FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PULMONARY AND ALLERGY DRUGS
ADVISORY COMMITTEE

Monday,
November 22, 1999

Versailles Ballrooms I and II
Holiday Inn-Bethesda
8120 Wisconsin Avenue
Bethesda, Maryland

IN ATTENDANCE:

CURTIS N. SESSLER, M.D., Chairman
Professor Medicine
Medical College of Virginia
at Virginia Commonwealth University
Pulmonary and Critical Care Medicine
5th Floor, South Wing
1200 E. Broad West Hospital
Richmond, Virginia 23219

IGOR CERNY, Pharm.D., Acting Executive Secretary
Advisors and Consultants Staff (HFD-21)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Members

BRENDA H. CONNER, Consumer Representative
c/o Matria Healthcare, Inc.
1850 Parkway Place
Marietta, Georgia 30067

NICHOLAS GROSS, M.D., Ph.D.
Professor
Department of Molecular and Cellular Biochemistry
Stritch School of Medicine
Loyola University of Chicago
5th and Rossevelt Road
Building One, Room A342
Hines, Illinois 60141

WILLIAM H. KELLY, Pharm.D.
Professor of Pharmacy and Pediatrics
College of Pharmacy
University of New Mexico

2502 Marble N.E., Room B-64
Albuquerque, New Mexico 87131

IN ATTENDANCE:

FDA Consultants

ANDREA J. APTER, M.D.
Associate Professor
Pulmonary, Allergy, and Critical Care Division
829 Gates Building
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania 19104

MARK S. DYKEWICZ, M.D.
Associate Professor of Internal Medicine
Division of Allergy and Immunology
Department of Internal Medicine
St. Louis University School of Medicine
1402 South Grand Boulevard
Doisy R-209
St. Louis, Missouri 63104-1028

ROBERT J. FINK, M.D.
Chairman
Department of Pulmonary Medicine
Children's National Medical Center
111 Michigan Avenue, N.W.
Washington, D.C. 20010-2970

JESSE JOAD, M.D.
Assistant Professor of Pediatrics
U.C. Davis Medical Center

Department of Pediatrics
2516 Stockton Boulevard
Sacramento, California 95817

MICHAEL S. NIEDERMAN, M.D.
Chief
Division of Pulmonary and Critical Care Medicine
Winthrop-University Hospital
Pulmonary and Critical Care Medicine
222 Station Plaza North
Suite 400
Mineola, New York 11501

IN ATTENDANCE:

FDA Consultants

WILLIAM M. VOLLMER, Ph.D.
Senior Investigator
Center for Health Research
Kaiser Permanente
Northwest Division
3800 N. Interstate Avenue
Portland, Oregon 97227-1110

Guest

JEAN G. FORD, M.D.
Florence Irving Assistant Professor
Harlem Hospital Center
Columbia University College of Physicians and Surgeons
506 Lenox Avenue, MLK 12-106
New York, New York 10037

C O N T E N T S

C O N T E N T S

PAGE

P R O C E E D I N G S (8:15 a.m.)

DR. SESSLER: Good morning. I'd like to welcome everybody to the Pulmonary and Allergy Drugs Advisory Committee meeting.

My name is Curt Sessler. I'll be chairing the meeting. My principal goals here, I think, are to engender lively discussion and to keep the meeting on time.

The issue, I'll read, for discussion today from your agenda. "The FDA published a notice of proposed rulemaking on September 1st, 1999, related to the phaseout of CFCs in metered-dose inhalers. The committee will discuss and comment on the NPR and on presentations made during the public hearing."

The agenda is published, and everybody should have a copy of that. In brief, there will be a number of comments made by Drs. Meyer and Jenkins to start. There will be a presentation by Erin Birgfeld, followed by a formal presentation by Dr. Robert Meyer, then time for discussion, and a presentation by Leanne Cusumano, and then a break at 10:30, and then open public hearing from 10:45 till noon.

If the public hearing doesn't extend the full duration to noon, we'll start the afternoon's agenda at that time and then break for lunch at 12, and then the afternoon will be devoted towards committee consideration

of the discussion points, and you should have copies of those as well.

I'd like to ask that the committee members and the members of the FDA and the EPA who are at the head table introduce themselves, and at this time, I'd also just remind the committee members and others that this is going to be recorded, so please speak clearly into the microphone. That's for Alan in the corner there, and if you would, then please introduce yourself and tell us a little bit about affiliations, and we'll go around the table and have all the committee and others introduced.

DR. FORD: I'm Jean Ford. I'm affiliated with Columbia University and Harlem Hospital Center in New York, and I'm a pulmonologist.

DR. VOLLMER: My name is Bill Vollmer. I'm a statistician and epidemiologist with the Kaiser Permanente Center for Health Research in Portland, Oregon.

DR. APTER: I'm Andrea Apter, Division of Pulmonary, Allergy, and Critical Care Medicine, University of Pennsylvania. My training is in allergy and immunology.

DR. FINK: Bob Fink, a pediatric pulmonologist

at Children's National Medical Center, George Washington University, here in D.C.

DR. GROSS: I'm Nick Gross. I'm a pulmonologist at Loyola University in Chicago.

DR. JOAD: I'm Jesse Joad. I'm at the University of California at Davis, and I'm a pediatric allergist and a pediatric pulmonologist.

DR. SESSLER: I'm Curt Sessler, Pulmonary and Critical Care at the Medical College of Virginia, Virginia Commonwealth University in Richmond.

DR. CERNY: I'm Igor Cerny, Executive Secretary, of Food and Drug Administration.

DR. KELLY: Bill Kelly from the University of New Mexico Health Sciences Center, Professor of Pharmacy and Pediatrics and Pediatric Clinical Pharmacology.

DR. DYKEWICZ: Mark Dykewicz. I'm Associate Professor of Internal Medicine and Director of the Allergy and Allergy Training Program at St. Louis University in St. Louis.

DR. NIEDERMAN: I'm Mike Niederman from Winthrop-University Hospital, Mineola, New York, and I'm a

pulmonary and critical care physician and Professor of Medicine at the State University of New York at Stony Brook.

MS. CONNER: I'm Brenda Conner. I'm a nurse educator with 22 years pediatric nursing experience, and I'm the consumer representative to the committee.

MS. CUSUMANO: I'm Leanne Cusumano. I'm regulatory counsel with the Center for Drug Evaluation and

Research at FDA.

DR. MEYER: And I'm Bob Meyer, and I'm the Director of the Division of Pulmonary and Allergy Drug Products at the FDA.

DR. JENKINS: I'm John Jenkins. I'm the Director of the Office of Drug Evaluation II at the FDA.

MS. BIRGFELD: Erin Birgfeld, Essential Use Program Manager at EPA.

MR. COHEN: Jeff Cohen, U.S. Environmental Protection Agency. I'm with the Stratospheric Protection Division, and we review the substitutes to ozone-depleting chemicals under the Clean Air Act.

DR. SESSLER: Thank you.

Dr. Igor Cerny will present the meeting announcements and conflict of interest statements.

DR. CERNY: 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 interested 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. Andrea Apter and Dr. Michael Niederman. A copy of the waiver statement may be obtained by submitting a written request to FDA's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In addition, several of our committee

participants have been involved in activities relating to the replacement of CFCs that we believe should be disclosed. FDA believes it is important to acknowledge these participants' involvement so that their participation can be objectively evaluated.

Dr. Curt Sessler has consulted with Hoechst Marion Roussel regarding asthma management.

Dr. Mike Dykewicz attended a Schering Plough Speakers Bureau training meeting regarding a product for asthma. He also previously participated as a subinvestigator in an AstraZeneca study of a product for use in asthma.

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

for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current

or previous financial involvement with any firm whose products they may wish to comment upon.

DR. SESSLER: Thank you.

Dr. Robert Meyer will give a welcome.

DR. MEYER: Thank you. I wanted to especially welcome the many new members of the Pulmonary and Allergy Drugs Advisory Committee. The FDA is very grateful for your service, and we look forward to your input on this important issue and important issues in the future.

I especially want to note that this is a holiday week, and we especially appreciate your willingness to travel and attend this meeting today.

I'd also like to thank Dr. Sessler for taking on the role of chair and look forward to a very productive time with Dr. Sessler as the chair of this committee.

I also want to note for the record, for the public and for the returning members, that the division has a new name that actually puts it more in concert with the name of the advisory committee. We've added the title or the name "Allergy" to our title. So we're now the Division of Pulmonary and Allergy Drug Products to reflect our regulatory purview better, and again it does bring it into

concert with the name of this advisory committee, and we also have had changes in jobs within the division.

I've assumed the directorship of the division since the last meeting of the PADAC, and Dr. Jenkins has moved upstairs, both literally and figuratively, to the role of Director of the Office of Drug Evaluation II. So he not only oversees the Division of Pulmonary and Allergy Drug Products, but also the Division of Metabolic and Endocrine Drug Products and the Division of Anesthesia and Critical Care Medicine.

I look forward to the committee's discussion of both the proposed rulemaking that we will take you through today, and we're not asking for votes today, but we very much look forward to and will note for the record your comments and your suggestions about the notice of proposed rulemaking, and Dr. Jenkins will talk further about that in a minute.

I think we have a very interesting discussion on board for tomorrow, quite different from today as well, and so once again, I'd like to thank the committee for being here and look forward to the ensuing discussion.

Thank you.

DR. SESSLER: Thank you.

Dr. Jenkins?

DR. JENKINS: Thank you, Dr. Sessler.

I'd like to first add my welcome again to the new committee members in particular, but to all the committee members for your willingness to join us here today for this very important discussion, and a very personal note of thanks to Dr. Sessler, an old colleague of mine, for agreeing to take on the position of chair. I share Bob's enthusiasm for working with you this year in your role as chair of the committee.

I wanted to try to start out our discussion this morning by trying to put this meeting a little bit into context as far as FDA's activities over the past decade with regard to the CFC phaseout, and I think this is important since we have so many new members of the committee.

I think as I look around the table, the only member of the committee who was here in April of '97 for our previous discussion of this topic was Dr. Sessler. If I'm wrong, please correct me, but I think this is a new issue for most of the members of the committee and possibly for some members of the audience.

So let me give you a little bit of a perspective on what the FDA has been doing over the past decade in this regard and where today's meeting fits into

that overall schema.

When it became clear near the end of the '80s

and the early '90s that the Montreal Protocol was going into effect and would be banning the use of CFCs in metered-dose inhalers, the FDA first turned its attention to working with companies on issues, such as what animal testing would be needed for the new propellants to make sure that they were safe for use in humans, and working with companies on advice regarding development of the new formulations of the non-CFC-propelled MDIs.

The division also issued a guidance document in September of 1994. That guidance was focused on the clinical development program for these new products. We tried to look out for sponsors, the types of studies that we would expect to see for the new reformulated non-CFC MDIs or the dry-powder inhalers to try to help sponsors understand what their development programs should look like, what questions they should be attempting to answer.

The focus of that guidance was primarily to encourage sponsors to demonstrate the comparability

clinically of their existing formulation to the new formulations that they would be developing to get approved.

As the development process continued, and we started to receive NDAs in the mid-'90s for review of some of these products, we internally focused some of our attention toward the issue of how are we going to make a determination in the future whether the use of CFCs remains

essential once these new products come into the marketplace?

That's an essential statutory role that the FDA has under the Clean Air Act, is in that we determine whether or not the use of CFCs in medical products is essential in consultation with the EPA.

So once it became clear that these new products were starting to be developed and come to fruition as NDAs, we turned our attention to how will we go about making those determinations of when a product is no longer essential and should be taken off the list of essential products listed in the FDA's regulations?

To accomplish that task, the FDA formed a CFC work group within the Center for Drug Evaluation to

Research. Dr. Meyer's currently the chair of that CFC work group, and the first product of that work group was an advanced notice of proposed rulemaking which the FDA published in March of 1997, and that advanced notice was really designed to seek public comment on various potential strategies that the FDA could use in making these determinations of non-essentiality.

