will actually be made worse with certain dry powder formulations, and it one thing to study it in a control study, but it is another to actually get information about this at 4:00 a.m. when someone is having an exacerbation. I think that is the kind of information which would be useful to have since I think the broader concept of comparability is that we know or we would be confident they would be roughly comparable, but we would be concerned and maybe a little frightened about what we don't know.

DR. AHRENS: You just addressed a lot of what I had in mind, but one particular aspect of the postmarketing surveillance studies -- well, first of all, I think if they are going to provide truly useful information to us, they are going to be difficult things to design, and I am again reiterating the idea that I think they would be better studies if they were focused on specific issues rather than just a very broad Med Watch type of marketing surveillance.

One important issue, one aspect of that again is how many patients were actually exposed to this, and carrying that to the level of the -- I think the terminology is reorganization of 2.125, and that is that I am not sure the idea of marketing for a certain length of time is maybe the best way to approach it.

Perhaps a consideration of how many, you know, some documentation of how many patients are exposed for how long and obviously along with that, how they are monitored and how we gather data from those patients.

DR. MURPHY: That is very good thought. Do you want to comment?

DR. CROSS: Dr. Jenkins already mentioned that one year is a little bit dependent on the quality of the data that is submitted.

DR. BARANIUK: Can I ask a clarification from the

EPA? Somewhere it was mentioned that 2005 is the final phaseout date. Can you --

MS. O'DONNELL: No, it is not the final phaseout date. The parties to the Montreal Protocol have several advisory groups or expert panels and advisory groups have been set up to advise them, and one of the groups has recommended that the parties to the Protocol consider 2005 as a phaseout date, but there has not been specific action on that.

DR. BARANIUK: So we are faced with the very real possibility of total ban on CFCs --

MS. O'DONNELL: Yes, absolutely.

DR. BARANIUK: -- regardless, so it is a question of with all of these studies we are talking about, how long is it going to take to develop and introduce new devices, get them through the approval process, do side-by-side comparisons, do the Phase IV surveillance in large populations, what is the time line looking like here? Can we get products on the market by 2005?

DR. MURPHY: Well, we already have one product on the market, and there is a number of others coming along.

DR. BARANIUK: The issue there is who has the current patents, if you want to get them on the market, then, everybody has to deal with the current patent holders

rather than develop new technology.

DR. MURPHY: Do you want to comment, John?

DR. JENKINS: As I tried to say in my presentation, there are a large, large number of products currently under development. I can't give you an absolute number. I know that Dr. Remetta, in her talk from IPAC, hypothesized that as many as 30 products could be in the marketplace by the year 2000, I think. That is their most optimistic assessment. Their more pessimistic assessment I think is 11 by the year 2000.

Again, those are IPAC projections. I think the point to emphasize is there is no hard and fast phaseout date for the use of CFCs in metered dose inhalers that have been agreed to by the parties to the Montreal Protocol.

One of the committees that were charged with addressing the issue did put out as a possible date for consideration, but we are probably a long way from the parties to the Montreal Protocol fixing an absolute date. 2005 is, what, eight years away. I suspect we are going to have a lot of products on the market before 2005.

Now, I am hearing a lot of postmarketing data suggestion. It could take a long time after a drug is approved to have all that data available, so all that has to be factored into the equation, as well.

DR. MURPHY: So I think you are hearing some ideas about sort of new things one might want to do, like study acute asthmatics to be confident about bronchodilators, and the postmarketing, obviously, that is going to be an issue for a number of patients that are coming.

Other thoughts about No. 2, about when you would feel comfortable phasing something out, other ideas to throw out about how these drugs might be studied? We heard nocturnal asthma.

Molly, you deal with the elderly a lot of in your studies. Do you have any concerns about studying the elderly, just like we talking about the children?

DR. OSBORNE: There are several issues in the elderly. One is certainly that they have a lot of comorbidities. Getting back to Dr. Li's comment, there are two issues here. One has to do with approval, another has to do with postmarketing surveillance. My guess is that the issues with the elderly have more to do in the postmarketing surveillance category than the approval category, so to just say something on that note very quickly.

It might be worth careful -- and this may have already been done -- forethought as to what the postmarketing survey might look like and whether it might be built in as a consistent one across devices and the new

kinds of formulations to include something like patient years, to include certain outcomes, such as nocturnal symptoms, health care utilization, patterns of medication use, quality of life, to include comorbidities, something that was tightly structured, determined in advance, that held across all products might at least be a first step, and it would have to, of course, be short.

But something like that might at least be thought about, and then adapting it to the elderly, you know, keeping elderly and pediatric populations in line with that is I think a better use of describing elderly than trying to fit them into the approval pattern. I don't think that is going to be germane.

DR. MURPHY: Go ahead, Curtis.

DR. SESSLER: One comment that is a little bit removed from the general thrust of these comments, but I think related to the launch versus orbit issues, is the manufacturing capability especially if we are talking about classes rather than individual drug entities or particular moieties, how assured will we be that the manufacturing is satisfactory to supply the needs if we have fewer options in terms of the phaseout issue.

DR. MURPHY: Do you want to comment on what you were looking at? I know Dr. Otulana talked about multiple

sites and other such things

DR. OTULANA: Yes, those are some. We did look at that issue. We did look at that issue as something fairly significant to look at. Like some of the other suggestions or proposals in the ANPR, we have not really got into the level of putting exact numbers to these, but it does make sense to look at where the drug is coming from.

If a drug has been manufactured in many places, it gives us greater comfort level, but again, we haven't come up with the number of sites that will be required.

DR. MURPHY: Does that answer your concern?

DR. SESSLER: I think as best as can be answered right now, but it is potentially quite a significant question. Our goal is at all costs to protect our patients, and we want to be confident that this drug supply is going to be adequate. If we are going to reduce the numbers within a class fairly dramatically, we want to make sure that we have that capability.

DR. MURPHY: John.

DR. JENKINS: Just to expand on that a little bit, I think what Dr. Otulana said is true, that we have not yet formalized any criteria for how we would look at that issue, but it is obviously a critical issue.

If you have an alternative product that is being

produced and being sold in the marketplace at a hypothetical million units per year, and yet the expected patient population for that drug substance is 20 million units per year, you are going to need some real assurance that that manufacturer can make 20 million units per year because we don't want drug shortages.

I mean one of the concerns we have is we really need the competence and the trust of the patients in this phaseout process, and if we phase out so quickly that we get into shortage situations, you know, they will be beating down our doors, telling us, you know, we need to look for new jobs because we haven't done our job right.

I think it is critical that we address issues like adequacy of supply and distribution networks. If a product is only being manufactured in one site, you know, there are national disasters, if it not in the United States, there could be political upheavals, et cetera, so we have to factor all that in, but we don't have a formula yet calculated, and I doubt that we will ever have a formula, but it is something that has to be considered.

DR. MURPHY: Do any of you from industry who have had this experience of running out of product have any comments about this? I know some of your have run out.

MR. DuVAL: Mark DuVal, 3M Pharmaceuticals. It

certainly is an important criterion and one that we considered in our proposal to the FDA, which includes this ability to supply requirement. However, most products today are suffering from the same thing. What I find here in the transition is that we are trying to impose a lot of things on an industry that already provides the assurance of an ability to supply.

For example, Proventil HFA, provided in two plants today, North Ridge, California, and [Lufft] Kingdom. There might be a third plant some day. But do we need a fourth plant or a fifth plant?

A lot of the requirements that we hear today just continue to be additive, and you have to wonder will there ever be a transition.

Let me address one thing on the 2005 date. The report to which Chris was referring actually says there will be a significant reduction of CFCs that will be allotted to companies by the year 2000. 2005, as I understand it, is an absolute outside target date for total elimination. So, we need a clarification on that.

DR. MURPHY: Chris, do you want to clarify that?

MS. O'DONNELL: Mark is correct, and the other thing is, as I mentioned in my talk, is that the parties have set up some pretty stringent criteria, and it is

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getting more and more difficult with regard to nominations, I mean in terms of sending them forward and the scrutiny that is being applied. The criteria, as I mentioned, that they are setting up is making sure that companies and countries are actively pursuing alternatives, are engaging in education with patients and medical community, that the transition is coming and that there will be a phaseout.

MR. DuVAL: Secondly, I negotiate supply contracts for CFCs on behalf of our customers and ourselves, and I am telling you Dupont has said we will be out of these very shortly. ICI has said we will be out of these very shortly. I think you are going to be faced with the prospect where irrespective of what you do on this committee, there will just be no CFCs someday and you have to start addressing it.

The final point I have is on stockpiling. There has been some very specific directives given globally and by the EPA that they are looking at stockpiles. There will no longer be stockpiling. People will no longer, companies will no longer get to have new CFC production for the MDIs, they will have to draw from their stockpiles, and when they are exhausted -- so, you know, it is an academic discussion, and we need to talk about transition, but there are some real realities that are superimposed on the whole process.

DR. MURPHY: Good. Appreciate those comments.

Thank you.

DR. LIU: I am sort of sitting here thinking maybe I am sort of the outsider, but you can sort of look at these devices as really new drugs, and they don't really have to be compared with anything or found to be equivalent to anything. I mean it is the same compound, it is a new device, but to some extent it can be viewed as a new drug application which they have to go through.

If you show that they work in a particular disease, and what is the recommended dosages, intervals, and that sort of thing, then, what is the big deal in terms of having to compare it to anything else except to tell patients that this is how this particular drug would be used?

I am not saying that you should not have any kind of attempt at equivalency to an old product, but to some extent the application, especially if what we are hearing about new formulations and the fact that not only the device but the excipients, I think it is a whole new technology and alchemy, if you will, for these different compounds is quite different. Then, why can't they just stand as new drug applications on their own?

I think part of the education process is to be proactive from the medical point of view in terms of

convincing patients or educating patients that these are reasonable drugs, and hopefully, there are assurances from various levels that they are actually effective, potent, and safe if used in terms of whatever the studies show.

DR. MURPHY: Courtney, you wanted to respond to that.

DR. CRIM: In essence, I would just like to echo what Dr. Liu just said. I hope I had alluded to that in my response to the first question, that is, in terms of when should it be considered a medically acceptable alternative. From my standpoint, it should be when it goes through the same rigors that any new product does in terms of showing that it is efficacious, that it is safe in the clinical trials, and then as far as when it does that plus when we can determine how one would use it compared to an old product, that is, if the dosing regimen is the same, so that there is no confusion as far as physicians and patients are concerned, to me, that is fine.

You know, it is other uses in terms of how well would it act in the middle of the night and this, that, and the other, I personally don't see that needs to be in the clinical trials, but I think it is something that hopefully clinicians and patients, as far as Phase IV type things, would learn.

DR. MURPHY: Good comments. Comments, responses over here?

DR. LI: I just want to make a similar comment and say that, first of all, the principle of comparability is going to be very important, because again taking the approval side a little bit different from the deliberate phaseout side, that many patients and in fact most physicians will expecting comparability, and if the new products were not comparable, then, it would add a whole new level of complexity that we probably don't need.

A comment on the side of the phaseout is to raise again the issue of something that is a little bit unclear is whether we need to deliberately design a structured phaseout in which case I think Phase IV or postmarketing type information is going to be important if indeed we have a system where we would deliberately withdraw a preexisting product on the market because there was an alternative available.

On the other hand, if there is going to be an evolutionary phaseout because the CFC reagents are no longer available, then, again perhaps we don't need -- if we are not going to deliberate phase out the product, then, I think the additional information and studies is less crucial and that we can approve a new product, and then the old products

will phase out without a design of our own.

DR. MURPHY: Yes.

MS. HUFFORD: If I could comment on that, I just want to clarify generally that the decision about the phaseout and timing of phaseout may be a little less in our hands than the discussion has suggested. I mean the fact is in this country, the production of CFCs is already phased out, it is already banned.