That, as I said, was seeking public comment, and as part of the public comment period for that advanced notice of proposed rulemaking, we had an advisory committee meeting in April of 1997 where we sought the input of the

committee. There were approximately 25 speakers during the open public hearing of that meeting, and then during the subsequent comment period to that advanced notice, we received approximately 10,000 comments from the public.

So our goal of getting public comment and public input far exceeded our expectations, and those public inputs and comments have been very helpful, I think, in helping us to move on to the next stage, which is where we are now, in that we have now published a notice of

proposed rulemaking which is basically the second step in the process towards finalizing FDA regulations about how to make these essential use determinations in the future.

That proposed rule, as Dr. Sessler noted, was published at the beginning of September. We're currently in the comment period for that proposed rule, and this meeting today is considered to be part of the public comment period for the proposed rule. So the comments from the committee, the comments from the audience today will be considered as part of the docket as we go forward with this process.

As Dr. Meyer said, we're not asking the committee for votes today. That's not the nature of the day's meeting since this is a public comment period for the proposed rule. We are asking, though, some very important questions to help us to further refine the proposed rule as

we move forward to the final rule as well as we move forward to actually implementing that final rule in the future to make determinations that products are no longer essential.

Many of those questions are engendered in your

talking points that are part of today's agenda. For example, we're very interested in hearing your views on what should we consider to be adequate alternatives to the CFC-propelled MDIs?

When should the FDA make the determination that the medical needs of patients who rely on CFC MDIs have been adequately met by the non-CFC products to determine that they're no longer essential?

What kind of post-marketing data should the FDA ask sponsors to develop or should sponsors be developing on their own for their non-CFC products to help in that assessment that they meet patient needs?

What are the important subgroups of patients that we should be thinking about as we're making these determinations of non-essentiality?

What does the committee think about the FDA's proposal that the essential use determinations will be made in the future on a moiety-by-moiety approach? That's one of the three possible options that was suggested in the ANPR in 1997. So now the agency following public input has

suggested that the moiety-by-moiety approach is the one we think would best serve patient needs.

And there's also a proposal in the proposed rule that we would determine that nasal corticosteroid products are no longer essential uses of CFCs. So we'll be interested in hearing the committee's thoughts on that issue as well.

Not all the issues that will come up today are listed in the talking points. So I encourage you, if we haven't thought of some things that you want to give us advice on, to feel free to do that.

With that trying to put the meeting into context, I want to emphasize that the FDA is not in any way trying to accelerate the phaseout of CFC MDIs. That term became very common in use during the 1997-1998 period when we were receiving comments on the advanced notice of proposed rulemaking, and I want to dispel that as being untrue. That is not our goal. That's not what we're trying to do.

What we are trying to do is to carry out our statutory mission under the Clean Air Act and the Montreal Protocol to phase out the use of CFCs in medical products but only when we're confident that the health and safety of the patients who rely on those products will be adequately served by the alternative products.

The FDA is a Public Health Service agency, and our primary mission is to protect and promote the public health. So that's our primary focus as we try to carry out this mandate, is to protect the patients who rely on these products.

With that, I'd like to say that I look forward to today's discussion, and I hope it will be a very fruitful input from the committee to the agency as we continue this process.

Thanks.

DR. SESSLER: Thank you, Dr. Jenkins.

The first formal presentation will be by Erin Birgfeld, the Essential Use Manager, Stratospheric Protection Division, Office of Air and Radiation, U.S. Environmental Protection Agency.

MS. BIRGFELD: Well, again, my name is Erin Birgfeld. I'm from the Stratospheric Protection Division at U.S. EPA, and I run the Essential Use Program there.

Really the purpose of my talk today will be just to highlight the importance of compliance with the Montreal Protocol and the importance of this FDA rule in that context.

Okay. What I'm going to talk about today is first some brief background, some ozone-depletion science.

We'll talk about the fact that there really is a problem.

Then we'll talk about the effects of increased UVB radiation hitting our earth's surface, and the effects specifically on human health and then on ecosystems and the environment.

Finally, we'll talk about the Montreal Protocol, just a little bit of background, and then discuss what are essential uses underneath the Montreal Protocol and EPA's role in the essential use process as a whole.

Okay. First, we have this little diagram. It's a cartoon of the ozone-depletion process, and when CFCs were introduced, I believe it was in the 1950s, they were sort of thought to be a miracle chemical. They were low toxicity, were very stable and subsequently found a lot of uses, both in the industrial sector and in consumer products, and as we later found out, they also contributed to stratospheric ozone depletion.

As you can see in this slide, you have CFCs being released from a bunch of different sources on the ground, becoming mixed into the troposphere, which is the area where we live and the lower atmosphere. These are

mixed and are never broken down. They don't rain out in rain, and it takes between two and five years for these chemicals to get up into the stratosphere.

Once in the stratosphere, they're subjected to very high levels of UV radiation that does break them down.

This releases the chlorine atoms, and it's the chlorine atoms and also actually bromine atoms that actually do deplete the ozone layer, and one chlorine atom is capable of destroying up to a 100,000 ozone atoms. So this is a pretty powerful process that's going on.

Subsequent to ozone depletion, there's less ozone to be soaking up those UVB rays, and we are receiving more on the earth.

Okay. Now, this is actual real data, not a cartoon, of the ozone over Arosa, Switzerland. This is the area where we have the most data, going the farthest back, and as you can see, the ozone layer is not at a steady state. I mean, it's really jumping all over the map.

This is the yearly means from 1926 to 1997. But as you can see from the 1920s all the way up to the

'70s, overall, it's pretty straight, the line is. There's no slope.

However, in the 1970s, after there was a lot of uses of CFCs, a lot of emissions, you can see a clear downward trend ending in 1997 where this data ends, and this is really a problem, and this is why this issue has come to the fore.

One of the questions that we often get is how do we know that it's CFCs that are causing these problems? Could it be another chlorine-containing chemical? And as I

stated before, CFCs are very stable and are mixed pretty much evenly throughout the troposphere, and it's only once in the stratosphere you start seeing them decline. So this is at CFC-11 declining with increasing altitude in the stratosphere, and again they're chlorine atoms and causing ozone depletion.

DR. VOLLMER: Just a question. That's projected now or that's actually --

MS. BIRGFELD: Yes. It's the best fit line, yes. It's the cartoon, I guess, again.

DR. SESSLER: I'm sorry to interrupt. If I

could ask all the committee members and everybody else to go ahead and speak into the mike, if you would, with questions, and perhaps if they're not clear for those in the back, you could repeat the question after the speakers.

MS. BIRGFELD: Okay.

DR. SESSLER: Thank you.

MS. BIRGFELD: Sure. So the next step is how does the reduction in stratospheric ozone translate into increases in UV radiation at the ground level, and here you can see this is a chart that looks at reduction of ozone in Antarctica versus the UV increase, and as you can see, it's quite substantial with 50 percent reduction in ozone, you get a 100 percent increase in UV radiation.

Okay. So right now, the ozone layer is at its

most vulnerable. The chlorine and bromine loading in the stratosphere was expected to peak before the year 2000. So right now, it's after January 1st, it's supposed to be declining, and hopefully we'll be on the road to recovery.

However, we haven't seen any increases yet in 1999. The Antarctica ozone hole was about 25 million

square kilometers big, and in mid-latitudes in the U.S., where we're interested, we've seen about a 5 percent total ozone loss since 1979. So this is not just a problem in Antarctica. This is a problem here as well.

You'll often hear when you're talking about this issue that ozone recovery is expected by the year 2050, but this date is contingent on full compliance with the Montreal Protocol, and that's something that's critical, and I think it just highlights the importance of this meeting, and just for your interest, everything that's purple in my little picture of the ozone layer is considered an ozone hole. That's ozone with less than 220 dobson units, which is how ozone is measured.

Okay. So now what are the health effects of increased UVB? As you know, skin cancer has been rising in this country. It's considered an undeclared epidemic. As you know as well, it's associated with UV exposure, exposure to the sun.

The incidence of melanoma, the most severe form

of skin cancer, and the one with the highest mortality, in 1935 was only one in 1,500. In 1998, it was one in 87. So

that's a clear increase. In 2000, it's projected the risk of getting melanoma is one in 75. And just some more scary facts. One American dies of skin cancer every hour, and over one million new cases are expected in the U.S. this year alone. So this is a problem.

Other health effects are cataracts. Exposure to UVB has been associated with cataracts. It's the leading cause of blindness, and there are 1.3 million cataract surgeries per year, and it's the greatest single line item in the Medicare budget.

Another effect of UV on the human population is immune system suppression. It's been shown that after sunburns, the immune system does not react in quite the same way that it would prior to when the skin is not sunburned, and this is an area of ongoing research, and then, finally, the issue of photoaging. We're all getting wrinkles a little early, I guess.

Okay. We're not the only ones on this planet. The ecological and environmental effects are also very important. Increased UVB has been shown to decrease crop yields. It's also been hypothesized to have caused loss of vulnerable species.

In this country and around the world, there's

been a dramatic decline in the amphibian populations. In addition, there's been deformities found in a lot of amphibians, and the hypothesis is that the increasing amounts of UVB may play a role in this problem, and the worry is that it's sort of like the canary in the coal mine, you know. These are the ones that are going to be hit first.

Next, we have damage to marine ecosystems in the Antarctica. Phytoplankton are adversely affected by increased UVB, and this is the bottom of the food chain. So subsequently, it affects the entire food chain.

Finally, this is actually a very interesting one. Increased UVB at the ground level actually can cause an increase of ozone layer in the troposphere. So the one that you all are concerned about that causes asthma attacks and increased hospitalization actually may be increased with increasing UVB, and then, finally, we have an issue with materials degradation. Plastics are falling apart much quicker than was anticipated.

Okay. So what do we do about it? The Montreal Protocol was the international agreement to address and solve the problem of stratospheric ozone depletion. It was signed by the U.S. in 1987, and subsequently there are over a 160 countries that are parties to this agreement.

Import and production of CFCs were banned in

1996 in this country, and, however, of course, as you all know, the Montreal Protocol and the Clean Air Act do provide exemptions for some things that are called "essential uses."

The definition of an essential use is under the Montreal Protocol is that if it is necessary for health, safety or is critical for the functioning of society, and there are no available technically and economically feasible alternatives.

Here, the essential uses under the Montreal Protocol were never meant to be permanent exemptions, which is why all the parties are undertaking the same transition in their own countries.

FDA's charged with providing the framework. FDA is charged by the Clean Air Act with providing the framework that will ensure safe and predictable transition to CFC-free inhalers.

It should be noted that metered-dose inhalers are the only significant commercial product in the U.S. for which CFCs are still produced. There's a common misconception, I think, among the lay public that CFCs are

still used in hair spray. Those were banned in the 1970s. So those have been gone away for a long time.

Other approved essential uses included, beyond just MDIs, are in the past Class I ozone-depleting

substances for laboratory and analytical uses. These are very small amounts, very pure, high grade, and methyl chloroform as a solvent for use in the space shuttle and Titan rockets, and again this is very small amounts.

Okay. So the process that I manage at the EPA is the Essential Use Process, and basically what we do is we receive applications from companies wishing to get CFCs to produce the MDIs. We review the data, and then we put forward the nomination at the meeting of the parties in Montreal Protocol.

There, the parties discuss whether or not to approve these CFCs for use in the U.S., and in the past, the parties have approved the entire U.S. request.

Finally, the last step is that EPA allocates the CFCs through a notice and comment rulemaking at the end of the year, and companies are able to order their CFCs and produce the MDIs, and that's basically all I have.

The issues and topics that I discussed, you can find in any of these places. Our home page is epa.gov/ozone. It's a good source of information, and then you can also talk to someone at our hot line if you're interested.