What we have been doing at EPA is working with folks from IPAC and folks from FDA, folks from the Department of State annually to request permission from the parties to the Protocol for essential uses, and that is how we are getting new CFC production.

But the TEAP report and its clarification that 2005 would be the outside time, I think is a very clear indication. That, as well as the increasing scrutiny in the international community, particularly from some countries who may not be as dependent on MDIs as we are, I think is a good sign that this is an issue that is fairly urgent.

DR. MURPHY: That is a good comment. Thank you.

Yes.

MR. BAROK: My name is [Michel Barok]. I am an attorney with Akin & Gump in Washington, and I represent [Medisol] Labs. However, my comment is specifically with

respect to the international scene and the Montreal Protocols. Along with EPA and with Mr. DuVal, I have had a chance over the past couple of years to attend each of the general meetings of the Montreal Protocols, as well as Working Group meetings, and I believe the panel is not getting accurate information about the international scene.

In the first instance, there is no uniformity in terms of decisionmaking in the international scene as to whether 2005 is an appropriate outside date. The TEAP panel, which is the Technical and Economic Assessment Panel, makes recommendations to the general group.

Those recommendations are not always followed and actually, historically, are often not followed, so to create -- the TEAP representation of 2005 to be a suggestion -- to create that as an absolute date that is solid does not reflect the international scene. In addition, in the international scene, there is a significant contingent of parties, countries, which are opposed to quick phaseout.

The third thing I want to point out is the "they" in terms of people out there in Montreal Protocol is the we, the "we" being the EPA. The EPA represents all of us. The EPA should be representing the comments of this panel.

If you as medical experts believe that a five-year or a ten-year period is insufficient, what other period that

you believe is sufficient to deal with the postmarketing issues you want, EPA ought to be going to the international scene and saying our FDA experts tell us we need this period, we can't accept the 2005 phaseout.

The EPA is not doing that, and the EPA contingent is actually working against some of the interests and discussions that I am hearing in this meeting. If the EPA wants to be aggressive in promoting what you recommend, it can do so. If it wants to bend to international pressure and present 2005 as a fixed obstacle, it can also do so.

So you have more say-so, I think, than you believe, and there is less immediate pressure than you are being led to believe.

DR. MURPHY: Dr. Hufford, would you like to comment?

MS. HUFFORD: Thank you. Yes, I would. I think the first thing I would like to clarify -- and I think this was also said by Dr. Jenkins, and it needs to be clarified from our point of view, too -- is that the TEAP is not a legislative body within the Montreal Protocol.

What the TEAP does, as was just pointed out by the representative from Medisol is make recommendations. However, I do think it is fair to say that the TEAP and the relevant technical option committees that work within it are

scrutinizing much more carefully U.S. essential use exemption requests, as well as essential use exemption requests from other countries.

The U.S. every year -- and I think it should also be clear that State, as well as EPA and FDA, participate in this process -- is representing the need of U.S. asthma patients. We have been consistently arguing for IPAC summaries and what the generic companies have asked for and will continue to do so, but I think we would be misleading this panel if we said that we could always unilaterally win on those points in the international community, and I think if we were to advise you not to plan for it, or to advise companies not to plan for it, we would be doing the U.S. asthmatic population a disservice.

DR. MURPHY: Good comments. Dr. Jenkins.

DR. JENKINS: Maybe Dr. Otulana can speak to the issue of the essential use exemption process and how the parties are addressing that, because as I mentioned, he is a member of the technical options committee for aerosols, and he just returned last month from the Mexico City meeting where they considered the nominations I guess for 1998 and 1999, and he can maybe give you a feel of what that technical options committee's view was on U.S. requests for CFCs.

DR. OTULANA: I think we have had comments regarding the year 2005 on some of the proposals from the committees to the Montreal Protocol. I would just like to clarify with regard to that, that it is true that the international pressure is increasing.

I think it is valid to say that the parties are now scrutinizing the exemption more closely than before. There have been suggestion of dates by final phaseout, but it is also true that none of these dates have been ratified by the parties. Some of the committees on the TEAP have proposed the year 2005, but there is nothing now that has been codified as the date to finally phase out CFCs, but it is true that there are pressures within the Montreal Protocol to move towards reducing the amount of CFCs allocated to different countries, and hopefully, to work towards phasing them out.

The take-away message is that no date has been set within the --

DR. MURPHY: But it is coming.

DR. OTULANA: But there is pressure to move towards reducing CFC use.

DR. MURPHY: And you can't go every year and beg for more years, so we have got to face this now.

DR. OTULANA: Well, right now the process is in

place for parties to ask for exemption, and that process is still in place. It hasn't been decided that the process will be suspended or will be revoked at any particular date soon. That process is still in place.

DR. MURPHY: And I think we are also hearing that CFCs are harder to come by, too. So, let's move on. I think that was a very good discussion. I appreciate allowance the clarity.

John.

DR. JENKINS: Just for interest sake, while we are on this issue of what as an acceptable alternative, we have one non-CFC inhaler out there. It has been on the market since January. I am curious if people on the panel would comment on are they using it, if they are not using it, why are they not using it, and if they are using it, what do they think.

DR. MURPHY: Okay. Let's just go around the room. Berri, why don't you start.

MS. MITCHELL: Well, we are using it. The biggest problem in being able to use it is that many of the managed care organizations that we work with do not have it on their formulary, therefore, it is not accessible to the patients, which I see as ultimately being a major problem as we move more into managed care and managed formularies. There is

limited access to certain medications, and this just happens to be one of them at this particular point in time.

If a patient does want to have access to it, or is requesting it specifically, and every once in a while we have somebody like that who might request it specifically, then, they have to go out and pay for it on their own, and so it is not part of their health care plan. That again creates a cost scenario.

Generally speaking, I would say I have had very positive feedback from the patients who have used it.

DR. MURPHY: Curtis.

DR. SESSLER: I have prescribed it a little bit, used it a little bit, and have had no complaints about it, generally, good reports.

DR. MURPHY: Vernon, the Network? Anybody in the Network using it? No?

DR. CHINCHILLI: Not that I know of, no.

DR. BARANIUK: The biggest problem I have had is brand loyalty. The patients like their old inhalers, and they don't see any reason to really switch to something that is different. I have had several people complain about a taste or for irritant effect.

DR. MURPHY: Dick.

DR. AHRENS: Very similar to what has been said

earlier. Experience is very limited based on brand loyalty and particularly cost considerations, which obviously is an important issue in how adequate postmarketing studies are really going to be.

DR. MURPHY: Jim.

DR. LI: Well, I have not used it. The main reason is my own practice tends to be a consultation practice, so patients are on a lot of existing medications including short-acting beta agonists, and I haven't felt the need to change.

DR. MURPHY: Carroll.

DR. CROSS: In Sacramento, we are a very managed care environment, and while we are using free samples left for the company and the clinics, we are not prescribing large amounts yet. There have been no complaints of my own personal nature. Some of my colleagues have, through hearsay, talked of stickiness and cleaning problems and maybe uneven distributions over the lifetime of the dispenser, but I would say that is only hearsay.

DR. MURPHY: John Jenne, you haven't used it?

DR. JENNE: It hasn't filtered down to the homeless clinic that I work in, but someday it will.

DR. MURPHY: That is what I thought.

DR. LIU: I have had a rare patient come in on it,

and it has not been a problem.

DR. MURPHY: Courtney.

DR. CRIM: No real experience for the reasons that are very limited with managed care and what they have been using.

DR. MURPHY: Molly.

DR. OSBORNE: We are obviously going to be coming back to the managed care topic. It is not on the VA formulary in Portland as far as I know, although on the university side it is certainly being marketed, and with all the issue that have already been brought up.

DR. MURPHY: Les.

DR. HENDELES: The HFA product, the wholesale cost to our pharmacy is \$18. The wholesale cost for the generic albuterol is \$3.57. So, our hospital doesn't stock it.

DR. MURPHY: Stan.

DR. SZEFLER: I see no reason not to use it, and I think it is getting increasing use in our hospital, but I don't see people in general as sensitive to the environmental issues as they are in Europe.

DR. MURPHY: Does 3M want to comment on the use of it, or make any comments?

MR. DuVAL: This is precisely what we have been telling health and environmental regulators around the

world, and this is one of the reasons the approval of generics has been so difficult for us, because you can't spend the kind of money that innovators spend in reformulating these products and then sell them at a generic price. It just will not happen.

So what you then have is you have an impediment to the market entry, and I know that Schering is really suffering under that. They can't get on formularies, they can't get the product picked up, and although we hear good experience with it, and we have a 6,000-patient postmarketing surveillance study in the UK that shows that we are not statistically significantly safer, but at least minimally safer, in the raw data, the environmental advantage of this product we have found from surveying you, the physicians, both in Europe and in the U.S., and Schering has similar results, show that you don't care about environmental benefits of the product, it is just a fact.

So, we are trying to sell it on other advantages, which we have been debating with Dr. Jenkins whether we are able to say that, because we have been asked to design a me-too product, and when you are a marketer, you want differentiation, and you have nothing to sell. So, you get out there and you can't sell a nondifferentiable product that is going to, by its nature, be priced higher.

So, there are barriers and impediments to market entry, and this group needs to address that, because if the law doesn't provide the incentive for the switch, the marketplace has demonstrated it will not.

DR. MURPHY: Good. Thank you for the comments.
John.

DR. JENKINS: The issue has come up a couple of times about the washing issue with the Proventil HFA, so let me take just a moment to speak to that.

I think it was Dr. Colice who pointed out that this is a new product, it is not the same product as the old products. Therefore, we may see that these products have differences in how you need to care for them or how you may need to use them or how they may taste when you use them, et cetera.

All the metered dose inhalers have instructions to wash the actuator on a regular basis. We know that patients generally don't do that. We have been working very closely with 3M and Schering to emphasize in their labeling and in their marketing that it is important to wash this product on a regular basis, but the data that we have seen so far suggests that if the patients are compliant with washing the actuator on a regular basis, which the labeling currently calls for at least weekly, that the product is safe and

effective, and you don't get into problems with the blockage of the actuator.

So, I think it is important that we not view that as a defect; it's a difference.

DR. MURPHY: Did you say that all the metered dose inhalers have labeling to wash?

DR. JENKINS: To my knowledge, all or nearly all have something in their labeling that recommends that the actuator be washed on a regular basis. Some actually recommend more frequent than weekly, although we know patients probably don't do that, and there haven't been a lot of problems with the CFC inhaler.

We are dealing with differences in formulation, we are dealing with differences in device, and those factors added together do in this product lead to more of an issue of clogging the actuator, but it can be dealt with, with regular washing.

DR. MURPHY: Comment by Nancy Sander, and then I am going to move on to Questions 4 and 5, so you can be looking at those. Nancy.

MS. SANDER: In your package you can refer to Charts Q1/2 and Q4, and what we did is we asked, of the short-acting bronchodilator inhalers ever used or currently prescribed, we got information about the prevalence there,

and then we asked prevalence of former short-acting bronchodilator inhalers, users claiming never to use that product again, and you can compare the number of Proventil HFA -- as with all the inhalers here -- with those who used it, and those who said they would never use it again, and out of 600 and -- I can't give the specific numbers off the top of my head -- one-quarter of the Proventil HFA users said they would not use it again.

Anyway, for all the inhalers across the board, it is on that chart.

DR. MURPHY: Thank you.

Let me read Question No. 4. I think this is a very important point. Is the therapeutic class approach for the short-acting bronchodilators and the inhaled corticosteroids appropriate, and is it feasible to phase out an individual drug member, or an active moiety, of a therapeutic class as alternatives become available?

I think this is something that we really need to spend some time on. Stan. We will just move around a bit and get some feeling about this.

DR. SZEFLER: I feel more secure about that in terms of the bronchodilator category than I do about the steroid category.

DR. MURPHY: And why is that, why would you say

that?