Thank you for your attention. I appreciate it.

DR. SESSLER: Thank you very much.

We have time for questions and comment on Ms.

Birgfeld's presentation.

DR. FINK: Do you have any estimate of the number of pounds or tons of CFCs used in MDIs in the United States?

MS. BIRGFELD: Yes. Actually, the essential use request for this year is going to be 3,700 metric tons.

DR. FINK: And how does that relate in terms of total CFC release into the atmosphere? Does that rank Number 1 or 2 or where does it rank?

MS. BIRGFELD: For this country, it does not. For release into the atmosphere, it doesn't. We're still dealing with the old CFCs that were produced prior to 1996,

and I guess the issue is that these are newly-produced CFCs. So we're adding to the bank of CFCs that are in the atmosphere.

One interesting thing. The MDI use for this year is about one percent of the use from baseline which is from 1987, but at the same time, this amount of CFCs are about the same as some developing countries use in total. So it's not an insignificant amount.

DR. SESSLER: Production in the U.S. How does that compare to worldwide production?

MS. BIRGFELD: Of MDIs?

DR. SESSLER: Yes. In actually other forms of ozone-depleting substances.

MS. BIRGFELD: Well, actually, to my knowledge, all the CFCs are actually produced in the Netherlands, and we import them for use in MDIs. I'm not entirely sure how we --

DR. MEYER: Can I comment?

MS. BIRGFELD: Yes, that would be great.

DR. MEYER: Amongst my other hats, I'm actually on the Aerosols Technical Option Committee for the United

Nations. So that's the committee that takes the first crack at the nominations, and Europe had been substantially higher than us in terms of their need because they not only produce for internal consumption but export extensively.

The United States does not export extensively in terms of MDI production. So Europe had been up in the 5,000 range as far as metric tons in terms of their requests. They're now coming down so that their request is very similar to the United States in recent years, and it's projected to perhaps even cross in the future.

These nominations are for two years in advance. So the 2001 nomination will be considered at this year's meeting of the parties, and the United States Government is preparing their nomination for 2002 or will be shortly.

MS. BIRGFELD: Questions?

DR. FINK: Since most use of CFCs is encapsulated or recycled, what proportion of the release

into the atmosphere on a yearly basis do the MDIs contribute?

MS. BIRGFELD: You know what? I don't know. I

can get back to you on that.

DR. NIEDERMAN: Do you have any estimate as to what percentage of the total asthma inhaler use has CFCs in it right now?

MS. BIRGFELD: I believe there's only one alternative out there.

DR. NIEDERMAN: But in terms of percentage of usage. In other words, there are some of the dry-powder inhalers and other devices.

MS. BIRGFELD: Right.

DR. NIEDERMAN: Do you know in terms of total usage what percentage is currently used with CFCs?

MS. BIRGFELD: I'll let the expert take that one.

DR. MEYER: I think that I can give you sort of rough estimates more than exact answers, but I think the CFCs are still the large majority of the asthma market as far as the inhalers go.

I don't really have a good handle for the recent figures of the dry-powder inhalers, but my impression is they've been moderately successful, but in the overall scheme of things remain a fairly small

percentage, and the approximate market share in terms of albuterol, of Proventil HFA, has been 8 to 10 percent of that market, and albuterol's perhaps 50 percent of the overall CFC use in inhalers in the United States.

DR. NIEDERMAN: So we could assume that currently 75 percent plus probably of all asthma therapy involves CFCs?

DR. MEYER: At least. I think that's a very safe assumption. It's at least that.

MS. BIRGFELD: Dr. Fink, I'd like to direct your question to my supervisor, Jeff Cohen.

MR. COHEN: I think, if I heard you ask what the comparison in terms of emission rates between an MDI and other uses of CFCs, most of the CFCs that are not used in MDIs are recycled. Refrigerators, older cars. Those emissions are controlled by service personnel and captured and continued to be recycled.

So theoretically, none of that would be released. In practice, some of it ultimately is, unfortunately, but we know that all of the CFCs when used as propellant in the MDI is released immediately to the atmosphere.

I don't know if that answers your question. I didn't quite catch all of it.

DR. JOAD: If CFCs in MDIs were the only source

of CFCs, what percentage decrease in ozone layer would occur over what time?

MS. BIRGFELD: Do you know this?

DR. MEYER: Well, I think these are interesting and in some ways important questions, but I think I do need to emphasize, and I think I put it in the talking points as well, that the decision by the U.S. Government and the world community in fact, a 164 other countries besides the United States, is that all uses of CFCs should be phased out over time, and that's the international committee commitment.

You know, if you look at any single use with perhaps some glaring exceptions, they tend to look fairly small, but when you've committed to the overall phaseout, that's the commitment. So we're not really here to argue whether that's a good thing or not. It is the way the international community and the United States is going to proceed. So we're more interested in discussing how to best get there.

MS. BIRGFELD: Thank you.

DR. SESSLER: Thank you very much.

Our next speaker is Dr. Robert Meyer, Director of Division of Pulmonary and Allergy Drug Products, and he

will be reviewing a number of different facets of this.

Bob?

DR. MEYER: I did fail to thank our EPA colleagues for being here today, and I do thank you both.

I think that this is a collaborative effort that we're undergoing here. We're both public health agencies in some respects, although we do clearly have different regulatory missions. But in any case, I think that this process is best accomplished by what in fact the EPA's Clean Air Act and their implementing regulations has required, which is that FDA and EPA move forward with this process in a consultative and collaborative way. So thank you both for being here.

This slide will mainly, I think, be familiar to federal workers, but we're in a season in the federal cycle of what's called the Combined Federal Campaign, which is a way that we get to donate from our paychecks to various worthy charities and other non-profit organizations, and it's led to a little bit of alphabet soup.

As you can see, they've got a very nice logo

supporting CFCs, and the reason I put this up is I was preparing this talk the other morning, and I had gone down to the cafeteria and was riding up with a woman who had an Egg McMuffin-type sandwich in a styrofoam box, and on the top of it, it said, "No CFCs," and she saw the CFC part of it only. I guess she didn't see the word "no," and she said, "You know, they're getting this CFC logo on

everything." So she was very impressed with that. But it can lead to some confusion.

I did want to just before I talk a little bit about the FDA history, I did want to talk briefly about why this is an issue for the FDA because I think some of the public comments that we received to our advanced notice of proposed rulemaking reflected some very genuine concern but some misunderstandings about the role of CFCs in inhalers, and in fact in other products as well as Erin Birgfeld mentioned.

Consumer aerosols have not had CFCs in them for over 20 years. So we are talking about the last substantive use of newly-produced CFCs in the United States, and in fact, it's important to realize for those

who don't know it that the formulation within a CFC-driven MDI inhaler is almost all, for practical purposes almost all CFCs.

So the drug substance that we're talking about, most of them are in the microgram quantities. So we're really talking about a spray coming out of these that is 95 percent, if not more, and in some cases more like 99 percent, CFCs, and because one of their good properties is they're pretty inert, other than how they act up in the stratosphere, they are rapidly taken in to the lungs through inspiration and then rapidly excreted or exhaled.

So in fact, for all intents and purposes, everything that comes out of a CFC MDI is rapidly released into the atmosphere. So one of the, I think, common misconceptions amongst the public were that either there was not a lot of CFCs in these inhalers to begin with or that the body somehow took the CFCs up, and they were not released into the atmosphere, particularly if you used a closed-mouth technique.

Well, I think the ozone science was fairly

young when the FDA joined other arms of the government, and in fact other public interest groups, in recognizing the dangers that the emerging ozone science represented, and I think some of the very early work that's subsequently led to Nobel Prizes was published in the '73-'74 range, and by 1978, the FDA had already published a federal regulation in final form that stated that CFC-containing products that FDA regulated in any food, drug, device or cosmetic would be considered misbranded or adulterated, unless it was deemed essential.

For the most part, these products that were deemed essential were products for inhalation for the treatment of asthma and chronic obstructive pulmonary diseases and other diseases where bronchospasm is a part of the pathophysiology, and the determination of essentiality was based on no technically feasible alternatives, that it

provided a substantial health benefit, and it actually allowed for environmental benefit, although I'm not sure I understand from 20 years on what they meant by that.

But in any case, it provided a substantial public health benefit, and that the release of CFC were

either small or justified given the public health benefit, and over the years, there was an original listing under 2.125, Part E, that had the essential use categories, and over the years, new additions were added through petitions and notice and comment rulemaking.

In other words, the agency would put out a proposal that a new classification be added to the essential uses. Public comment was received, and then the agency proceeded accordingly.

The preamble to the final rule to 2.125 back in 1978 made mention to the fact that these essential use listings were considered to be temporary. Everybody, I think, felt that at some point in the future, reasonable alternatives would exist, so that these products would no longer meet the essential use criteria by which they were added to the list.

However, despite that intention that these listings be temporary, there was no formal removal process that was put into that regulation, and I think Dr. Jenkins did a very nice job of bringing people through some of the

background as it relates to the FDA's role in all this, but clearly by the mid-1990s, particularly as some of the alternative products were in the latter stages of testing, it became clear that FDA needed to take a more active role in the U.S. transition away from CFC use in medical products, not perhaps as much -- and again not to get confused about us accelerating the phaseout, so we were not taking an active role to accelerate it, but to be responsive and to fulfill our mandate under both the Clean Air Act and the Food, Drug and Cosmetic Act.

Basically, as we moved forward, as we envisioned being a part of this, the U.S. transition away from CFC use, and in fact ozone-depleting substance use, we saw a role for the FDA in the overall transition that was as follows.

We thought as time went on, that we needed to define acceptable alternatives to CFC-based MDIs. I think it's fairly clear that the alternative propelled MDIs, such as the approved albuterol sulfate using HFAs or hydrofluoroalkanes, also you'll see those mentioned as HFCs, hydrofluorocarbons, that those would be, I think, a pretty neat fit as an alternative product.

They act very much in the similar fashion to the CFC MDIs. There are some differences, but obviously they're a very similar product.

We at least thought that for some patients, if not all, that multidose dry-powder inhalers might fulfill the role of being an alternative in terms of convenience and effectiveness of the product.

I think we're fully cognizant as are others that dry-powder inhalers in fact may have some down sides in some patients, particularly these, by and large, are patient-driven devices. So people with very low flow rates may in fact have problems generating sufficient flow rates on some devices to allow for full delivery, that being, for instance, perhaps very young patients or patients with very severe airways disease.

The other potential problem with dry-powder inhalers is since many of them contain lactose as carriers, they tend to be somewhat sensitive to moisture. So the manufacturers need to design ways to protect their products from moisture, and in some cases, once they're taken out of their overwraps, they can be stable for reasonably short periods of time compared to alternative propelled MDIs. But again the manufacturers are aware of this and responding to that.

But there are some limitations as far as the neat fit of multidose dry-powder inhalers to MDIs, and then there are other products that are in stages of development

that may in fact represent reasonable alternatives to MDIs,

and I won't spend a lot of time on those, but I think the agency's fully aware that other products may be coming, and that other products may in fact serve a very useful role as alternatives as the technologies are perfected and approved.

We certainly saw it as the agency's role to monitor the availability of these alternatives for each drug product and class as they're developed, and then clearly to define criteria that would have to be met to make determinations that products that are already listed as essential under our regulations and therefore referred to by the Clean Air Act regulations, a way to remove those when they were no longer truly essential uses.

To do that, because, as I mentioned, the original 2.125, our original regulation involving CFCs in FDA-regulated products, did not have a clear means for removing essential use listings, we needed to modify our regulations that confer essentiality on the CFC products to allow for them to be, if you will, taken off the list as it is clear that they meet reasonable criteria for being no

longer essential.

Of course, as those products became available and proved to be medically acceptable, we would then need to go ahead and modify our essential use listing.