DR. SZEFLER: I think the bronchodilator category pretty much if you go down the line, they have very similar durations of effect, whereas, with the inhaled steroids, there is still a lot unknown about the different dose ranges in terms of efficacy and adverse effects, and I pointed to before the new NIH guidelines, saw enough in the literature to develop different categories of dosing guidelines, so that in a way has to be respected to look at the inhaled steroid category.

DR. MURPHY: Thank you.

Les.

DR. HENDELES: I think our previous discussion about the lack of use of the Proventil HFA is testimony that for at least the beta agonists, you need to have a therapeutic class approach. Otherwise, they will never switch.

My concern about the inhaled steroids is that it just depends on how it is done. I mean if you had new products and Flovent was not part of that, and they were going to eliminate the class, I would be very upset because I consider that agent to have some superior effects.

On the other hand, if you were going to phase out, let's say, Azmacort, I don't think it would be a big loss.

DR. MURPHY: Well, there it goes. There is your prejudices again coming right out.

DR. HENDELES: Well, let me open my mouth and change feet.

DR. MURPHY: I hope RPR didn't pay your way here today.

DR. HENDELES: I will pass the mike.

[Laughter.]

DR. OSBORNE: Now, let me say the opposite. No, just kidding. I do have some concerns about taking each agent in Class I and lumping each one as equal to the other and the same with Class II. That is one comment.

The other side of that coin is from talking informally, it appears that there are many companies who will be eager to have their new devices or new drugs with their new propellants come to market very quickly if we indeed take a therapeutic class approach, and if the time lines are appropriate, it seems as though a therapeutic approach would be fine given some of the issues already brought up in terms of dose response, potency, and toxicity are taken into account in that they are not comparable across drugs.

So, I think, in general, the sense I get is that actually the drug companies have been extraordinarily

proactive, probably much more so than we are hearing today in actually addressing basically a therapeutic class approach, and my guess is that by the FDA taking this approach, the FDA has been enormously successful in promoting proactivity by the industry, and I actually have to congratulate both.

DR. MURPHY: Thank you.

DR. CRIM: I guess I would say, you know, sort of echoing what I think Stanley and Leslie alluded to, looking at the short-acting bronchodilators, I personally have a problem per se with them being lumped in terms of a particular therapeutic class that one can, once you come up with alternatives, you can phase that out.

With the steroids, I am likewise viewing things like Stanley, in that we recognize that there are differences in potencies as far as systemic corticosteroids, and at least I guess in terms of like, you know, testing hyperemia or things of that particular nature, there appears to be a difference in potency as far as the steroids are going to use inhaled.

So, I guess the concern I would have would be more so from the standpoint of the corticosteroids as opposed to the short-acting bronchodilators as far as the beta agonists, because at least anecdotally, they appear to be

roughly interchangeable, whereas, I have concerns about the corticosteroids.

DR. MURPHY: Dr. Otulana, do you want to respond?

DR. OTULANA: As you go around the table, I think it will be helpful for us if members will comment on, not just the therapeutic class approach, what would be the comment on combining the individual active moiety approach to the therapeutic class, do you think that will alleviate some of their fears or will it make it worse. That will be a very helpful comment.

DR. MURPHY: Let's just start back, so if the active moiety is the same, you would be willing to eliminate it?

DR. OTULANA: That is the second part of that question, where we will remove individual members of the class in addition to removing the entire class when the three alternatives and all the other criteria are met. So, we would like some comment on that additional approach, of taking out, say, albuterol, for instance, while leaving the other members in the beta agonist class until the full criteria are met for the entire class.

We would like some comments on that.

DR. MURPHY: Les.

DR. HENDELES: Could you give us an example,

Tunde, for the inhaled steroids, how that would work? I mean describe a scenario for us.

DR. OTULANA: If we have beclomethasone reformulated, for instance, and the CFC-free alternative meets all the criteria for the active moiety, we will remove all beclomethasone products that are currently available. That will count as one alternative for the steroid class.

Then, say, Azmacort comes along and it is reformulated, and again the reformulated product meets all the criteria, we will remove Azmacort or triamcinolone. We will need a third alternative before we remove entire therapeutic class or steroids, then, whatever that is.

DR. HENDELES: Let's say that third alternative was fluticasone, would you then take flunisolide off the market?

DR. OTULANA: Correct, if the current proposal stands.

DR. MURPHY: That is Question No. 5.

DR. HENDELES: I think that strategy has merit, but again, it would depend upon what was being eliminated and whether there was any documentation that that agent was in any way different.

DR. MURPHY: Is that a fair enough comment for you?

DR. OTULANA: We note that, yes.

DR. OSBORNE: Briefly, I have no trouble with that paradigm for the Class I agents. I do have problems with that paradigm for the Class II agents, and the reason is I am not sure that having only two active moieties replaced, given even that there would be three different kinds of dispensing, is enough to appropriately address all the differences between the five Class II agents that are listed.

DR. MURPHY: Stan, what is your feeling about that?

DR. SZEFLER: By Class II, do you mean steroids? I would share your concern. I think there are differences with the steroids.

DR. MURPHY: So you would say with bronchodilators, that would be fine rule.

DR. SZEFLER: Yes, I can live with the bronchodilators. The steroids, I have some concerns. What Les was pointing to was fluticasone being different, and I would feel there would be a shortcoming if there was this scenario that he developed, and then that left the MDI fluticasone off, because, you know, there are situations where there are young, severe asthmatics, and that may be an advantage.

DR. MURPHY: So you are saying that there has to be some way to cover inhaled steroids in the young children.

DR. SZEFLER: Right, and they have to be looked at within the subcategory.

DR. OSBORNE: Actually, I will go out on a limb and say I think fluticasone needs to be considered as a separate active moiety that needs to be replaced with another active moiety, separate perhaps from the others in Class II.

DR. MURPHY: Courtney.

DR. CRIM: Just to reiterate what I was saying, that I think the corticosteroids are different, and I would have a problem with taking that global approach with the cortical steroids as I would with the bronchodilators. I think they would have to be looked at differently, because I am concerned about the differences, there may be differences in potencies, so that is you were to, let's say, eliminate beclomethasone, and let's say, flunisolide and triamcinolone, and then, let's say eliminate -- because you now have three alternatives -- fluticasone, that might be a difference, because there may be different doses that you would use with, let's say, fluticasone CFC, that you would not use with beclomethasone, for example, that you would have to change have you would dose it. Those are the

concerns I have.

DR. MURPHY: So, how many do you need in that class? We were given the number two. So, you said two is fine in the beta agonist, but in the inhaled steroids, it is not fine. So, you are saying that we should have fluticasone as definitely one?

DR. CRIM: No, I think what needs to be looked at is whether or not there is significant differences in potency from a clinical standpoint to make that broad sweep with the cortical steroids, as I feel one can with the beta agonists. I think the beta agonists are close enough in terms of their efficacy and dose reponse that you could probably eliminate, but I am not quite certain that there may be the same case with the various types of cortical steroids. That is what I am saying.

DR. MURPHY: Okay. Les, and then we will go on around.

DR. HENDELES: On the other hand, if you had numbers on the relative potency topical to systemic ratio for each of these compounds, and you had a compound X that had the same potency ratio as one that was available in a non-CFC, but it wasn't available, then, I would have no problem eliminating it, but I think the problem we are all feeling is that we really don't know that topical-systemic

ratio of potency.

DR. MURPHY: Stan.

DR. SZEFLER: I have had discussions up until August of 1996, until fluticasone was approved, I put them all together in a microgram per microgram basis, based primarily on the one study that put them all together, that came out of Iowa, that Richard was part of, in terms of model, and for that point I challenged them to be different, and I think until fluticasone came along, I considered them the same, but when that came along, I put that kind of in a different category of the four inhaled steroids presently available.

So, I would say two classes, and within the inhaled steroid class, they could be split. The NIH, the expert panel broke them into three classes, and I had trouble with the second and third class, but I could go along with it, I think, based on the rationale, it was just as arguable as what I was saying before. So I would say two classes.

DR. LIU: I guess I am going to disagree a little bit. I don't have this problem. I think that steroids could be treated the same way. I think, in reality, it is unlikely that any of the major inhaled corticosteroids are going to disappear because of a change in formulation.

I think that the FDA approach of grouping two major classes that are essential parts of the recommendations and everything is a good one. It is a combination of incentive and coercion in terms of getting people to make the changes, and I basically think it is a sound approach.

I don't have the same concerns about these things disappearing, and I think it is a good way to bring about a change, and I think all of us think is coming.

DR. MURPHY: Good. John.

DR. JENNE: I thought when the original question was asked, when you said combining the two approaches, going back to the adrenergic compounds, that one of the commentators had suggested that in terms of accelerating our departure from CFCs, that if one moiety was successfully produced in an HFA or a DPI, that that compound itself would be then taken off, I mean the CFC would be taken off, and the others would still be in the running.

Wasn't that the original issue, and that sounded to me like a good method of getting CFCs down fairly rapidly, but not destroying all the opposition or all the competition, I should say.

DR. OTULANA: That would be the scenario if we do not adopt the therapeutic class approach.

DR. JENNE: Is that what we are discussing still or have we drifted into some other things here?

DR. MURPHY: We are really discussing whether the availability of three acceptable alternatives consisting of two active moieties.

DR. JENNE: Well, that is a little different, but I think we need to have at least two moieties in the adrenergics and two in the corticosteroids. I am concerned about development of new drugs. It seems like what is happening is we are going to usher in sort of a static era where everybody is concentrating on getting on the delivery vehicle.

DR. MURPHY: Do you want to comment on new drugs coming along, John?

DR. JENNE: Well, I mean for example --

DR. MURPHY: I was asking John Jenkins, if that is a valid concern or if new drugs are coming along to be developed.

DR. JENNE: We have never undertaken salmeterol for perhaps technical reasons, but the only long-acting adrenergic agent we have is salmeterol, and I don't think we should close our minds to the possibility that new drugs will be coming along, and we ought to have a process that is still encouraging to new drug development.

DR. JENKINS: Let me first address and explain once again what really we are asking. The therapeutic class approach, if it stands alone, would mean that none of the members of the therapeutic class would be phased out for the use of CFCs until you had three alternatives, at least two of which are different active moieties and at least two of which are MDIs.

That, for example, could mean that if you had 10 albuterol HFA-MDIs, but you didn't meet the criteria for the phaseout of the therapeutic class, you would do nothing until you met the criteria for the therapeutic class.

The alternative, the addition we are talking about would be maintain the therapeutic class strategy where you would still phase out the class when you had three, two active moieties and two MDIs, but in addition to that, phase out individual members of the class as they individually meet the criteria.

So, under that scenario, if albuterol had an alternative that met all the criteria, you could phase out CFC use for albuterol, but you would still have CFC use for other members of the class. If terbutaline came along and had an alternative that met the criteria, you could phase out use of CFCs for terbutaline, and then if you had one more, either albuterol or terbutaline product that met the

criteria, then, you would phase out the whole class.

So, those are the two pathways. One is don't do anything until you take the whole class off. The other one is maintain the class approach, but get there incrementally by taking off individual products as you get there.

Coming back to the question of are people just focusing on developing new drugs, are they just focusing on developing alternatives and reformulations or are they focusing on developing new drugs, there are companies that are focusing on developing new drugs, new steroids and new bronchodilators.

So, whether it is less or more than they would be doing if they didn't have to reformulate the old drugs, I can't say. If anyone from the audience wants to comment on that, I will let them do that.

But are we clear now on the therapeutic class strategy, because I know it is confusing --

DR. MURPHY: I think what might be helpful is if you drew it, and then people could talk about it a little clearer. Can you draw it on an overhead or is everybody clear on it?

DR. JENKINS: I have never thought about how to draw it.

DR. MURPHY: I think how do we get the information

to you, do you feel you have gotten useful information from this discussion or do you feel it is too muddled?