We wanted to do all this in a manner that

allows adequate time for public input, and certainly involving the advisory committee where appropriate, such as today, and again to work with EPA and other interest groups to coordinate the U.S. efforts.

The overall transition away from ozone-depleting substances is larger certainly than the FDA, and I think there is certainly other components of the government beyond both FDA and EPA that need to be brought in and other components of the public in fact.

Just for those who don't live and breathe regulatory processes, I thought I'd take a minute to go through the rulemaking procedures that FDA and other regulatory bodies go through.

The FDA is set up and basically has its authority through the Food, Drug and Cosmetic Act, but

that, as broad as that is and as detailed as it is to read, it is in fact just a framework for, in many ways, for how we are supposed to act through our regulations, and it is through the regulations that we implement that authority in a way that is binding both on us and on the public.

So the FDA and the CA Act is sort of the overall umbrella, and the regulations provide a more detailed manner for which we and the public are meant to proceed, and the usual pathway for creating a new regulation is to publish it in the Federal Register in the

form of a proposed rule which means that we put out some of our background thinking, and in fact what we call a codified section, which contains the actual rule itself.

We then allow for a comment period, generally in the 60-to-90-day range, for the public to respond to it, and once we get those comments back, it's considered then, thought about any changes that would need to be made to the proposed rule. We then proceed to publish a final rule which specifically answers the comments received during the comment period.

Because we anticipated that this was an

important action from the public health standpoint, and that there might be some controversy to it, and in fact because we were really just taking our first best effort at this, the FDA chose the additional step in this case of what's called an advanced notice of proposed rulemaking, which in essence kind of repeats the cycle, so that you do an advanced notice of proposed rulemaking, comment period, then you put out the proposed rule, another comment period which we're in now, and then the final rule.

We did this as a way to allow for broad public input prior to issuing any proposed rule in a manner that we perceived would be the most fair and equitable.

So again the advanced notice of proposed rulemaking or what I shall refer to as the ANPR was the

initial proposal for modifying the FDA regulations to allow for the removal of the essential use status of products currently listed in our regulations when appropriate, and that was published for comment on March 7th, 1997.

To go through it very briefly as far as what the codified section of that announcement notice of

proposed rulemaking said, we proposed four criteria that we would need to consider and that would need to be fulfilled for a CFC product to be no longer considered essential.

We, first of all, wanted there to be adequate alternatives, and I will get more into this in a minute, but we thought there would be a variety of ways that one could state whether there were adequate alternatives and not moiety-by-moiety, a class approach or a hybrid of the two.

We certainly would want to know that there are adequate production capabilities and supplies of the alternatives to meet the needs of the population that medically depend on these products.

We'd want to know that there's adequate patient acceptance. I think that it is important to realize, and I'm sure most of you all do, that the drug approval process does assure that the product is sufficiently safe and effective for its intended use, but that's rather different from knowing that in millions of patients, it will provide

them the same kind of benefit or use as the current CFC MDI products.

And then, finally, we had proposed in that ANPR that if those top three criteria were met, that we felt sure there were adequate alternatives, there were adequate production capabilities and supplies, and there was evidence of adequate patient acceptance, that we would presume that all important subgroups were served, unless we had evidence to the contrary.

Let me spend a little bit of time talking about the ways one might define adequate alternatives. The first one up here was not in our ANPR. We did not consider it, and I'm not sure that it's actually a very viable way to proceed from the United States' perspective, but that would be a product-by-product basis. So that if a particular product, and I will just use one, like let's say Ventolin were reformulated, that you would only take away the essential use listing for the Ventolin CFC if there were a Ventolin HFA available, and you would not consider any other drugs containing the same moiety, albuterol, or other drugs in that therapeutic class.

This seemed to have particular problems in that it in many ways seemed to reward manufacturers who were not moving forward with the transition process and would leave a lot of products on the market for perhaps a longer period

of time than really justified from a public health perspective.

It also was quite different from the way the current regulation listed essential uses. It didn't list products, it listed moieties in essence, or in some cases therapeutic classes.

Then three ways that the ANPR proposed we do go would be the moiety-by-moiety approach, which means in essence drug substance-by-drug substance approach. The reason we have to use the word "moiety" there is for FDA purposes. Albuterol and albuterol sulfate are technically different drug substances, although they are the same active moiety, and we do consider albuterol and albuterol sulfate to be essentially the same for these purposes. So I'm going to be using the term "moiety" here, but you can take that to mean the same as a drug substance.

So that would mean that when there was sufficient alternatives for any one drug moiety, for instance beclomethasone, that you would then invoke the other criteria and then make the determination whether that use of CFCs was still essential or not, regardless of what else was going on in that therapeutic class.

So if we were talking about the case of beclomethasone, you would ignore what was happening with any of the others, with fluticasone or with triamcinolone,

any of the other inhaled corticosteroids.

Partly as a response to the way the current regulations are modified and partly for reasons of feeling like there can be some crossover use within well-defined classes, we also proposed that we might take a therapeutic class approach.

In essence, there were three classes of therapies listed in our current regulations or there are, and those would be in more modern wording than was published in 1978, the inhaled corticosteroids, the intranasal corticosteroids, and then the bronchodilators or the adrenergic bronchodilators.

So we thought particularly for the inhaled corticosteroids and the shorter beta agonists, that one way to potentially proceed would be to do this on a therapeutic class approach.

In other words, if you were to take the inhaled corticosteroids, when you had products representing at least two of the moieties within that class, where there were at least three distinct products, two of which had to be MDIs, we thought that it might be reasonable at that

point to invoke the other criteria, and if those were all met, then to take away the essential use listing for the entire class.

One thing that the therapeutic class approach

does, at least for these two distinct categories, is it allows for dealing with some products that might have reasonably small markets and where the manufacturers were not perhaps interested in reformulating for their own purposes, for either economic or other considerations.

It would be a way to assure that the -- when it made sense to remove the essential use listing for the entire class, that that would happen, and some products, even if they were not reformulated, might lose their essential use status.

Finally, laying out the moiety-by-moiety approach and the therapeutic class approach, it also seemed reasonable to offer the alternative of what we would call the hybrid approach, which is to do the moiety-by-moiety approach on every drug substance that's currently included in the essential use listing, but when the therapeutic class criteria was met, we would also act on that.

Again we had the advisory committee meeting regarding the ANPR on April 11th, 1997. As Dr. Jenkins mentioned this morning, we had substantial interest in public comments at that point. We had about 24 or 25 people offer their suggestions or comments to the agency as well as receiving important advisory committee input, and we also were quite successful in terms of gaining public comments. We in fact received over 9,800 or in the range

of 9,800 comments, which is one of the larger numbers of comments to the dockets, certainly in the Center for Drugs' history. So it was quite a vigorous response.

Many of these were patient-generated comments, and while reflecting very real concerns on the part of the patients, they often represented somewhat incomplete information or understanding of what we were actually proposing at that point.

In addition to these patient-generated comments, we also received very broad input from various professional organizations, from the regulated industry, patient advocacy groups, environmental groups, and other

important constituencies in this matter.

The advanced notice of proposed rulemaking also led to several congressional hearings, and we certainly received input from other components of the government in terms of considering this.

Once the docket closed, the CFC work group set about the rather large task of reviewing each and every comment because we did review each and every comment and responding accordingly, and we tended to have some baskets of comments that we thought, like many of the patient comments, represented very real concerns and things we should answer because they tended to form themes in a thematical way, and then we had rather more substantive

comments that were from again patient advocacy groups, professional organizations, the industry and so on, and I think to sum up some of the substantive opposition that we received, there was substantial concern about our proposal to operate or to proceed in using a therapeutic class approach.

I think many people or many commenters saw this as being too restrictive, as being anticompetitive, and in

fact I think some people saw it as being antipatient, that if a patient were doing well on something that was not being reformulated but, you know, other things in the class had met the criteria, and the criteria in addition were met, that patient would be subjected to perhaps losing their inhaler at some future date despite them not being a direct alternative.

I'm not going to spend a lot of time on this, but there was some concern about the misbranded and adulterated provision which exists in the current regulations, where if a product was no longer considered essential, it would be considered misbranded and adulterated under the Food, Drug and Cosmetic Act, which is sort of the most Draconian wording of the FD&C Act and basically makes it illegal under FDA law to sell the product.

I think these commenters felt like perhaps we

would make the determination better under the Clean Air Act.

As Dr. Jenkins earlier mentioned, there was

concerns about accelerating the phaseout, and I think, as Dr. Jenkins said, we certainly want to be responsive to the changing environment. Maybe I shouldn't use the word "environment," but responsive to the transition as it goes on, but we do certainly see as the FDA, as our primary mission, protecting the health of the patients who rely on these products throughout the transition process and not accelerating the phaseout.

There have been concerns raised about the patient access and cost concerns as the transition continues, and, finally, there were concerns about how some of the rather general criteria that we laid out for consideration when products were no longer essential, how those would be specifically evaluated.

I'm going to pause there and turn the microphone over to Ms. Leanne Cusumano from our Regulatory Policy staff. I think we'll save questions as far as Leanne's presentation and my presentation until after Leanne's presentation.

MS. CUSUMANO: I'm Leanne Cusumano. I'm with CDER's Regulatory Policy. I'm a regulatory counsel there, and for those who've seen the proposed rule, my name's

listed there in the contact section, and I worked with Dr. Meyer and the CFC working group to review all of the comments and to be responsive and to put together the proposed rule, and Bob brought us to the present and where we are, and you'll see a little bit of a development of how we ended up with the proposed rule.

I'm going to talk about three major provisions of the proposed rule. First, how we propose to eliminate essential uses; second, the possibility of adding new essential uses; and, third, what kind of enforcement will be taken under the proposed rule.

First, and I put this first because I think it's what most people are interested in, the question of how are we going to eliminate essential uses under the proposed rule, and Bob went through the three alternatives that we've laid out in the advanced notice of proposed rulemaking, and based on the comments and based on consideration of how this would work best, we selected the moiety-by-moiety approach, which, as Bob had explained, is drug substance-by-drug substance. Basically we have a technical definition in our regulations for moiety.

We talk about supplies, post-marketing data and how patients are served, and I'm going to step through each of these step-by-step.

First, in addition to having moiety-by-moiety,

we are also looking at products delivered by the same route of administration with the same indication and approximately the same level of convenience of use. These are all factors that patients have expressed as being very important to them in their ability to use their asthma or COPD treatments adequately.

In terms of supplies, we want to have supplies and production capacity that exists or will exist at levels sufficient to meet patient needs. It's no good if an alternative exists, and the patients are not able to get it. So we want to make sure the manufacturers are able to get the product to the patient in adequate levels.

Third, we want to be able to look at at least one year of United States post-marketing data, and although we're interested in looking at foreign data, we also want to see the U.S. data because U.S. populations are different, our health care system is different, the foreign data would be supportive, but, in particular, we're interested in U.S. data, and one of the specific things that we asked for in the proposed rule was for people to tell us what kind of post-marketing data we should be looking at.

We have some general ideas, but we're

interested in hearing what other people think we need to look at, and, finally, how are patients served? We want to

know that patients who medically require the ODS, the ozone-depleting substance product, the CFC MDI, are adequately served by available alternatives, and I put the word "all" in there because we're not looking just at necessarily the product containing the moiety that's replacing it but at the whole market of available alternatives, and again we asked for comments, for people to tell us how we can make this determination.

Okay. So we've got that list of things, of items. Those four factors are what we're going to look at in determining whether we're going to eliminate an essential use.

We also have three other factors that we are going to look at. These are ors. If any one of these four criteria are met, then we will put out a proposal to remove an essential use. We talk about what's going to happen after January 1st, 2005, what happens if a product is no longer marketed in a CFC formulation, and then about nasal

steroids, and let me walk through each of those.

January 1st, 2005. As both Erin and Dr. Meyer had said, the essential use exemptions were never meant to be permanent. So the question is: when are we going to accomplish the phaseout? When is it going to happen? Well, we don't know when it's going to happen because it's really very dependent on what products are in the pipeline,

but one of the things that we thought is, after a certain period of time, and in this case, we picked 2005, we would look at the products that are on the market that are still unreformulated, and we would say, okay, do we still need that unreformulated drug, and we would make that determination by looking at the original essential use criteria.

Basically does it still meet those criteria, which are, there's still substantial technical barriers to reformulation. Does that still exist? Does the drug still provide an important public health benefit? And is the release of the CFCs still warranted or not significant?

If the answer to those questions are no, we can reformulate or there's no important public health benefit

or the release is not warranted, then we would consult with an advisory committee in an open public meeting and say should we propose the removal of this product, even though it hasn't been reformulated? So that's what the 2005 date is about, and again I emphasize this is an or.

We can either go by the four criteria I talked about first, moiety-by-moiety, with the patient service and all those other things, or after 2005, we can do it this way.

Now, what about if a drug is no longer marketed? In the proposed rule, we are suggesting removal

of the essential use listings for products no longer marketed, and there's four products that are listed right now in our current regulations that are no longer marketed in a CFC formulation, and they're these four: contraceptive vaginal foams, intrarectal hydrocortisone acetate, and I'm not going to describe polymycin beta sulfate-bacitracin zinc-neomycin sulfate soluble antibiotic powder without excipients, metered-dose nitroglycerin human drugs administered to the oral cavity.

These are all for human use. So we're proposing to remove these essential use listings. The parties to the Montreal Protocol have not granted use of CFCs for these products in years, if ever, and they're not on the market in a CFC formulation. So there's really no point in having them in our regulation.

The other proposal that we are making is to remove the essential use listing for nasal steroids. Why? We're proposing that there are adequate alternatives out there without the CFC formulations. Also, that there's widespread use of those alternatives, sufficient supply. The manufacturers have been making them, and the patients have been able to get them, and again the parties to the Protocol have not allocated CFC use for these products ever. So if they're being manufactured at all, they're being manufactured with pre-1996 chlorofluorocarbons.

There's no new production of CFCs for these products.

In the proposed rule, we asked specifically for comments on the timing of the removal of the essential use allocation for nasal steroids, and what we proposed is that one year from the date we finalized the rule is the date

that the rule would go into effect.

So you know, we're at the proposed rule stage, in the comment stage. We have to read the comments, take them into account, publish a final rule, and one year from that date would be the date we would remove the essential use listing for nasal steroids.

So those are the four ways we could remove an essential use from our regulation. Either it meets those four initial criteria under the moiety-by-moiety approach, it's no longer marketed or after January 1st, 2005, the total market is sufficient to serve patients or with the nasal steroids, if they fall in the nasal steroid class.

So how do we add new essential uses? Well, we know that addition of a new essential use had better meet some pretty tough criteria because otherwise, they're not going to get CFCs for that year from the parties to the Protocol.

So the criteria we look at, we're proposing to look at would be that there are substantial technical barriers to formulating the product in a non-CFC or a non-

ozone-depleting substance formulation, that this product provides an unavailable important public health benefit, that you can't get it from some other non-ODS drug, and that either the release of the ozone-depleting substance is not significant or that it's warranted in light of the public health benefit and kind of the theoretical example that we toss around is, well, what if we found a cure for AIDS that could only be formulated in CFC use? You know, you'd want to have some kind of mechanism in place for that kind of eventuality.

So let's say we go ahead and make all these changes. We implement the proposed rule. How's this going to work? Right now, in our regulation, we have adulterated and misbranded provisions, and that's been in that regulation since the 1970s, like Bob talked about, but the primary enforcement for this would be under the Clean Air Act, and EPA regulates products from all around the country, all kinds of different agencies.

Even though they don't regulate the product itself because it deals with an environmental issue, they have the authority under the Clean Air Act to take enforcement action against the product if it doesn't comply with the Clean Air Act, and that would be the primary means.

What does that mean in simple speak? It means

that is you're not an essential use in FDA's regs, you would not be able to market your product in the United States anymore under the Clean Air Act.

As Bob said, we got quite a number of comments on the advanced notice of proposed rulemaking, kind of woke us up and said we need to get more information out there, so people know what we're doing and have accurate information.

One of the things we did was develop a web site at this address. We've also brought it to the advisory committee. We want people to have the opportunity to comment. We had a conference call with interest groups on the date the proposed rule was published, September 1st, 1999, to make sure that they and their constituents know what we're doing and know accurately what we're doing, and also we worked with them at their request to help them in writing articles or in any way that we can in disseminating accurate information.

So far, and I have to update this because on Friday, I got one more, we've gotten four comments on the proposed rule. Let me tell you the comment period closes on November 30th, and in my experience, we routinely get comments on the last day, particularly from big companies or interest groups, that kind of thing. So I'm sure we

will be getting more, but so far, we've gotten four. One,

parents of an asthmatic, two doctors, and the other one was from the Service Employees International Union, a branch of AFL-CIO.

Overall, the comments have been very positive. There is still concern about the cost of replacement products. A statement that switches can be difficult, which we all know, and that's part of the reason that we are so involved in public outreach and public education.

So I'm more than happy to answer any questions. I'm sure Bob is, too.

DR. SESSLER: Questions?

DR. GROSS: How was the date 2005 arrived at? Was that arbitrary? I'm just wondering is that too far in the future or maybe not far enough? Was there a response reaction by industry?

MS. CUSUMANO: I haven't heard one yet. I think it was pretty arbitrary. It's not necessarily that on January 1st, 2005, we will do this, but that we can, and we won't do it before that.

I think Bob wanted to add to that. I'm sorry.

DR. MEYER: Yes, I did want to comment on that because for folks who are more intimately involved in the Montreal Protocol process, there's also been some language through some of their technical and economic assessment panels and so on about most of the transition being

complete in developed countries by 2005, and we didn't choose 2005 to marry to that date, but we were trying to project from the United States standpoint when might we have enough products to start thinking about some of these other products that remain on the essential use listing but really are not being reformulated, may not be still meeting the criteria for essentiality, and it happens to coincide by that date, but it wasn't meant to marry to it because I think, quite frankly, for the United States, 2005 will be sort of mid-transition, not late transition.

I think that we'll still have some use of CFCs at that time point, and again as Leanne said, it's really important to understand. From that day onward, we would have that pathway for us, but it's not like we're going to be convening this group on January 1st, 2005, to wipe out

the rest of the essential use listings.

DR. GROSS: But you didn't get a reply from industry?

DR. MEYER: We haven't heard any yet. At least we've got public comments coming today.

DR. FORD: One of the criteria for determination of non-essentiality is the presumption that all subgroups, including young children and people with very low air flow, would be served.

Now, what is the process for obtaining the

evidence that in fact that is the case? Because I believe in your presentation, you said unless there's evidence to the contrary. How will you obtain the evidence, and how will you evaluate it?

DR. MEYER: Yes. I think that's an important point because some of what we're proposing here, as Leanne spoke to and as I alluded to as well, are still fairly general ideas, and I think the -- particularly what's now come to be the criteria that patients' needs are met, that those patients who medically rely on these products, for us to know that their needs are being met.

We have some ideas on that, but we're not entirely set on a pathway for us to evaluate that, and that's actually something we'd be very interested in the committee's opinion on.

DR. JOAD: In your original class rules, when you did it by class, you required that two of the alternatives be MDIs, but then when you went to the moiety-by-moiety, you don't have anything about that.

Is there a reason why you didn't include that or were you thinking of including that in your hybrid? What happened with that?

MS. CUSUMANO: I think that, and we say this in the proposed rule, that we expect that generally, the ratio will be MDI for MDI, but technology's progressing, and

there may be alternatives coming that are better than MDIs or just as good as MDIs, and we didn't want to lock in to requiring an MDI when there might be something even better.

DR. NIEDERMAN: If you take the moiety-by-moiety approach, does that discourage developing alternatives for any patented moiety? In other words,

what's the incentive for somebody who has a patent on a specific moiety, nobody else can produce it, they have an MDI? If the criteria is that there has to be a replacement for it, what's the incentive to develop that replacement since there's no competition?

MS. CUSUMANO: I mean, that's true generally, that any time you've got --

DR. NIEDERMAN: And there's pressure to develop.

MS. CUSUMANO: I don't know if there is more pressure in the class approach than there is with this because people know that the phaseout's coming. Either you're going to develop it or eventually --

DR. NIEDERMAN: But you're allowing -- I mean, I can conceive that if I have a unique and highly effective product, I'm going to get the essential exemption, and there's absolutely no incentive to go through the cost in developing an alternative, as long as the moiety approach is used.

DR. MEYER: I guess I'd say two things to that. I think that it is clear, and it's important, that we

emphasize repeatedly, along with the EPA, that these essential uses for CFCs are on a year-by-year basis now, and that they are intended to eventually go away. So hopefully at least the manufacturers have that knowledge.

But I guess one thing that we realized about the moiety-by-moiety approach, although it clearly was -- the message we got was that was the best way to proceed. It allows for -- well, it does not allow, I should say, for sort of a neat cleanup of these products that aren't being reformulated, particularly sort of the ones that have the very small market, and there really is not an economic advantage to a manufacturer to reformulate it, and that's really why we came up with this approach, that at some date in the future, we would need to start looking at the market and all the available treatments and see whether the public were being served, even if that particular moiety wasn't being reformulated.

DR. NIEDERMAN: But I think the danger is if you have one of these products that has a big market, and again as long as it's a unique product without competition, and it has a big market, it's probably even less reason for them to reformulate it.

DR. MEYER: Yes. I think the other thing that

is difficult in this kind of forum to talk about is that we are writing this with a fair amount of foreknowledge about what is being reformulated and what's not.

We know the pipeline pretty well. So I guess it's always so uncomfortable as a regulatory body to say trust us on this, but we did write this with a reasonable knowledge of what the pipeline is.

DR. SESSLER: Dr. Vollmer, you were waiting patiently earlier.

DR. VOLLMER: I think it's been answered.

DR. SESSLER: If I may ask, cost is certainly something that's an important issue and obviously ties into Dr. Niederman's question.

What are the strategies to address that in terms of older products that may be reasonable substitutes and yet optimal, particularly within the next five or six years?

MS. CUSUMANO: One of the things that industry has told us is that for name brand products, they expect the replacements to be about the same price as other name brand products.

So if you've got a name brand and a name brand, you're talking about approximately the same price. So that wouldn't be a cost problem. The only product that has a generic out there right now is albuterol, and that's a

question, because the generic is less than the innovator product. How is that going to affect the market? I don't know if we have a good answer for that yet.

DR. MEYER: No. I think another thing that we would welcome committee thoughts on is how much of a barrier to access is cost.

DR. SESSLER: Right.

DR. MEYER: I think that that's an important issue for us to consider. So I'd very much welcome committee comments on that.

DR. NIEDERMAN: Is the HFA propellant patented or is that available widely?

MS. CUSUMANO: It is patented.

DR. NIEDERMAN: So again, you could not get generic albuterol HFA?

MS. CUSUMANO: Not right now, you can't. But there's no barrier to innovation.

DR. GROSS: Can I ask a question about non-safety or hazards of alternatives? It occurs to me that for the first 20 years or so of CFC use, they were thought to be ideal agents with no medical problems, and

environmental problems weren't known about at that time.

But what do we know about HFAs or other alternatives in terms of these long-term possible risks? I mean, obviously I understand that right now, they're

believed to be safe environmentally, unless I'm wrong, but I mean, how can we be sure that the alternatives that are being developed don't actually have some worse impact than CFCs?

I mean, you know, I understand this is very difficult to predict, but one doesn't want to jump out of the frying pan and into the fire.