DR. JENKINS: I think we are getting very useful information, but we all recognize that the therapeutic class proposal is difficult in concept to understand, and that is why we have tried to reiterate it numerous times. I think we are getting good comments, but I just want to make sure everyone understands that there are two different proposals for therapeutic class.

One incorporates the other and adds the addition of phasing out individual members as you go to getting to enough alternatives to phase out the class.

DR. MURPHY: Stan.

DR. SZEFLER: Let me just get a clarification on one point, John, that you raised. Take albuterol, for example. Now that we have an HFA, a year could go by, no major problems, and then that would open the pathway to eliminate the CFC albuterol.

DR. JENKINS: That is the potential scenario under the combined therapeutic class and individual member approach, but again, let me emphasize that we need to implement a final regulation that gives us the criteria, so we are at the Advanced Notice of Proposed Rulemaking, we need to get to a final rule, but once we have the final

rule, if it said what our Advanced Notice Proposed Rule says, you are correct. If we had one albuterol, a year passes, we think we have adequate data, there is adequate supplies and production capacity, all patients are served by that product, then, under the combined therapeutic class approach, then, FDA could propose to eliminate the use of CFCs for albuterol.

Again -- I want to emphasize -- that again would be notice and comment rulemaking. We would put out a proposed rule saying we propose to eliminate albuterol, we would receive public comments, and then we would finalize the rule.

DR. MURPHY: Let's just take that one example and just going around, does anybody have trouble with that example?

MS. MITCHELL: I think the alternative can be true that this provides enough incentive that -- because the area of contention seems to be more along the inhaled corticosteroids, and all of those different inhaled corticosteroids could come up with their own options that are non-CFC.

I mean I think we are kind of putting a blindfold on and not -- or blinders on -- and not recognizing the fact that this may indeed turn out to be a stimulus for everybody

to go ahead and move forward, and maybe that is an overly optimistic view of it, but I would have to appreciate the work that you have done on this and look at it from that particular standpoint.

I also understand you take out an individual patient who says, boy, this is the only medicine that could ever possibly work for me.

DR. MURPHY: We are going to get to that in a minute.

MS. MITCHELL: Because there is certainly that patient satisfaction aspect of things, but the bottom line is we are moving, you know, this is a law, we are moving to non-CFC products.

DR. MURPHY: John.

DR. JENKINS: Let me just in very general terms, because I can't speak to individual companies and what they are doing or what individual products are being reformulated, but in a general sense, there is a lot of development activity out there, companies are working very hard, there is not really a concern in my mind that we are not going to have reformulations of the market leaders in these categories.

We may not see reformulations of all the members of the categories, because the companies may simply decide

it is not worth their time or effort, if they are only selling 1 percent of the market for a bronchodilator -- and I am not going to name a specific one -- but if they are only selling that much drug, they may not undertake the effort to reformulate that product.

So, even if we don't have this type of phaseout criteria, once the CFCs are gone, that product would be gone, because the company is not undertaking to reformulate it, but for the market leaders, you know, the important bronchodilators, the important steroids, and the important members of the other class, there is a lot of activity, and the companies are not going to walk away from those big market shares, but they may walk away from the small market shares.

DR. MURPHY: So is that a concern to this group, that we don't have 20 choices in the categories, that people would walk away? I am not hearing any concern.

Curtis.

DR. SESSLER: A couple of quick observations. I think the beta agonists may be a little different than the inhaled corticosteroids in that it may be that delivery is more important than drug in the sense that the drugs are fairly comparable, at least the leaders are, but this is rescue therapy we are talking about, and if there is the

effectiveness issue, not the efficacy, but the long-term followup in terms of failure of device in rescue situations, I think that is a part that we really haven't touched on.

We have concentrated more on drug than on delivery, and it may be more important in that situation, in the acute situation.

The second thing is there are nine questions and a lot of discussion. Generics are not going to go away or maybe they will, which would be very unfortunate, and I think a lot of the discussions have not yet centered around the role that generics may play in this and how they should influence our decisionmaking, and I would be interested in hearing some thoughts about that.

DR. MURPHY: That is a good point. We heard a lot this morning or we heard five minutes, I guess, about the generics this morning. Do people have comments, Jim, Dick?

DR. AHRENS: In concept, I think the basic idea of the class phaseout makes a lot of sense to me. I think it is a very well thought through kind of thing. It clear is there to provide some incentive to all the companies to really move this process along as rapidly as possible, and in fact, put some competition into that.

I have heard a lot of concern, particularly about inhaled steroids and fluticasone specifically. Without

getting into the merits of the debate of whether that is really something different or not -- which could be debated -- let's just take that for now as a given.

That is obviously a drug with a fairly large pharmaceutical concern behind it, and unless there is some, unknown to us at least, absolutely insurmountable barrier to coming up with an alternative, a suitable alternative formulation, it would seem to me that that ought to happen as well and as rapidly for that compound as any other.

What is clear also to me from this discussion is that this phaseout is going to happen. It is only a question of exactly what the date is, how many years in the next decade or so before that is going to happen.

So in the I think really unlikely event that there is some insurmountable barrier to developing a suitable alternative for fluticasone, if that were really true, then, we are going to have to get used to it sooner or later anyhow, and we might as well get used to that fact.

On the other hand, I think it is likely that fluticasone will have an alternative preparation developed as rapidly as any other, and I see no reason to think that this scenario is likely to come to pass where the three preparations that trigger the class phaseout don't either include fluticasone at that point or very shortly

thereafter.

If I am not mistaken, there are already alternatives in terms of dry powder inhalers on the market in other countries, are there not, for fluticasone?

DR. JENKINS: Yes.

DR. AHRENS: And the generics, I mean I think it really unfortunate that there is going to be a rise in costs when this does take place, but again, it is not a question of if it is going to take place, it is simply a matter of when and we are just going to have to face the fact that part and parcel of that process is going to be a rise in costs at the time, unfortunate, but it is a fact.

DR. MURPHY: Jim.

DR. BARANIUK: This is a theoretical point based on your recommendations. If I owned a patent for the albuterol HFA, I would be rushing out to set up an alliance and market terbutaline HFA, isoproterenol HFA. There is three products, three bronchodilators on the market, two of which are MDIs. As of the date of the third one, according to this rule, all other beta agonists will be taken off the market, is that correct?

DR. JENKINS: I think your premise is correct. I think you are trying to get at the issue that there is incentive built into the therapeutic class approach, that if

you have the technology, you are going to --

DR. BARANIUK: We are going to monopolize --

DR. JENKINS: You are going to make use of it to try to get your competitors off the market.

DR. LI: It would be only correct if those other products met all the comparability requirements, which may well not be the case in that hypothetical situation. It would be unlikely that an inhaler form of isoproterenol, for example, would meet all the comparability requirements that are present.

DR. BARANIUK: Comparable to that, comparable to the same drug or comparable to albuterol?

DR. JENKINS: The comparability assessment, when the new formulation is approved, the comparability assessment is to the existing CFC formulation of the same drug.

DR. BARANIUK: So I think you could easily show that.

DR. JENKINS: This is not just a numbers game, as I have tried to emphasize. It is not just a goalpost that you reach as we are proposing at a certain set of numbers and you are home free. There is all the other criteria that have to be met, of patient acceptability, serving patient needs, and supply and production capacity, safety data from

the large postmarketing experience, et cetera.

I thought what I heard you getting towards was the idea that there might be some built-in incentives in the therapeutic approach that it may really stimulate companies to want to move faster, because they can take out some of their competition under that approach.

DR. LIU: Could I just clarify something? It certainly doesn't mean that the other companies that would "be at risk" are taken out, could not develop their own. It doesn't stop them from their own development. I think that is an important point to make, it doesn't eliminate those drugs. It depends on whether the company wants to invest in development.

DR. BARANIUK: Sure, it does, because it means that if you are the first out, you have got your three products out there, and it may be a couple of years before you can be back on the marketplace to compete.

DR. MURPHY: John, do you want to comment on that?

DR. JENKINS: Again, there is nothing stopping all companies today from working to formulate new products.

DR. BARANIUK: Based on this discussion, they had better be working on those.

DR. JENKINS: And I can assure they are. In fact, we are dealing with so many sponsors, I can't keep track of

how many sponsors. We are not just dealing with the Glaxos and the Scherings and the 3M's. As the speaker earlier, you know, Day Laboratories, a traditional generic company, Dura Labs, Sepracor, there are a lot of companies getting into this area, because some of the products we are talking about, the drug substance is no longer on patent. Albuterol is not on patent. So anyone who develops a formulation can work towards getting that approved.

DR. BARANIUK: Which means that the day when we eliminate the competitors, the CFCs, may be very, very soon. It may not be 2005 as we have heard threatened. It may be when those three products are out, and it could be this century.

DR. JENKINS: That is pure speculation. Right now we only have one product approved, and it depends upon how rapidly the companies are able to get those products through their required testing and submit the NDAs, what, if any, problems show up in the NDA.

I do want to emphasize what some of the people from the industry said. This has not been an easy process. Some companies have started a reformulation effort and thought that they had the product going in the right direction, they have gone into clinical trials, and found that they had to start all over again.

Every components of these MDIs is being reengineered, redesigned, reformulated, because it is not a simple matter of taking out the CFC and dropping in the HFA. So, it is not proving to be simple. So, while there is a lot of people working on it, it hard to project when they will get over the hurdle and be on the market.

DR. MURPHY: Dr. Otulana.

DR. OTULANA: Two quick points. I think it is unfortunate that we cannot discuss individual products that are in development, but I think it is worth reassuring the committee that in coming up with those criteria, we did look at the activities and the pharmaceutical industry.

There are some scenarios that have been mentioned that are very unlikely to develop. That is as much as we can say. As John said earlier, there is a lot of activity in the areas of the market leaders, and in coming up with some of the criteria that we are proposing, we have looked at lots of models of what may happen when these drugs reach approval.

Also, to point out that we do have a lot of judgment built into the policy. I don't think we will take out, for instance, a whole class if what we have is three alternatives at the bottom of the list, drugs that are used by only 1 percent of the population, so the FDA will have

some discretion to look at what these alternatives are.

Based on what we know now, most of the market leaders will be reformulated and most likely will be available at the time of the phaseout.

DR. MURPHY: I would imagine that it would come to something like an advisory committee meeting before something was phased out. Do you think that is true, John?

DR. JENKINS: That is one possible scenario, that we might revisit some of these issues in the future before advisory committee panels.

MS. HUFFORD: I just wanted to make a very brief point. I think you are expressing an optimism about the regulatory process and how quickly it moves. That is probably unwarranted. This is the very first step in the whole process. It is a very deliberative process. There is a set of comments that have to be gone through. They will be gone through I know very carefully.

The next step in this regulatory process also would have to be subject to notice and comment. Then, there would be a final rulemaking. Then, there would have to be probably ANPRM proposal and final associated with removing things.

So, I think that probably a worry about a very near-term change is not justified.

DR. BARANIUK: So, the companies could have their products on the market before the rule is made.

DR. MURPHY: Right. I would like to move on if it is okay with you, John. Do you think you have enough comments in this area? I know you didn't want a vote.

DR. JENKINS: I still don't know that we got a real feel from the committee. I heard people say that they had concerns about one class or the other, but I don't think you got much of a response to your question about if you have a concern, and two is not enough, then, how many do you need, and also I don't think we got much of a response on should we adopt just the focused therapeutic class approach, and not do anything until the class as a whole meets the criteria, or should we adopt the hybrid approach where individual ingredients could be phased out as we go.

DR. LIU: I think part of that was that I assumed that it was the hybrid approach, at least from my point of view in the discussion. I think that it allows you a certain amount of flexibility in terms of the class with a lot of different -- I mean I like this system because it has got both. I certainly would go for the hybrid approach where if there is something like albuterol, it has a large market share, a lot of generics, a lot of different preparations out there, that you could single that out even

though the class as a whole could be preserved just because of that particular drug just to give an example, but I like the fact that built into the system is a way of singling out certain drugs within the therapeutic class, if, in fact, they are ahead of the pack in terms of alternatives and that sort of thing, but I like also the fact of the therapeutic class approach.

DR. OSBORNE: I also support the hybrid approach, and I have had my fear allayed about the Class II drugs.

DR. SESSLER: I will stand opposed to the hybrid approach just because of the albuterol example, frankly, and the generics. Why have the generics out of there for two or three additional years before the class as a whole reaches maturity and makes the transition.

I mean albuterol is available, yes?

DR. MURPHY: Right. So you would take out albuterol --

DR. SESSLER: No, I would not, I would oppose that. I think that if one does that, and you are singling out your available generic, that although we accomplish theoretically getting the CFCs out a little bit earlier, it is an unfortunate -- I guess it is an unfortunate coincidence that the first drug that would be affected by that would be generic albuterol.

DR. MURPHY: Dick.

DR. AHRENS: I also agree with the hybrid approach, and while I really understand the comments that you make, I feel like cost is an issue, but I first and foremost need to think about patient safety.

My preference would be that this happened for a drug at a time, at least one drug initially, so we can gain experience with this process, as opposed to, bam, a whole class disappears all at once and we have no CFC alternatives remaining.

So, to me, it hedges the bed a little bit. Let's suppose that the admittedly unlikely scenario comes to pass that we wind up with problems with transition to an HFA when there is a wholesale, widespread conversion.

What is clear to me, I guess from this discussion today has become clear to me, is that this transition is going to happen fast, no matter what -- let me explain that -- it is going to happen fast no matter what. It is going to happen fast sooner or because of all the market disincentives to the transition, even though other replacement inhalers are on the market, the widespread transition is not going to occur until it is forced, and then it is going to happen fast.

So it is going to happen fast either sooner or it

can be many years from now, and it is still going to happen real fast right then, as soon as it becomes forced, and before then I think that the market penetration of the replacement inhalers will be quite small unless there is a DPI or something that seems to have a clinical advantage.

Barring that, it will happen fast later. With that said, I would rather get experience with it happening with one compound first, and then have the whole class disappear second rather than going directly to -- waiting for the whole class to disappear in terms of CFC.

DR. MURPHY: John.

DR. JENKINS: I would just like to point out that we use two terms a lot. We talk about transition and we talk about phaseout. We have already started the transition, and the transition is going to continue. You know, every new product that we approve continues the transition. The phaseout or the criteria we are outlining in the ANPR, and that is phaseout of our essential use exemptions for CFCs are still a bit down the road, because it depends upon the introduction of the alternatives and their acceptance, but the transition is already started because we already have an alternative out there.

Just for information, if you would like for me to briefly address the issue of how this policy applies to

generics, I can do that.

DR. MURPHY: I think that would be helpful. Would you like to hear that since the generic issue was raised?

DR. JENKINS: Dr. Otulana had been planning to correct this issue earlier because several of us kept referring to drug products, and I think Dr. Otulana accidentally said that the individual drug products would be listed in our reorganized 2.125.

What he meant to say was that the individual drug substances would be listed. So, we are not going to list Ventolin in the regulation, we are going to list albuterol. So, that listing covers all the CFC products that contain albuterol.

So once the criteria would be met to phase out the essential use exemption for albuterol, the phaseout would apply to the innovators, as well as the generics.

On the HFA and the DPI side, most of those products are going to come onto the marketplace with three years of marketing exclusivity, meaning that FDA could not approve a generic for at least three years, because that is the protection the innovator is given for their efforts to bring the product to market.

Proventil HFA was approved in August of 1996, so their exclusivity for marketing purposes would expire in

August of 1999. In theory, FDA could approve a generic in August of 1999 that would be substitutable for Proventil HFA.

That is how the process approach is going to work. The essential use exemption applies to the drug substance, not to a specific product, so the generics will go at the same time the innovator containing the same drug substance goes, but we are going to have a rolling effect over time for example, it is possible that a generic could be approved to Proventil HFA prior to the albuterol essential use listing for CFC is being eliminated.

So, you may not see a gap between the availability of an albuterol generic and the availability of an albuterol HFA generic. Albuterol is the only inhaled product that is currently available as a generic.

DR. AHRENS: Could I ask a quick clarifying question?

DR. MURPHY: Yes.

DR. AHRENS: So that is in terms of the exclusivity. We heard something from Sepracor earlier about barriers to availability of HFA, I presume 134A and 227. Are there any patent barriers in addition to what you just talked about, that might prevent a generic company from coming forward with a generic in that time frame? That is,

not related to the drug compound, but related to the propellants.

DR. JENKINS: I am not a patent attorney, but I know that there has been a patent issued recently to 3M for the use of 134A and metered dose inhalers. How that will impact on the ability of other companies to utilize that technology to develop alternatives, I really can't address because I am not a patent attorney. If 3M wants to address that or their competitors want to address that, I will leave that to them.

DR. MURPHY: Does 3M want to comment?

MR. RICE: Charles Rice with NAPM. There are patents attached to the 3M technology. You have heard Sepracor mentioned, that the technology is not being made available to branded companies. It is also not being made available to generic companies.

So, your presumption that there would be a generic Proventil HFA before 1999 or by 1999 is fiction. It is not going to happen. The word that was used here is monopoly, and that is what you are creating, and we need to have more dialogue with the generics industry to resolve this issue, because it is a major issue, and we not talking about pennies at all. Managed care is going to have a voice, health care entities across the country will have to have a

voice.

DR. JENKINS: Would you like to state an alternative?

MR. RICE: To you in the proper forum, yes. I have got to catch a flight.

DR. MURPHY: May 1st, right?

DR. JENKINS: May 5th.

DR. MURPHY: Thank you for your comments. Go ahead and comment.

DR. HANDLEY: My name is Dean Handley. I work for Sepracor, and I am aware of this patent issue. There is a presumption on the committee that simply since the HFAs are available, one can access them. That is not true. In fact, those that hold patents are by design not obligated to allow you access to it. They can choose their partners as they see fit. They complement their strategy and their economic profile. In there would be incentive to do so.

Secondly, this unintended monopoly is a realistic concern. You spoke about innovative products, which now would be faced with the additional hurdle of gaining HFA technology. We simply just elected to disengage and go another way, and you may find that you suppress the development of new and innovative technologies by virtue of the burden you place on them.

That still presumes that once they get to a point of development, they could, in fact, access that technology. It is highly encumbered by excipients and other forms that makes small companies like us unable to compete either financially or physically in that area. It is a very common consequence in this industry, as well, but by the change in regulation -- and we have heard it several times before -- you create this unintended monopoly, provide a chronological distance and separation between the two companies, that some small companies can't compete, in fact, are not invited to do so.

We have several documents that can support this public statement.

DR. MURPHY: So what would be your solution to this?

DR. HANDLEY: I don't have a solution so much as a clear definition of the problem, and I wanted to change the concept that one can simply just go out and access HFA technology, you cannot, and to the point that it is financially expensive, that could be understandable and realistic in terms of companies as long as you can pay for it. Small companies don't have that kind of commitment to available resources.

Having said that, we need to balance it with the

Montreal Protocol, and come out to considerations that minimize the use of them.

Thank you.

DR. JENKINS: Again, I am not a patent attorney. My comments were that it would be possible for the FDA to approve the generic from exclusivity issues for Proventil FHA in 1999. The patient issues would be things that would have to be dealt with. If 3M wants to address their patent, if you want to allow that, that's fine.

DR. MURPHY: Dr. DuVal, do you want to -- or Mr. DuVal?

MR. DuVAL: I wish I were a doctor, I am just a JD.

As to the patent issue, back in 1988, we started a project that we called Project First, and our whole goal was to be the first in the world with a CFC-free technology, and we succeeded. We spent a lot of money doing that, and just as new molecular entities, drug molecules are patent protected, we, as 3M, have 50,000, 60,000 products, and we believe intellectual property extends beyond just the world of pharmaceuticals, so, yes, we have intellectual property in this area that we are very proud of, and it was issued just recently, and we have notified our customers of that, we have notified other companies.

We are sharing our technology actively with, as I said, seven different companies and 11 different drug molecules. We are in negotiations with four other companies on seven other drugs, and these companies will continue to sell their products under their own trade names, and in some cases, they are new products, so there will be new trade names.

That is a lot of -- you know, we are willing to share our technology with everybody. Some of the companies in this room were offered this technology five and six years ago, and refused it. They didn't think we would be first.

We raced to develop the technology and at least with respect to 134A, it looks like we have been successful, but with respect to Proventil HFA is a good example. We could have come out with our own brand albuterol in the U.S. marketplace, we did not. We sought out folks, and one of those folks ended up signing a deal with us, and it is today Proventil HFA.

We are only working on a couple of other molecules that are proprietary to ourselves. Beyond that, we are happy to keep everybody in the marketplace, on the market and their own trade name, and we have been sharing our technology to do that.

We are open to negotiate with anybody. I don't

even know this guy from Sepracor. I negotiate all the deals.

DR. MURPHY: Maybe you could meet in the bar later.

MR. DuVAL: Yes, I negotiate all the deals, and I have never met him.

DR. MURPHY: Thank you for those comments. I think the goal of today is to really get a lot of discussion and dialogue going, and I really appreciate the restrained manner in which people are -- and the respectful manner everybody is treating each other. Everybody is doing a good job. You are doing a good job. I will give you a short break if you do a really good job.

Courtney.

DR. CRIM: My comment is going to encompass actually a couple of things. I am changing my viewpoint in terms of how I had originally said I would separate out the beta agonists, the short-acting bronchodilators to the cortical steroids. It sort of encompasses some of the comments made by Dick Ahrens in that, one, I view my role here today as addressing the question as to whether the process that the FDA is proposing is appropriate, and not getting up into corporate strategy, which I think the discussion recently got off into.

So, therefore, in the context as far as the process, I agree with this hybrid approach. It seems to be reasonable in that particular context. If some particular products fall by the wayside after this process gets eventually implemented -- because my sense is by the time this process finishes the transition, so to speak, would probably be the year 2005, and therefore, I think some of these new types of formulations will probably be on the market by then. So, therefore, we probably in essence will be talking about that which occurs after the year 2005, once this whole process goes through this review, and re-review, and this final program eventually gets implemented.

So, therefore, once this program gets implemented, then, I think we will be dealing with these corporate strategy type issues, which I personally don't think is germane to us. So, therefore, as far as the process is concerned, I guess I really now do not see a difference in terms of the corticosteroids either, that is, if a product comes out on the market, and it is found to be efficacious and safe, then, you can eliminate that particular product.

If the generics go by the wayside because of that, again, I don't look upon that as my role here on the FDA advisory committee, but a corporate issue, which I don't I am really -- I personally don't think any of us are really

here to address.

It would be nice to have generics, but in terms of advising the FDA as far as whether their process is appropriate, I really see no problems with it, even with the corticosteroids now.

DR. MURPHY: Good. Thank you. Molly?

DR. OSBORNE: No, thanks.

DR. MURPHY: Jim.

DR. BARANIUK: Can I ask Dr. Jenkins one question? The FDA policy is to remove CFC-containing products from the marketplace, correct? In due course.

DR. JENKINS: I am sorry. Say that again.

DR. MURPHY: That is the law.

DR. BARANIUK: Exactly. It is policy to remove CFC-containing products from the marketplace.

DR. JENKINS: The Clean Air Act implements the Montreal Protocol ban, and that is geared towards eventually being a complete --

DR. BARANIUK: We understand each other. The question is will you approve any new product that contains CFCs?

DR. JENKINS: We have addressed that issue internally, and currently we do not feel that we have the regulatory or statutory authority not to approve a

CFC-containing product if it is shown to be safe and effective.