MS. CUSUMANO: And I can answer part of that, and maybe I'll ask Bob to answer after, too.

First, part of the development program is we're using the same moieties that we've been using for years and years. So then you're just talking about the interaction between whatever propellant you're using and the product, and there has been extensive testing on HFA.

I know IPAC's been involved in it. We've got quite a lot of data, much more data than we ever got on CFCs before we started marketing them is my understanding,

and as far as environmental impacts, I think we know that HFA has a very small impact, and it's something that's considered acceptable.

So I think we're at a better knowledge level than we were with CFCs.

DR. MEYER: Yes. Let me pick up on that, and I'll invite the EPA to comment as well.

As Leanne said, the testing for the HFA was in

fact very extensive, and in fact, the pre-clinical testing in terms of the toxicology and so on was as extensive as what would be done for many new drug products. In fact, more extensive than what might be done for some new product drugs.

I think the FDA felt that was very reasonable given the type of chronic use that these get, and the fact that they represent such a large proportion of the formulation.

As far as the HFAs go, they have no ozone-depleting potential at all. So they're very good in that standpoint. They do have some global warming potential,

and in fact, HFAs are amongst the gases that are proposed to be controlled under what's called the Kyoto Protocol or basically the Greenhouse Gas Protocol.

But there's some important things to bear in mind there. One is that the HFAs are actually less potent global warmers than the CFC alternative or the CFCS they're meant to replace. So in fact, from the global warming standpoint, they're a better trade-off because the CFCs have more potency.

The other thing is the difference between the Kyoto Protocol and the Montreal Protocol is quite substantial in terms of the Kyoto Protocol is talking about controlling greenhouse gases and not eliminating them, and

so the Montreal Protocol is talking about the elimination of ozone-depleting substances. The Kyoto Protocol is talking about an overall control, and I should point out that, to my knowledge, it's not been ratified by the United States, but the countries have the option of how they sort of get to their target.

So if we can do that by trading off carbon dioxide for HFAs, it does allow for sort of a neat

balancing, and so that, as far as I'm aware, is the only known consequence right now from the environmental standpoint of HFAs, and I don't see it as a major hurdle for the future.

I think people realize that this technology, the HFA MDIs, is very important, that there's been a lot of industry outlay of capital to develop them, and I think that because of the way the Kyoto Protocol's structured, even if it were ratified, it wouldn't put the MDIs at risk. I'd welcome EPA comments on that.

MR. COHEN: I don't think there's anything that we can add to what Bob just said. There was also some interest in these HFAs or HFCs as a risk in terms of refrigerant use, and there have been other clinical studies looking at exposure to folks. I think they were conducted in Europe recently, in the Netherlands, and those turned out to be clean.

So we're very comfortable with any health risks associated with these --

DR. GROSS: Are you going to be monitoring that

in the future? The risks, possible risks using alternatives? I mean, is that something you follow year-by-year and make sure that there isn't some kind of hazard that's becoming apparent or having approved an alternative like HFA, you just say okay, that's it, wait until something shows up?

DR. MEYER: Well, I think from the FDA's standpoint, that we feel quite comfortable with the pre-clinical testing that we have and in fact the human testing that we have.

I think sort of in the back of our minds as far as these formulations overall, including the HFAs, part of the reason we wouldn't just make a determination that it's a particular alternatively-propelled MDI as a suitable alternative the day it's approved is because there are questions about how patients will react to the formulation overall, and I think that we will be interested in monitoring that in total, and I don't think we have a lot of concerns about the HFA health because we've seen some very good data about their safety, and they are reasonably inert compounds.

But we have the overall question about how

these do in the wider use, and that's at least a small part of that.

DR. SESSLER: Did that answer your question, Dr. Gross? Did you have EPA implications with your question as well?

DR. GROSS: Are there any?

MR. COHEN: I think, as Bob said, we're pretty comfortable with the completeness of the data that's been collected so far. There have been no reports, no anecdotal indications that any exposure to HFAs in other uses have caused any problems.

DR. MEYER: Actually, let me make one more point on that just before we turn to the next question, and that is that, as Leanne said, there was not this level of testing when CFCs were first used, and in fact, in some of the head-to-head toxicology testing, HFAs also looked like they had an advantage over CFCs. Particularly some of the CFCs at very high exposure levels caused cardiac arrhythmias, and the HFAs seem to have less propensity than at least one of the CFC propellants in terms of that.

DR. FINK: With at least one product, albuterol HFA, it's been available for years. You said it had about 8 to 10 percent of the market. It seems like voluntary application of these rules may not be adequate to drive the market, that there may need to be some sort of tax or

disincentive on CFC products because if you take the example of albuterol, where there is an acceptable reformulated product available, it's not being prescribed and used, even though studies have shown it may be superior to the CFC-containing inhalers in terms of clinical efficacy.

MS. CUSUMANO: Albuterol's kind of in a unique situation, and that's kind of the reason that having that one as the alternative first is maybe not predictive of the rest of the market just because albuterol does have generics.

What we've seen in some other countries, in some of the European countries, where you've got moiety-by-moiety replacements, is that there's a faster change in part because the company's not interested in having two production lines.

So it'll be interesting to see what happens here, but I'm not sure that albuterol's the model for it.

DR. MEYER: You know, I think the other thing I would say to that comment is that the FDA is only part of the overall U.S. transition process, as is the EPA, and I think that there are other ways the government has to look at this and figure out the best way to proceed in terms of

incentives to the transition and accomplishing the transition.

So I think we're trying to do our best part from what we're being called to do, but issues, such as cost and, you know, the government perhaps stepping in to facilitate the transition in terms of the payment system and so on, are really beyond the purview of the FDA.

DR. SESSLER: Dr. Apter?

DR. APTER: I was wondering, with albuterol, there's a propellant that's somewhat comparable to CFCs with the inhaled steroids and also with the nasal steroids. The propellants, I believe, for the inhaled steroids, the propellants are in development. For nasal steroids, there's not a comparable propellant on the way.

I think that the delivery system for aqueous versus gaseous propellants are very different.

DR. MEYER: There's actually two propellants that have been developed, being HFA or HFC-134A, which is in the currently-approved Proventil HFA product. The other one that is being put forward as a reasonable

pharmaceutical alternative propellant would be the HFA or HFC-227EA, and it really is the choice of the manufacturer as to how to best reformulate.

It's just step back for a second and say it's been a very technically-challenging process for the manufacturers because the different solvent capabilities of the gases that we're talking about, because of different

vapor pressures and so on, it's really required a reengineering of the MDI. It's not just taking out CFC-11 and 12 and putting in HFA-134A or 227EA. It really represents reengineering the product substantially, and that's been a big technical barrier.

But there's no a priori reason why any of the current MDIs could not be reformulated. There are some challenges to doing that, but in one of those two gases, and I think that we would anticipate that such products will continue to be developed, both for nasal and oral inhalant.

MS. CUSUMANO: This was something I didn't include in my presentation, but we've got it in the proposed rule. There's only three active moieties marketed

as a nasal steroid, beclomethasone, budesonide and triamcinolone, and beclomethasone and triamcinolone are also marketed in non-CFC formulations.
So really, it's just budesonide that there's no aqueous solution for.

DR. MEYER: Actually, since the proposed rule, there is now.

MS. CUSUMANO: There is now?

DR. MEYER: Yes.

MS. CUSUMANO: Okay. So.

DR. SESSLER: Dr. Kelly, and then Ms. Conner.

DR. KELLY: Going by the moiety-moiety approach, just reflecting back on the albuterol HFA, there was an attempt, I think, when it was produced to make it essentially equivalent to the CFC product, but in the existing approach, it seems like, and I think it's a good idea, that the new products don't have to be equivalent.

In other words, two puffs equal two puffs, and so if a new product that's being developed delivers more drug, for instance, so it could be used as one puff in

replacement of two puffs twice a day or whatever, that that would be an acceptable alternative, and so the moiety-to-moiety approach is sort of giving away to the equivalency approach.

DR. MEYER: Yes. I think we have never really proceeded with an equivalency approach. I think actually some other regulatory bodies have used more of sort of a bioequivalency approach to all this, but I think we've realized that there may be differences in the products and maybe by design or maybe by happenstance, but we've allowed for that, and if you consider the criteria that are in our notice of proposed rulemaking or were in our ANPR, we never really called for it being a direct one-to-one switch for that reason.

We wanted to allow for some either intended or unintended differences, although certainly in the case of

unintended differences, we wanted to have enough data to understand what those differences were before we'd consider an adequate alternative.

MS. CONNER: It just seems to me that there's an overall acceptance that the transition is going to be to

an HFA-type inhaler, and I wondered with this pipeline knowledge that you have, if you see any other trend towards different delivery devices.

I know we have dry-powder inhalers and other type actuated systems that, unfortunately, they are affected by inspiratory flow, but do you see other pharmaceutical companies or even some of the generic companies looking at new delivery mechanisms as opposed to new propellants?

DR. MEYER: I think it's clear that this whole transition process has been a signal to some companies to think about other ways of delivering the drugs for inhalation that are as roughly convenient as MDIs but perhaps don't use a pressurized gas to deliver them, and I suspect that those products will become available over the period of this transition.

I think the other thing to bear in mind, particularly for sort of the broader discussion of what, you know, when we convene these meetings after the January 1st, 2005, date, of what the market is like, is even if a

multidose dry-powder inhaler's not perhaps in some people's opinions a perfect replacement product for an MDI, that doesn't mean there aren't substantial number of patients who don't use them and benefit from them.

So if you look at the overall market, they may substantially help us towards the transition but maybe not on a direct moiety-by-moiety approach.

DR. SESSLER: Dr. Dykewicz, and then Dr. Niederman.

DR. DYKEWICZ: I'd just have a clarification I'd like answered. As proposed by the moiety-by-moiety approach, I understand that if there were a non-CFC alternative preparation for that moiety, then the CFC preparation would be considered non-essential with some provisions.

To some extent, it gets back to the question of Dr. Joad about the newer moiety-by-moiety approach would not specifically consider metered-dose inhalers as a requirement.

Now, the problem that I could foresee is that you might have a non-CFC alternative product, the dry-powder inhaler, that may not meet the needs of all important subgroups. For instance, children may not have a good inspiratory flow.

So if I'm understanding this correctly, even

though it's not specifically stated, if an assessment is made by FDA that the alternative DPI product would not meet all patient subgroups, that would be a reason for continuing the essential accolade for the CFC MDI?

MS. CUSUMANO: That's right, and one of the things that I think it's important to remember is that moiety-by-moiety includes things like convenience of use, but it also says for the same indication.

So if you've got the MDI down to six or younger, and the DPI is only down to 12, you don't have the same indication. So you've got a missing product.

The other part of that is, okay, so, we've got the moiety-by-moiety approach, but one of the or's is after January 1st, 2005, and this is what Bob was talking about, do you have not just DPIs out there that are serving 12 and above, but HFA products or other products, you know, other types of alternatives that serve that younger population or the population that can't use the DPI? If so, then we would look at removing the essential use for that moiety.

DR. NIEDERMAN: I was just going to say, I don't think there's any question that we'll have alternatives to MDIs and DPIs. I know I've seen, for example, a liquid inhaler device that's miniaturized and portable and probably would work as well.