DR. BARANIUK: So you will approve CFC-containing products?

DR. JENKINS: Yes

DR. MURPHY: You said you didn't have the authority not to is what you said.

DR. JENKINS: Right. As part of this process, we will be gaining some of the authority not to do it as we eliminate essential uses. We are planning on making it more difficult for new essential uses to be added, so that further new molecular entities, et cetera, are being formulated in CFCs will be much more difficult, but as far as approving generics containing CFCs or approving new drugs with albuterol or any of the other currently approved products, we do not currently have the statutory or regulatory authority not to do that.

DR. MURPHY: Jim.

DR. LI: I just wanted to get on the record as saying that I believe the therapeutic class approach, you know, coupled with the individual member approach makes a lot of sense to me. I think the reason that it does is that I believe it will accomplish its two main goals, one of which would be to at least set out a plan for an orderly

phaseout of CFC-containing inhalers, and second, and probably more importantly, I think it does offer adequate safeguards for our patients with asthma, and it really in a way sets a floor for the minimum number of choices and available agents of two or more therapeutic classes.

I am reassured, in fact, by some of the comments from members of the agency that the hypothetical, worst-case scenarios are really not likely to occur.

DR. MURPHY: Does anybody disagree with Jim's approach vehemently?

MR. MADOO: I would like to interject here. As we construed this meeting, conflict of interestwise, we were seeking input towards this process. We are not in the process of creating a de-facto vote or some other machinations. It is important because the conflict of interest profile of the participants precludes formal voting -- or de-facto voting per se.

DR. MURPHY: So, is what I am saying de-facto voting?

MR. MADOO: Well, I mean if you do an aggregate, I guess.

DR. MURPHY: I just want to make sure John gets enough input and is getting the input that he needs. Do you feel you are?

DR. JENKINS: Yes.

DR. MURPHY: Stan? One comment.

DR. SZEFLER: I just have one point of clarification. We have talked about HFAs as being environmentally safe, and the question I had asked you before, I would just like to get a clarification on this issue.

When I have done some reading on this, there has been some numbers attached.

DR. MURPHY: So this is going to be for the EPA.

DR. SZEFLER: Correct. There has been some numbers attached to CFCs and HFAs, and the numbers that I recall are 12 for CFCs and 8 for HFAs. Is this an environmentally significant different number or is there a 10 cutoff that is safe?

MS. HUFFORD: I guess I would need to know in what context those numbers were developed. I can tell you that the environmental concern that has been raised to the extent that there is one -- I believe there are no toxicological concerns -- but the environmental concern about HFA-134A has been global warming. It does have a measurable global warming potential, as does CFC-12, but there is currently not even an international framework convention, let alone any domestic law or regulatory framework to address it.

DR. MURPHY: So HFA doesn't do anything to the ozone.

MS. HUFFORD: No, because it does not contain chlorine, but it does contribute to climate forcing.

DR. MURPHY: Which we will hear about in five more years.

DR. SZEFLER: That is precisely why I asked the question.

MS. HUFFORD: Does that address your issue?

DR. SZEFLER: Sufficiently confusing.

DR. MURPHY: What I would like to do is allow everybody to stand up and stretch a bit, and then I would like to come back to the question about sub-populations, and I would like to have you think about if there any evidence for that, and then take a quick look at the individual active moiety approach in which there is only one marketed product, so I would like to focus on those two questions as we finish out here.

Let's take a quick five minutes.

[Recess.]

DR. MURPHY: If everybody could move towards their seats, especially the committee could move towards their seats. I have a couple more really exciting questions to address, and some very important information that I think we

need to bring out. People are turning in their name tags to me. I don't think this is a good sign.

I think we have lost Molly, so someone is going to have to speak up for the elderly, and we have lost Courtney, we have Carroll, and we have lost Berri. She said someone had to speak up for children, so I will leave that to Dick, and the consumers.

I would like to move on to this patient sub-population question. I want everybody to really think hard about this and to think hard about evidence for this.

Are there patient sub-populations that can only be treated with specific members of a therapeutic class and if so, what are the characteristics of these patients and what type of data are needed to establish a specific claim for treating these patients?

This is the patient that we have all experienced who says that unless they get isoproterenol, they are going to drop dead. So what evidence is there for this, and perhaps we are going to need for the gene for the receptor and more work to definitely define this, but what are your feelings as a group?

I am just going to move around. I would also like to invite anybody in the audience especially from companies, if you have had reports of this. I know Dr. Wilson has

worked extensively in New Zealand. What are your feelings about this?

Curtis.

DR. SESSLER: I will put a different twist on it again. Instead of looking at it as a drug, I would like to look at delivery and just be certain that we are satisfied that the patient with acute severe asthma can properly trigger and actuate devices that we are looking at as alternatives to CFC-driven MDIs. I am thinking of beta agonists specifically as rescue therapy.

DR. MURPHY: But as far as one beta-2 agonist versus another along the line of, say, selective beta-2 agonists, you haven't encountered --

DR. SESSLER: I don't have any specific thoughts on that, no.

DR. MURPHY: And you have not encountered somebody that says I can only be treated with terbutaline?

DR. SESSLER: I think in my experience, it is rare enough that it is probably not a major factor to be considered from my standpoint.

DR. MURPHY: I think the second part of this question is what type of data are needed to establish a specific claim for treating these kind of patients, how would you deal with that patient?

DR. SESSLER: Are you referring to the acute severe asthma type of patient now?

DR. MURPHY: The patient that says they can't tolerate drug X, that they need drug Y, what should the FDA do with that, how are they going to respond to that? You haven't encountered that kind of patient.

DR. SESSLER: Right.

DR. MURPHY: Yours is more around the metered dose inhaler versus the nebulizer kind of question.

DR. SESSLER: That is a twist that I would like to put on it. Since I don't treat children, for example, I don't have a large elderly population, I am not as focused on differences in specific medications, but I think being primarily an intensivist, some of the issues of the breathless patient who is trying to actuate a metered dose inhaler are important to me, and so that is I guess the focus. How to test that, I think is a little bit difficult. I think the postmarketing issues will bring some of that out.

DR. MURPHY: Good. Jim.

DR. BARANIUK: I think for the patients who believe that one drug is better than the other, first, I would like pulmonologists and everyone to go out and try to recruit those patients and see if they really exist, and

then I think it would be straightforward to use a double-blind placebo-controlled type design to see if the patients can tell the difference between two drugs or have relief preferentially with one drug or the other. I think that would answer it.

DR. MURPHY: Have you encountered anyone that you believe truly --

DR. BARANIUK: No. I have got some who believe that the yellow inhaler is the best one for them, and that's it, so the colors are critical.

DR. MURPHY: So we need different colored containers, but the same drug.

DR. BARANIUK: Absolutely. The triggering in the elderly, I think is critical. It is difficult for people to coordinate the breathing. I think that we have seen that in every clinical study, there is a first week improvement even in placebo, and I am sure that that is just because the study coordinators have finally taught the person how to use their inhalers, and they are doing better, the elderly critically important there, the younger kids.

The role in allergic rhinitis in children between zero and 6. With my population of Vancenase pocket inhaler, there is no alternative. Kids will not use liquid spray. They don't like having all of that stuff sprayed up there

and dripping in their nose. It is hard for them to use anything these.

If you show them how to use this, they get a short, quick puff and there is no sense of junk in there. They are very happy to be compliant with that drug.

DR. MURPHY: Does anybody else want to comment on that? That is the first comment on the nasal MDIs.

DR. HENDELES: I agree with that, and I think even with the ones that are freon-propelled, there seems to be differences in terms of whether it burns or whether they get nosebleeds, and there are many people who really like the aqueous solution, there is no question about it, but we have patients that won't use that, so there needs to be some kind of an MDI type device for the nose, but it also needs to be gentle, slow and warm apparently.

DR. BARANIUK: And a spray that the patient doesn't have to sniff, so in a child, for instance, they have difficulty sniffing, so it needs to be propelled, so the medicine will be shot up into their nose and then carried backwards by ciliary transport.

DR. MURPHY: So, we are hearing that there is a need for a non-CFC nasal spray.

Dick, do you have a comment about that?

DR. AHRENS: No, I really concur with the kinds of

things that have been said so far.

DR. MURPHY: Do you have a comment about the sub-populations?

DR. AHRENS: Not that really hasn't been addressed, I mean feeling the pediatric mandate that you have given me in terms of specific compounds, I don't really see --

DR. MURPHY: You haven't encountered somebody who said, you know, that you could actually prove that they couldn't take albuterol, for instance?

DR. AHRENS: The way you initially asked the question, I think maybe I am reading between the lines incorrectly, but sort of implied that there was a real question as to whether this was real or not, and I have that very same question. My honest guess is that it is not real, but I think what was mentioned about maybe we ought to look at it objectively, and not make that assumption is a really valid point.

DR. MURPHY: So if this kind of report came in to the FDA, then, you would suggest that the next step would be some kind of a placebo-controlled --

DR. AHRENS: Maybe the next step would just be to find out how many of these folks are really around, you know, some kind of survey approach. Again, I think maybe I

encounter one of these patients every couple of years, I don't see a lot of them. Maybe other people see more than I do, but my guess is when you make a survey to find out how many people seem to be around who are really like that, it is going to be quite small, and that may preclude more than a very simplistic way to look at it objectively, but you ought to find out if they are there and look at it as objectively as possible.

DR. MURPHY: Have you had this a lot in reporting to the FDA?

DR. JENKINS: We occasionally do get complaints from consumers or from physicians that, for example, when a product for a manufacturing reason goes off the market, patients complain that that is the only drug I can use, and I really need by my bronchodilator X, and I don't want to put any names to any of these, but we do get those complaints from not only patients, but also from their doctors, who say that this patient really needs bronchodilator X, and I have tried them on bronchodilator Z, Y, W, Q, and they just don't do as well.

It is usually anecdotal. I don't know that I have ever seen any actual, you know, blinded cross-over data to show objectively that it was true.

DR. BARANIUK: If I can answer, I think that part

of the problem is this is an older problem when isoproterenol and epinephrine were more widely used, and the patients got an intense sympathetic reaction, and then would switch to albuterol with a lesser reaction. There is the sensation that it is not doing as much for you.

DR. MURPHY: Let me just go around the panel, and then I will take the audience.

DR. BARANIUK: Can I add one other point?

DR. MURPHY: Yes.

DR. BARANIUK: I think the device is a critical issue here. We have an unmet need here for people who can't use MDIs, who I think that is a marketing advantage here. If we come up with new devices that will be easier for populations to use, I think that product will sell itself regardless of what it is propelling.

DR. LI: I think if we sort of distill this question to mean whether the proposed strategy is likely to orphan a significant number of patients by eliminating medications that they need, and for which there is no substitute, I think that is very unlikely.

Having said that, certainly there are scenarios where a patient will not tolerate a particular drug, which is a different issue than saying that there is only one drug which is effective for the patient.

For example, there are patients who use isoproterenol, who have a paradoxical bronchospasm to isoproterenol. Certainly, with delivery systems, there are patients, for a variety of reasons, who are unable to use metered dose inhalers adequately, but I think that those patients will be adequately dealt with, with the strategy.

Having said that, I think part of the reason this issue comes up is that in clinical practice, we see patients with asthma, who may not be well controlled for a variety of reasons, and the usual clinical strategy is to make changes, so if they are aerosol corticosteroid A, and they are not doing well, then, we might change to B for perhaps no good reason.

Perhaps there is some theoretical rationale for it, and perhaps that may not be effective, and then we move to C, and finally the patient is under some good control, and so it is tempting to surmise that this patient can only be controlled with aerosol corticosteroid C, but I think everyone recognizes that the evidence for that is shaky, and yet I think we should just keep in the back of our minds that there may be, in fact, it has been said, we don't know everything there is to know about these aerosol corticosteroids, about differences in safety profile, differences in drug potency, receptor binding, and so on.

So, I think it is a legitimate question, but in actual practice, I think it is very unlikely that we are going to orphan any individual patient groups.

DR. MURPHY: I guess John Jenne left. We might want to get his opinion on this, because he has certainly worked a lot with the beta-2 agonists.

DR. AHRENS: Could I ask a very brief clarifying question related to this?

DR. MURPHY: Yes.

DR. AHRENS: I guess the way that the proposed regulation or whatever the correct terminology is, that we are reviewing today, is written, that the burden to provide this proof would be on whoever thought that this was correct, which would presumably be most likely the company who was going to have their product withdrawn, or perhaps if there were some clinicians around who felt very strongly that this was real, that it would be an obligation for them to try to find funding to accomplish the study, not for the agency or the company that developed the replacement, et cetera.

DR. OTULANA: That is a deliberate policy, too.

DR. AHRENS: I guess I think that is appropriate to put the burden of proof there. I mean it may be real or the opportunity ought to be there, but that is where the

burden of proof should be.

DR. MURPHY: It is just developing a policy for it.

DR. MURPHY: Mark, do you want to comment?

DR. LIU: I don't have any other comments.

DR. MURPHY: Have you seen this?

DR. LIU: No.

DR. MURPHY: Les.

DR. HENDELES: I am the person at the University of Florida that always gets the calls when there is an asthma drug problem, and when the Warrick generic for albuterol came out, in a white actuator, I got loads of calls. It turned out that all those patients were switched from Proventil to Warrick's generic, and guess who owns Warrick? Schering. So, they were actually switched to the same identical product with a different label, a different color, and that caused the problem.

I have never seen anybody that I would categorize as being a sub-population. There is occasional patients that claim that two puffs of albuterol makes them have tremors or gives them a headache or gives them some tachycardia, and if you cut them to one puff, they do fine.

So, I don't think there is -- you know, the policy clearly will have a second moiety, a second drug, and you

will be able to switch a person to that, so I don't think it is a problem.

DR. MURPHY: Stan.

DR. SZEFLER: I don't think I see the issue in terms of the beta agonists, but I would argue for an issue being present in terms of steroids, because there have been patients who have not done well on conventional therapy, and then when fluticasone was introduced or when we had it available, before it was introduced, they did remarkably better, and I don't know if the reverse would happen, that if was taken away, that they couldn't do better with a substitute now that they are doing well, but I just don't see the problem with the beta agonists. It is anecdotal, and I haven't had the opportunity to study those patients in a controlled way, but I would say definitely with the inhaled steroids, there are sub-populations that benefit.

DR. MURPHY: Respond better to other inhaled steroids?

DR. SZEFLER: Right.

DR. MURPHY: John.

DR. JENKINS: Do you think that finding or that observation is really related to a difference in the molecule or do you think it is related to a difference in the dose, maybe you are giving the right dose of the second

molecule, whereas, maybe you weren't giving the right dose or the patient wasn't using the device correctly?

I am just wondering. I recognize that there are different potencies of inhaled corticosteroids, but given the right dose of each drug, do you think patients respond differently?

DR. SZEFLER: I think in those severe categories, you always wonder if it is the compliance more so than the dose, but I think dose for dose that they have been on, I think there is a difference in the molecule.

DR. HENDELES: I tried to address that category. I know for growth in children, that there are certain drugs where there is conflicting data and there are other drugs where you have never seen a case report.

So I suspect that there are some differences in the side effect profile between drugs in the inhaled steroid class, and I think that there is probably some where there is a difference in potency topically. I know there is one that doesn't taste well, and we get a lot of patients that come back that stop taking it, because they didn't like the taste of it. So, I think those kind of differences exist for the inhaled steroids.

DR. MURPHY: Comments from the audience? Dr. Wilson.

DR. WILSON: I am Doug Wilson from Boehringer Ingelheim. I have had some experience, but it is in the clinical arena and since I have been with industry. I think we can predict the following sequence. There will be a small sub-population depending upon the delivery device in children and older patients where they are not able to effect enough of an inspiratory flow or enough of a coordination to deliver it.

I think with inhaled powders there is some evidence that some very severe patients with very severe obstruction and COPD usually cannot generate enough of an inspiratory flow to move the powder. I think it is a small population, but I think it exists.

The second population are those who, rather like Democrats and Republicans, have very profound brand loyalty and no matter what you do you cannot change them.

I think the third group is a curious one that you are not able to identify from clinical studies, and that is, what may be either significant or relatively insignificant taste differences that materially affect the patients.

We made what we thought was a relatively trivial change in a gasket with the agreement with the agency, because it had a lower degree of extractables. In tastes within the company, we could not distinguish a difference.

We did a clinical study. The patients could not distinguish a difference. And we had hundreds of complaints from the field when this went out there, because we had a million patients on this who said we cannot continue to use this product because of taste, and that settled down, but it took two years to do so.

So I do think even with modest changes, profound education is required, and I think the period of 12 months may be too short to capture that information even with large exposure. But I think that aside, I think with comparable chemical moieties, in general, you are not going to find differences. You may find very modest differences with beta agonists sometimes, which relate either to the potency or sometimes to the lipophilicity because it might then affect some of the side effects with regard to tremor.

DR. MURPHY: Kathy, you want to comment?

MS. RICKARD: Kathy Rickard, Glaxo Wellcome.

We are talking about individual drug substance like albuterol, but you have to remember that the excipients in each of the compounds may vary from formulation to formulation. The patient may not have a problem with the drug substance, they may have a definite problem with excipients, which I believe are well documented in the literature. So we have to be very careful that we don't

just talk about the drug substance, but all of the components of the formulation.

DR. MURPHY: That is a very good point.

Would anybody else like to comment? Yes, Mary.

MS. WORSTELL: I am Mary Worstell with the Asthma and Allergy Foundation of America.

Again, in the document that I handed you, one of our task force concerns was when you have a temporary intolerability or contraindication, such as women who are pregnant, and availability of optional products.

DR. MURPHY: Thank you. Nancy, did you have anything to add on this? From the lay organization, do you get a lot of calls about this?

MS. SANDER: Actually, in our study, we found that there was a lot of concern that the inactive ingredients be considered equally to be active ingredients, and that by our nature, people with asthma are a little quirky.

DR. MURPHY: Speaking for yourself?

MS. SANDER: Speaking for myself. But the other speakers also elaborated on the things quite nicely, so thank you.

DR. MURPHY: John, is that enough information?

DR. JENKINS: Yes.

DR. MURPHY: So nobody has really seen it. I mean

we have seen it, but we aren't sure we believe it.

Let's go to this question of where there is only one marketed product. Is the individual active moiety approach appropriate for categories currently listed in 2.125 for which there is only one product marketed, and that would be ipratropium, nedocromil, cromolyn?

DR. OTULANA: Salmeterol, epinephrine.

DR. MURPHY: So that would mean that once there was a non-CFC available, that the other one would go off.

DR. OTULANA: Correct.

DR. MURPHY: Stan, how do you feel about that?

DR. SZEFLER: I think this was the example that I gave before in terms of, say, albuterol, and then an HFA replacement.

DR. MURPHY: No, this is where there is only one marketed product, so it would be like nedocromil or ipratropium would be an example.

DR. SZEFLER: So if there was an HFA replacement.

DR. MURPHY: Yes, the other one would go away.

DR. SZEFLER: I could go with that.

DR. MURPHY: Les.

DR. HENDELES: First of all, I have a question about epinephrine and what is going to happen to it as a result of all this, and I was wondering if we could address

that first, John.

DR. JENKINS: What is the question?

DR. HENDELES: What is the impact of this plan on over-the-counter epinephrine?

DR. JENKINS: They will be impacted in the same way that all the other products are impacted in that they contain CFCs, and they will be subject to the same CFC phaseout process that the prescription products are.

Is your question will the reformulated product also be OTC if an epinephrine product is developed, is that the question?

DR. HENDELES: Yes, can they reformulate it and would it be OTC then, or would it then be prescription?

DR. JENKINS: I don't think I want to answer that question right now because we would have to discuss that with the individual sponsors proposing, and we would have to have internal discussions about that, because there are issues related to OTC availability and we would have to talk about that more internally.

DR. MURPHY: Why is epinephrine not a beta-2 agonist, why is it separated out?

DR. JENKINS: We didn't separate it out because it is not a beta-2 agonist. We separated it out because it an over-the-counter product, and we didn't think it was

appropriate, for example, if you are in the camp that believes that over-the-counter epinephrine is a product that should be available to consumers, then, we didn't think it was appropriate for prescription products to be alternatives for the over-the-counter product.

Now, we recognize that there are another camp of people who think that OTC epinephrine is not a good idea, and it shouldn't be available. We actually discussed that issue a couple years ago before this committee, and the committee I think came to the conclusion that they didn't think that there was a need for over-the-counter epinephrine, but Les' specific question, I think I would rather not give a specific answer to today.

DR. HENDELES: The reason why I asked that is it would seem to me that the company has no motivation to develop a non-CFC, and they could just leave it on the market as long as they can, and there is nothing in your policy that would take it off the market.

DR. JENKINS: Well, that is actually something I was addressing during the break with Dr. Bilstad. One thing that we didn't highlight, Dr. Otulana addressed it very briefly in his presentation, where he said that we recognize that this is a dynamic process and that we would need to reevaluate our policy as the transition continues onward and

look at due diligence.

If you actually look in the ANPR, there is a statement in there that the FDA proposes that we would reevaluate the strategy one to three years after the final rule that we are talking about developing today is implemented to decide if changes needed to be made, and so that might open up the possibility that companies that are not showing due diligence might have their products reevaluated and decide whether or not those products continue to be essential even though there is no alternative for that individual drug substance.

So, the idea is not to give anyone a free ride forever and ever.

DR. MURPHY: That is a good point, Les. Thanks for bringing that up.

DR. HENDELES: Then, the cromolyn, nodocromil, I would suggest you might consider putting those together in the same category since they are pharmacologically nearly identical in terms of their actions, and then maybe that would solve that problem.

DR. MURPHY: Mark.

DR. LIU: I really don't have any problem with this individual.

DR. MURPHY: Substitution, okay.

DR. LI: I think the approach is sound. I would make the comment that the way this policy is structured, that the powder formulation could then substitute or could then be considered an alternative for the metered dose inhaler of one of the substances, so that when the delivery device changes like that, it is likely that a few patients will not be able to use the new device, but you will probably capture some new patients with the new device, with, say, the drug powder, and you will be able to capture patients who would benefit from the new formulation, who could not use the metered dose inhaler, so probably it may actually balance out in the long run, but you may affect negatively a small number of patients.

DR. MURPHY: Thank you.

Dick.

DR. AHRENS: I also think it is a sound policy, and I think it goes hand in hand with the so-called hybrid approach. I mean if we are going to do it for individual products in one of those classes, then, it is certainly sensible for those that are in a class by themselves, as well.

DR. BARANIUK: At a past meeting, we discussed the generic equivalence for albuterol and the standards for that. Are those reasonable standards for assessing the

equivalence of one delivery device versus the CFC delivery device if we come up with a metered dose inhaler?

DR. JENKINS: I am not sure I understand the question.

DR. BARANIUK: I guess it is to say if a company comes out with a dry powder Intal, cromolyn, can you use the theoretical framework that was developed by Dr. Anthracite, I believe, for equivalence in order to assess the comparability of the two products, or can that new device have its own dose response, can it have a different dose, for instance, can it deliver four times more than the CFC-containing product?

DR. JENKINS: The latter scenario is possible. We have not mandated that albuterol always have 90 micrograms per dose or per puff, so you may see dry powder inhalers of albuterol that may deliver 200 micrograms or 400 micrograms or whatever, and some of that relates to the efficiency of the device, so it is not as important how many micrograms you are delivering as it is what the clinical effect, the safety and efficacy of that device is compared to the old product.