25 I think the problem, and I'm not sure how it's

1 going to be addressed, and maybe we can't address it, is
2 the cost issue, and I think as was pointed out with
3 albuterol HFA, the lack of acceptance has to do, I'm sure,
4 more than anything with the cheap price of the generics
5 compared to the much greater price of the HFA, and I think
6 it is probably a very relevant thing to look at because I
7 think that the HFA has not been adopted widely probably
8 because it's just much more expensive, and I think that in
9 terms of defining essential use as meeting all people's
10 needs, unless we can find a reasonable way to provide
11 alternatives that are equal in cost to the current
12 generics, I think it's going to be very burdensome on
13 certain populations to make this transition.
14 MS. CUSUMANO: Like I said, albuterol is the
15 exception to the rule because of the generic.
16 DR. NIEDERMAN: But it's a good example of, I
17 think, what's going to happen. I think it's not an
18 exception. I think it's a glimpse into the future of
19 trying to deal with this issue.
20 DR. MEYER: Well, again, I think that, as

Leanne said beforehand, I think it's clear, most clearly the case with albuterol that there's a generic now, and that has changed the economics of the market, and I think that that's why Leanne is saying it most clearly looks like an exception to us.

For MDI replacement products, it does appear from what the industry has said, and in fact Proventil has held this out, is the price will be essentially the same. I believe the Proventil HFA is within a few pennies of the Proventil CFC.

DR. NIEDERMAN: But not comparable to the generics.

DR. MEYER: Correct. But, again, albuterol is the only drug substance right now that has a generic available. So presumably if you're talking about Drug X, and it's an inhaled corticosteroid, and it's reformulated, it will be reasonably priced, and the other thing, I think, to bear in mind, now that I'm saying that, this has not been one of the questions, but these are sort of the way that we thought we would respond to the transition.

It's entirely within the companies' options, and in fact some companies have indicated to this, that if and when they get their alternative approved, they may in fact want to stop marketing the CFC sooner than we would perhaps remove the essential use listing. That is their prerogative, and although we might have some at least theoretic concerns about that, that's the way they could proceed, and obviously CFCs are getting more expensive, and there's some economic reasons why you wouldn't want to be running two production lines.

So I think when we first started the ANPR process, we really hadn't anticipated the fact that we might in a lot of cases not even have to invoke this because the companies may be making a switch on their own even faster than we might be proposing.

DR. SESSLER: Dr. Ford?

DR. FORD: I think that in addition to the cost issues that Dr. Niederman spoke to, one of the considerations as a potential determinant of use of the alternative products is going to be the extent to which practitioner populations are being reached in terms of

their awareness of what the alternatives are, and I think that as is mentioned in some of the documents, there has to be a major effort in terms of making sure that people know what's available, and I suspect that a lot of that information is within the specialist population right now, including the availability and potential benefits of Proventil HFA, for example.

MS. CUSUMANO: That's absolutely true, and I mean that's one of the reasons that we're so involved in education. I know Bob participates in NAEPP, National Association -- National --

DR. MEYER: National Asthma Education Prevention Project.

MS. CUSUMANO: Asthma Education Program.

DR. MEYER: As has the CFC work group, and in fact, the industry itself has, through its consortium called IPAC, has been producing documents. We worked with them and NAEPP and EPA and other professional groups and patient organizations to produce a document called "Why Your Inhaler is Changing," and I know there will be other

efforts, both from the NAEPP and, I'm sure, from the industry, in terms of education.

I think the clear message we're getting from our colleagues in the U.K. is that education is perhaps best timed for when the transition's really happening, and right now, we're sort of in the early phases, but I know that it's been our experience that Dr. Jenkins and I and other folks from the FDA have spoken at many public meetings, such as the AAAAI annual meeting and so on, and there's been some interest, but, quite frankly, the last time I spoke at the AAAAI, the room was pretty full, but it was mostly industry people there, and I think that for a lot of practitioners, it just hasn't hit yet, that this is something they need to grapple with now, and so I think we'll really intensify, we meaning both the FDA and other components that we interact with, really intensify our efforts as the transition really starts happening.

DR. SESSLER: Dr. Kelly?

DR. KELLY: What are the issues with the

generics? I mean, you should know if anybody's trying to develop any new generics or if there's any drugs available?

If basically it's a moot point, except for albuterol, then the cost issue is probably not a major issue. It would seem hard to develop a generic for, say, beclomethasone right now. You're not going to be given the essentiality based on the fact that it's just a generic albuterol -- I mean, a generic beclomethasone.

DR. MEYER: I'd rather not comment on the specifics of your question. I will say that the moiety-by-moiety approach doesn't specify what kind of product it's in. So if beclomethasone is considered -- I might even use beclomethasone -- let's use something else.

DR. KELLY: Okay.

DR. MEYER: If Drug X were considered an essential use of CFCs, that really doesn't discriminate whether it's a branded or a generic use.

There was something else I wanted to talk to there in that question, and I'm forgetting -- oh, well, I was going to say even if it were only albuterol, were only albuterol, albuterol is such a large product in this market, that it would make the cost issue very meaningful in and of itself because it is such a big player in the asthma market.

DR. SESSLER: I'd like to bring it back to

cost, but from a little bit of a different perspective and perhaps more immediate, and that is really the nasal corticosteroids.

The proposal seems very reasonable, but I guess there must be some differences in cost for the various products that are available currently, and I'm guessing that perhaps the lower cost items would be CFC rather than the aqueous.

I guess I'm seeking some information first, some data on cost comparisons, and then if there is impact in that area.

DR. MEYER: Do you have the economic analysis piece there?

MS. CUSUMANO: I don't think I have figures comparing the aqueous versus the CFC part, but I do know that the four manufacturers marketing five CFC nasal steroids constitute less than 20 percent of the market. So.

DR. MEYER: I think when we looked at this, it did not appear to be a substantial barrier. We did have an economics analysis as part of this rulemaking process, and I know that we did look at that issue. I don't remember the details offhand, but it did not seem to be a substantial issue.

The other thing with the nasal corticosteroids

is that it's a very different part of this than the inhaled products because they're not considered essential from the Montreal Protocol standpoint, and I think that we're really talking more about timing of our action rather than whether to do it or not.

DR. JENKINS: If I could just add to that, Curtis. All the nasal corticosteroids are branded products. They're not generics.

DR. SESSLER: Right.

DR. JENKINS: So again, that takes away that element of the cost comparison.

DR. APTER: While we're on the subject of the nasal steroids, which, of course, nasal diseases aren't usually life-threatening like asthma, and even though you mentioned those figures about aqueous capturing a large part of the market, my own clinical experience is there's not a lot of data comparison, is that some people don't tolerate the aqueous as well, and that some people don't get as good delivery with the aqueous versus the aerosol, and so it may be important to encourage an HFA-like preparation to come forward.

DR. JOAD: On average, how much less is the generic albuterol than the brand name? Just ball park.

DR. MEYER: I don't really know the answer as far as what it costs the patient. As of months ago, there

was not a huge difference. I think that's been expanding over time at the wholesale level. So I think that at the wholesale level, we're probably talking in the mid-20s for the branded products. The generic products, I've heard figures quite low actually, down at least for one of the so-called generics, and I'll just say so-called generics, down in the $3 to $4 range at the wholesale level.

I don't have personal knowledge of that, but that's what I've heard through some of my contacts. So it had been much more, sort of $17 to $25 type of comparison, and I don't know how that translates to what patients actually pay.

MS. CUSUMANO: It's one of the issues that we've struggled with because certainly one of the types of comments that we heard was about cost, yet there's very little within our authority that we can do about cost, and so I mean that's one of the issues that we wanted to bring

here today, to ask what kind of innovations or what kind of thinking outside the box can we do to address this issue?

DR. NIEDERMAN: But, again, to put it in perspective, generic albuterol makes up what percentage of the albuterol market? Do you have any guess?

MS. CUSUMANO: I don't know.

DR. NIEDERMAN: Of the MDI albuterol market?

MS. CUSUMANO: Do you know, Bob?

DR. MEYER: Taking sort of the non-regulatory definition of generic, it's a large majority now. It's, I think, in the range of about 70 percent, if not more, 80 percent.

DR. NIEDERMAN: I mean, one obvious focus of this would be on the managed care companies because I know in my patient population, they don't want the generics necessarily. They're being driven to it by their health care plans, and certainly a major lobbying effort on behalf of some of these non-generic new products probably has to be done at the health care plan level even more so than at the patient level.

DR. DYKEWICZ: Revisiting the incentive issue, that is, the incentive for the manufacturers to develop alternatives that Dr. Niederman talked about earlier, as I see this, there's really a two-stage process.

The first stage, moiety-by-moiety, doesn't really have a major incentive necessarily for the manufacturer to come up with an alternative, but the second stage of the proposed regulations is that in 2005, there would then be the assessment made about whether an agent were essential, whether a product were essential, and I could easily foresee, and maybe this is potentially the intent, even though it's not stipulated, that at that point, there really would be a therapeutic class assessment

made, that you have a product for which there are a number of other alternatives of different moieties, and that on that basis, the manufacturer would lose its ability to continue to sell the product because there were alternatives, and if they didn't ask the manufacturer to have an alternative preparation that was non-CFC, they would lose that part of the market.

Essentially, is that correct how that might

play out?

DR. MEYER: I think in essence that's correct. I mean, in some ways, we're, I think, viewing it that future assessment is being perhaps even broader than just a class approach in fact, I mean, because you're really trying to look at the entire market, and what patients' needs are, and how they're being addressed by the market as it is at that point.

But in some respects, it does have some analogies to what the therapeutic class approach we had previously talked about. It's just not as restrictive in some ways. It's sort of a more broad look at where the market sits, and at what point does a non-reformulated product represent such minimal use or not meet the other criteria that we really can't justify the CFC use in that product any more?

DR. VOLLMER: I have a comment relative to the

presumption that we won't be seeing new CFC generics for corticosteroids or other products that are going to be coming off market.

If one makes the case, for instance, that for albuterol having a low-cost CFC alternative as compelling reason for not taking it off the essential list, then it seems to me it opens up the possibility for arguing that the reason for providing an exemption for being essential is that we can now roll out a new product which is substantially cheaper than what you would be getting as a non-CFC alternative.

I don't know where things stand at FDA and the government regarding this. Is this going to be an option offered to people? Is this going to be even on the table for discussion?

DR. MEYER: I certainly don't want to leave the impression that we're presuming that there will not be any further generic CFC products.

From the very strict legal mandate of the FDA, we do not really have the authority to say there should not be any more generics. In fact, it's quite the opposite. Really due to the Waxman-Hatch amendments to our Act, there's a presumption that generics should be approved, unless some criteria met, and the CFC considerations don't factor into that.

Again, I think it's important to realize the FDA's addressing the transition within the wider government, and that there may be other components in the government who might, for instance, feel that even if we approved it, it should not get essential use allowances.

So just from the FDA's standpoint, if all other things were met, including being able to show bioequivalence for a product that was no longer protected by patent exclusivity or by marketing exclusivity, then if data were provided to us to show bioequivalence to the innovative product, we would need to approve that product.

Again, I think it's important to realize there are discussions outside the FDA, and in fact at the Montreal Protocol level, about how wise it is to have any new CFC products approved. But that's a discussion in many respects, although we're involved in it, it's a discussion beyond the FDA.

DR. SESSLER: Mike?

DR. NIEDERMAN: I'm sure it would be unwise to think about putting some sort of tax which would be passed on to consumers on a product that continued to have CFCs, but is the reverse possible?

Is there some sort of economic incentive that can be given to companies that develop non-CFC devices so that they could bring the costs down and make them more

competitive with the generics and put pressure on the generics to do similar types of maneuvers? Is there any mechanism for that?

MS. CUSUMANO: Certainly, there is, but it's not something FDA could do on its own. It's something that would have to be passed by Congress, an amendment to the Act or an amendment to the Tax Code or something like that.

DR. NIEDERMAN: So it's not something we can really reasonably consider.

DR. MEYER: I think you could make reasonable comments, but just because FDA doesn't necessarily have its own authority to do it, I think it's important that we get all comments.

DR. GROSS: Can I ask a related question? Supposing a drug company came to you with a completely new entity that they wanted to deliver by inhalation, and they were proposing to use a CFC propellant for that. What would the agency's position be on that?