I think I understand the question is for these reformulated products, can they follow the paradigm that was used for approval of generic albuterols, and the answer is

yes and no. Some of that paradigm is useful for establishing dose response, but you need to remember that the new formulations are new drugs, they often have different excipients, and different devices, so there are additional needs for more extended studies for those for safety purposes, as well as durability of the efficacy response.

So, the paradigm that is used in the generic albuterol approval standard is useful for these reformulated products, for example, in their dose-ranging studies, but we have not been applying those rigorous bioequivalence criteria that are applied to the generic products, but we have also been expecting more extensive clinical data, because again, the generics are, by design, copies of the innovator. So, some of the issues related to excipients and different devices, et cetera, are built into that program.

DR. BARANIUK: So it would back directly to something like cromolyn if it was shown that that drug was more effective if there was 10 times more that the patient actually inhaled, and they came out with a new device that delivered that amount of material, that would be considered an appropriate substitution because it gives a better effect, but it is the same drug?

DR. JENKINS: It could potentially be considered

an appropriate alternative to the CFC product. We don't want to limit innovation to develop better drugs as part of this phaseout, so if people develop a better delivery system that is more efficient, or gives you a better response for a given dose, we don't want to restrict that.

Again, it would come to assessing how well that alternative product meets the needs of the patients who were served by the CFC product to decide whether the CFC product could be phased out.

MS. SANDER: Could I interrupt for just one minute?

DR. MURPHY: Sure.

MS. SANDER: We posed that same question in our survey --

DR. MURPHY: And could you state how did you --

MS. SANDER: We gave a scenario that said under the individual moieties, if a powder preparation, a multidose powder preparation was to take the place of any one of those medications, how would you feel about that, and 60 percent said they would be unhappy with that. However, they were not unhappy with having an MDI, a single MDI.

Thank you.

DR. MURPHY: Thank you.

Dr. Wilson.

DR. WILSON: We do have a little concern about the individual moiety, active moiety, as it relates to a single replacement, particular for our drug Atrovent, which is used chronically, long term, for older, sicker patients.

Firstly, we have profound evidence that there is no safety disadvantage to its long-term use on chronic exposure, and we have had some evidence from a multiplicity of studies that the bronchitis exacerbation rate is reduced relative to either a beta agonist or placebo, and whether that can translate into clinical benefit remains to be established, but because of the complexity of any new formulation that comes in with regards to its excipient, I don't think that the answers that you have an equivalent and safe drug for an older, sicker population with very long-term exposure would be able to come with 12 months exposure in the community, and I think that we would argue for a significantly longer period to evaluate that.

Secondly, with a multidose dry powder, I think it is difficult to, on first principle, to assume that you will get exactly the same result or a comparable result, and the difficulty there is that once you withdraw that, of course, there is no going back in terms of replacement.

So, I don't think it is an impossible deal, but I think it a very significantly difficult deal, together with,

of course, the issue of persuading the other patients over that time. So I think we would caution against saying yes, this is doable, this is straightforward, we would caution against a multidose powder being the same as an HFA, and I think that we would suggest that a longer period of evaluation in the market would be appropriate before pressing to withdraw the CFC in that particular population.

DR. MURPHY: Thank you for the comment.

Any other comments? Let's just take a quick look at the last two questions. What incentives can be used to stimulate the use of alternative products by physicians and patients as they become available? I think we have heard a lot from 3M today around the problems.

Let's go around and just see if there is ideas. Let's start with Curtis.

DR. SESSLER: That is a tough one. Price is an important incentive, more and more, obviously, and some of that is out of the hands of physicians and patients and into other organizations, and price certainly doesn't appear as a positive incentive in some of the proposed changes, unfortunately.

I don't have a real good answer. I think for the patients who are not satisfied with their care, that this is great, there are new alternatives for the patient who does

not do well with the conventional MDI, the dry powder, or some of the other potential delivery devices, it may offer some real benefits.

For the patient who is real happy with what they have got, I think you are going to be hard-pressed to find something that is good.

DR. MURPHY: Thank you.

Jim.

DR. BARANIUK: Detailing, leaving samples in doctors' offices, coupons, advertisements in Newsweek, negotiate with the formularies and get the HMO price down, advertising, advertising, make it the trendy thing, appeal to the green side of the patient, that this is the environmentally safe inhaler. You might want to talk to perhaps an environmentally-sensitive HMO. They might be more interested in putting this on formulary.

DR. MURPHY: Dick.

DR. AHRENS: I hope that that kind of approach works, but my statements earlier were a little more cynical than that, saying that I am reasonably convinced that widespread -- John, what is the right term, I think you scolded me because I used the wrong -- phaseout, not transition, is not going to happen until it is forced, until the alternative CFC-containing product is off the market.

So, at some point, that is going to have to be a forced change. I really hope I am wrong, and I think it would be wise to try to at least make that sort of thing work. Short of that, I really don't know.

Comments I made earlier about wanting to know more about the relative efficacy, for example, may have sounded like they would be obstructionists at that process, and I want to make it clear that I think this transition needs to take place, and not the comments about physicians as a whole notwithstanding, I would like to believe that I am environmentally sensitive enough to think it would be better if it happened sooner rather than later.

My only concern is that when it is made, that we have all the information that is not too difficult to obtain, to try to hedge our bets to make it as properly as possible and know what to look for, that we have as much information as we can have in a scientifically valid way, and not deny ourselves information that is relatively easily available.

DR. MURPHY: Good. Thank you.

Les. Oh, I missed Mark.

DR. LIU: I am hiding here. I think the best incentive would be to set a deadline, at least judging from my own experience with these kinds of things, they are sort

of put off if they are sort of unpleasant.

To some extent, if this approach is sort of hazard in terms of there will be eventually test cases or drugs that will probably come up, and perhaps classes eliminated, and I think that would certainly be an entre to a more widespread ban or enforcement of the ban and elimination of the exemption. Then, they force the whole issue.

I just think, as someone was saying before, it is not a matter of if, it is a matter of when, and I think moving along in this, in sort of stepwise, and not sudden approach is a good one.

DR. MURPHY: Les.

DR. HENDELES: I think the two things that would influence patients are availability and cost. If they lose their chance to get it, I mean the availability of it, they would switch, and if the cost of the CFC all of a sudden skyrocketed because of the difficulty or the supply and demand on CFC, that might very well stimulate them.

I think people are much more willing to change than the consumer groups have indicated today. Most prescription benefit plans and managed care programs are now moving towards a formulary, so that you can give a patient a prescription for drug A, but if that is not on the formulary, it is either \$15 co-pay and take the one that is

on the formulary or it is pay \$60, and so people will switch. They will make their doctor switch unless there is a real compelling reason not to.

The same thing is happening with people who use mail order pharmacies. My niece, who is well-controlled on two puffs of Aerobid twice a day, sent in a request for a refill along with her \$5 co-pay, and got back Azmacort with a letter saying they called the doctor, and the doctor gave permission to switch it. So, she had to accept that. It turned out that the doctor was just intimidated by the process, and could have actually, in that situation, stood their ground, but they didn't.

So, I think that those kinds of things are happening right now, and it is happening more frequently, and so patients are not going to be opposed to this kind of switching, especially if the health care professionals reassure them that they are going to have the same therapeutic effect.

DR. MURPHY: Good.

Stan.

DR. SZEFLER: I was trying to think through the comments, and trying to think of win-win here, and being sensitive to what Mark DuVal had said in terms of almost a punishment for being an innovator, and having a higher price

and trying to recover, and maybe one method around that is for government to align with government to align with government, and a lot of government contracts for health care are kind of in that line, and if some pricing structure should come or that become the preferred drug, then, I think the price would at least be a compensation for the company that was the innovator, standing behind the principle that evolved from the government.

So, that might at least carry it through the survival phase of being the innovator, and then allowing the phaseout of the other drugs. But I think there has to be a win-win, or I think price is too much of a driving structure in the environment that right now is not overpriced, so there has to be that kind of orchestrated movement.

DR. MURPHY: Thank you.

Is anybody in the audience from a managed care organization? I would just like to hear your comments.

I would like to ask 3M, do you have any more wisdom to share with everybody, experience to share with everybody?

MR. DuVAL: I think I am flat-out of wisdom, but I think all the comments here are very practical, and they are very real, and that is what we have seen in the marketplace. Unless there is a deadline, unless you do your part, I would

ajh

have to ask you the question: Are you prescribing Proventil HFA today when you have albuterol patients?

So, we just have to ask that of you. I know where we sell the product in Europe, we are comparably priced. Some countries we are lower, some countries we are slightly higher. On the average we are lower in Europe. We can't control Schering's prices, but they are very competitive in the marketplace, as well. Their prices quoted really were AWP prices, those aren't real prices in the marketplace, but it is a very competitive environment out there, and I can tell you one thing. If Schering is too high with Proventil HFA, I can promise you MaxAir and MaxAir Autohaler will come in with a lower price, and we will keep them competitive.

DR. MURPHY: Thank you.

DR. BARANIUK: One other thing I forgot to mention is if there is a new device that comes out that is easier to use, or the patient can use once a day, or they can slip it in their pocket to carry it around, I think that is going to be a very real advantage for the patient.

DR. MURPHY: Good. Lastly, I will just ask any of you if you have any comments on this last question. What incentives can be used to stimulate pharmaceutical manufacturers to reformulate CFC products?

I think we have discussed this today. Does

anybody have anything else to add? Les.

DR. HENDELES: The manufacturers have indicated that if the FDA process was more swift, they might be more willing to do it or if they loosened up some of the criteria on the manufacturing/chemistry area. Apparently they are very stringent, and I have heard comments that that would stimulate more innovation if they could get it through faster.

DR. MURPHY: Does anybody want to comment on this from manufacturing, do you want to comment on this question from anybody besides what has been said?

Nancy, did you have a comment?

MS. SANDER: Yes, thank you. I am dying to make it, too. Consumers or patients are actually very willing to make a change. They are very environmentally aware, in fact, probably more so than people who don't have asthma.

The thing that they ask is that the change be one that incorporates their concerns, and they are asking for many of the same things that physicians are asking for, but in particular, they do want to feel confident that their medication will deliver to them in the middle of the night or when they want to jog or when they are at work, and they don't want to suffer in the process, and that is the bottom line.

DR. MURPHY: Thank you.

Comments from the FDA? John, do you have any closing comments?

DR. JENKINS: Are we done?

DR. MURPHY: We are done.

DR. JENKINS: I think it has been a very useful discussion, and I think some of the comments that we heard, not only from the committee, but also from the audience today, were useful and raised issues that we will be pondering and discussing.

We recognize this is an incredibly complex and difficult area. The process I think we have gone through has been very useful because it is always easier to criticize something than it is to come up with a proposal on your own, so we took the ball and developed the first proposal, and now we have given people something to shoot at, and it is easy to pick apart and point out flaws that we can now reconsider and hopefully make for a better proposal when we come with the proposed rule after reviewing the comments.

I suspect that there have even been people in the audience today who have thought of new things that they want to comment on, so they do have until May the 5th to submit the comments to the docket. The mechanism for doing that is

included on the ANPR, and I would encourage you to do that. We will be looking at those, I can assure you. I think Doug Wilson from BI was an example where I think he changed his whole presentation because of the comments.

It is often hard to write a document to say everything you want it to say, and hopefully, the presentations today have clarified some of those issues and have allayed some concerns that people had, but may have also raised some other concerns, and we would like to hear those, because we want to do this process correctly, and we can only do it by getting input from all of the different stakeholders, so we can boil it down and come up with the best proposal we can.

DR. MURPHY: Thank you. I would like to thank the members of the EPA that were here, all the members of the committee, and all of you in the audience.

Thank you very much.

[Whereupon, the hearing adjourned at 4:42 p.m.]