DR. NIEDERMAN: Leanne laid out what -- we're changing our criteria for adding new essential uses to be even more rigorous than they currently are, and in fact, if you read what's currently in 2.125, if we were to take a very, very hard line about that, they're pretty rigorous

already, but these raise the bar even farther, and basically, unless it was clear that it was a major

therapeutic advance, we're talking about a new moiety, major therapeutic advance that was otherwise not available, that there were technical barriers for it being formulated in something other than CFCs -- what's the other one? I'm sorry.

MS. CUSUMANO: Substantial technical barrier, important public health benefit, and the release warranted in light of the use.

DR. MEYER: Yes. That might be the one place where we and the EPA would engage in a discussion of sort of environmental risk versus benefit. Overall in this process, the risk assessment and the commitment to get rid of CFCs has been made. So we're not engaging in that kind of discussion now, but for new use, we're talking about potentially doing so.

DR. GROSS: Sorry. I didn't understand that. When you say non-engaging in that kind of discussion now, what do you mean? You won't entertain new submissions that

contain --

DR. MEYER: No, no, no. I was actually talking about -- no, no. I was talking about we're not, as I said earlier, here today to debate, you know, how much of an ozone-depletion risk the current MDI use is and that sort of thing.

But what I'm saying is in the future new use, I

think we have to really look at what would be the known hazard to both the ozone depletion and in fact to the overall accomplishment of the Montreal Protocol compared to the public health benefit.

So we're not in this rule or this proposed rule, we're not closing the door to such circumstances, but we're, I hope, sending a very clear signal that it's going to have to be very clear that there's no other alternative for delivering this moiety, and this moiety is really providing a benefit that folks won't get otherwise.

DR. GROSS: Well, I mean, the question really is what is the incentive for the companies to develop an alternative propellant form of that, because as was pointed out earlier, if the drug is patented, and there isn't an

alternative, it's a new entity, what is their incentive to --

DR. MEYER: Well, their incentive right now is if they do not have an approved essential use, they're not on the current list, they're going to have a very tough time getting on it. So if they're in early drug development, they really should be looking to develop that in either an alternatively-propelled MDI or some other alternative device rather than go the CFC route. I hope that signal's quite clear.

DR. GROSS: So essentially what you're saying

to the company is that we're going to set the bar much higher for your drug if you're proposing to market it with a CFC propellant than if you were to use an alternative environmentally-acceptable one, is that right?

DR. MEYER: Yes, yes, and in fact, and I would again invite any comments from the EPA in this regard, but it's not just us setting that bar higher, but the U.S. nomination has to be approved by the parties to the Montreal Protocol. So it's really the international

community that's raising the bar substantially, too.

DR. SESSLER: Any comment from EPA?

MR. COHEN: Again, Bob summed it up pretty well. I think it's worth noting that, as Erin said, the U.S. nomination up till now has been approved year-by-year since 1996, but there's no guarantee that that will continue, especially as other countries pursue their own transition.

DR. SESSLER: Dr. Vollmer?

DR. VOLLMER: I must say that I'm generally very favorably disposed towards the NPR. I want to echo a concern that Jean raised earlier. The one issue in removing the essential status for a drug, the fourth one, the special populations, there was a presumption, as was pointed out, that if the first three criteria are met, then all needs of special populations are met, and the sort of

bar for our becoming that is really put back on the industry to say if you think that's not the case, then give us evidence of that.

Presumably there would be enough of a -- I mean, if you can show that there's a market out there, then

there's an economic incentive for them to do that. On the other hand, the smaller the market gets, then the less economic incentive there will be for them to go out and do whatever analyses they're going to be required to do.

Can you speak a little more to how you see this working?

MS. CUSUMANO: First, I'd like to say that the substantial or the subpopulation that we had in the advanced notice of proposed rulemaking changed a little to patients who medically require the ODS are adequately served by alternatives. So very similar.

I think what you said still applies, and I guess the second part of that is we have this idea, and we understand that there may be patients who can't use the alternatives, and we're not sure how we're going to figure that out, and that's one of the questions that we have for the committee, is how are we going to decide?

A lot of the comments that we had on the original advanced notice said a subpopulation of one is very important to that one. So on the other hand, I know

sometimes we get comments after a company has removed a product from the market, you know, on its own that say I needed that product, what am I going to do without it, and --

DR. MEYER: Yes. I think that, as Leanne said, we have shifted the language away from a presumption that these subpopulation needs are being met to really wanting some level of showing, and it's not necessarily the burden of the company to do that, but I think this is going to be a difficult issue and one that we would certainly very much welcome input on because it is clear that when certain products have gone away because the manufacturers have stopped marketing them, you have a vocal minority of patients who earnestly feel that that's the only product that can control them, and so we know that will exist.

I guess I could cite my experience during residency when the VA would switch from one producer of albuterol to another. These products were substantially the same, and at some point in the past, I understand they might have even come off the same production lines, and patients would complain bitterly that this one doesn't work as well as that one.

So we know that because of the variability of the disease that we're talking about, that being asthma and chronic obstructive pulmonary disease, that patients tend

to -- if their disease happens to exacerbate when they switch inhalers, whether it was due to that inhaler or not, they may well form the conclusion that it was that inhaler. So these are some of the difficult things.

I do think it's important, because I don't think we stressed it earlier, to realize that we are in the notice of proposed rulemaking as in the ANPR stating that these removals of essential use listings will be through further notice and comment rulemaking.

In other words, if we wanted to delist albuterol at some day in the future, we will need to publish a proposed rule saying we propose to take albuterol out, these are the reasons why, and I would suspect, particularly for some of the drugs like albuterol, that that will entail bringing this committee back together, hearing more public commentary and really considering that as a part of it.

So at least even if we don't have every single iota of data we need, I think we are envisioning a public comment process that will allow for other people to bring in data that will be helpful to us in making the determinations.

DR. SESSLER: Thank you.

I'd like to go ahead and take our break now.

I'd like to thank the committee for their thoughtful

questions, and the FDA and EPA personnel for their thoughts.

It was rather free form and covered a lot of different areas which I hope we will focus in on specific areas for more complete discussion in the afternoon session.

Please be back at 10:45. We'll start promptly with the opening public hearing.

Thank you.

(Recess.)

DR. SESSLER: Good morning again. This will be the open public hearing component, and we have four listed speakers. In addition, we will open it up after those individuals have spoken to any others who wish to speak before the committee.

What I'd ask of the speakers is that they tell who they are and where they are from and who they represent and also a mention of any disclosure of conflict of interest.

I would also ask that the comments be limited

to 10 to 15 minutes, please.

Our first speaker is Ballard Jamieson, who is Secretary and Legal Counsel for the International Pharmaceutical Aerosol Consortium.

Mr. Jamieson?

MR. JAMIESON: Over here?

DR. SESSLER: Yes, please.

MR. JAMIESON: Good morning. My name is Jim Jamieson. I'm the Secretary and Legal Counsel to the International Pharmaceutical Aerosol Consortium, or IPAC, as it is commonly known.

IPAC is an association of leading manufacturers of metered-dose inhalers for the treatment of asthma and chronic obstructive pulmonary disease. Its members include AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Glaxo Wellcome, Medeva Americas, Inc., Norton Healthcare, Ltd., Rhone-Poulenc Rorer, Inc., and 3M Pharmaceuticals.

IPAC was created in response to the mandate of the Montreal Protocol. Its goal is to ensure a smooth and efficient MDI transition that balances public health and

environmental protection. To this end, IPAC serves as a source of information and analysis on the MDI industry and facilitates its participation in the implementation of the Montreal Protocol worldwide.

Members of IPAC are firmly committed to the MDI transition. In 1990, MDI companies 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 around the world have been involved in the

development of non-CFC MDIs. MDI companies have already spent $1 billion in this effort and will spend much more to complete it.

In May 1997, IPAC submitted comments on the FDA's advanced notice of proposed rulemaking. On April 11th, 1997, IPAC presented its views on the ANPRM at the public hearing of this committee.

We appreciate this opportunity to participate in this hearing today. Later this month, we will submit written comments to the FDA on its proposed rule. I will now summarize IPAC's comments on the proposed rule.

The proposed rule provides for a moiety-by-moiety approach. IPAC supports this approach as the primary criteria for examining safe and effective non-CFC alternatives for existing CFC products. This approach, in our view, strikes an appropriate balance between ensuring the availability of vital medications and discontinuing the use of CFCs.

The proposed rule establishes several criteria for an alternative to a CFC MDI. For example, the proposed rule provides that a non-CFC alternative must feature the same route of administration. IPAC supports this criterion.

Inhalation is the preferred route of administration for the treatment of respiratory disease.

To ensure the continued availability of inhalation therapy, a CFC MDI should only be replaced by a product with the same route of administration.

The proposed rule provides that a non-CFC alternative must feature approximately the same level of convenience of use. IPAC supports this criterion, and as

the FDA notes, patients value the compact size and ease of use of MDIs. This criterion ensures continuing patient access to therapy with this same level of convenience.

The proposed rule states that supplies and production capacity for a non-CFC alternative must exist at levels sufficient to meet patient need. IPAC supports this criterion. This criterion would safeguard against interruptions in patient access to vital medications during the transition to non-CFC MDIs.

In the preamble to the proposed rule, the FDA states that a non-CFC alternative should be manufactured at multiple manufacturing sites if the CFC MDI is manufactured at multiple manufacturing sites. IPAC believes that the requirement of multiple manufacturing sites is unnecessary where an MDI company demonstrates that a single manufacturing site is sufficient to supply patient need.

MDI companies may consolidate manufacturing activities at a single site for non-CFC MDIs. These single sites will feature supplies, storage and production

capacities as well as safeguards against disruptions in manufacture which virtually eliminate risk of product

shortages.

Under the proposed rule, the FDA would require at least one year of U.S. post-marketing use data for non-CFC alternatives. In addition, the FDA would consider foreign data supportive of U.S. post-marketing use data if U.S. and foreign formulations, patient populations and clinical practices were the same or substantially similar.

Finally, the FDA would not require a post-marketing study if available data, including more traditional post-marketing surveillance data, are sufficient to support a finding that the CFC product is no longer essential.

IPAC supports consideration of post-marketing data. IPAC proposes that the requirement for one year of post-marketing use data in the United States be reduced if foreign post-marketing use data is sufficient to support a finding that a CFC MDI is no longer essential. This approach would eliminate unnecessary delay in discontinuing the use of CFCs.

Finally, IPAC believes that existing processes provide post-marketing use data sufficient to support a finding that a CFC MDI is no longer essential. Accordingly, IPAC believes that Phase IV post-marketing

studies should not be required for this purpose.

Under the proposed rule, the FDA would determine whether patients who rely on a particular CFC MDI would be adequately served by non-CFC alternatives. In making this determination, the FDA would consider whether adequate safety, tolerability, effectiveness and compliance exists for the indicated populations and other populations known to medically rely on the CFC MDI product.

IPAC supports this criterion. This criterion ensures that vital medications will remain continuously available for all clinical subpopulations.

Finally, the proposed rule provides that after January 1, 2005, a CFC MDI will no longer be essential unless it provides an unavailable important public health benefit which warrants the release of CFCs into the atmosphere.

IPAC supports this approach. A target date for the review of remaining CFC MDIs would mark the final phase of the transition to non-CFC alternatives and give physicians and patients a general sense of the time frame for its completion.

In sum, IPAC supports many important elements of the proposed rule. There are, however, several areas in need of clarification concerning, for example, the issue of multiple manufacturing sites and post-marketing studies.

In addition, IPAC believes that the proposed rule should require every new CFC MDI product to meet all essentiality criteria. In our view, the Clean Air Act mandates a product-by-product essentiality review for all new CFC MDIs, if any there be.

We note that leading public health organizations support this approach. We will address the legal aspects of this position in our written comments submitted later this month.

We appreciate this opportunity to appear before you today. As our comments indicate, we are generally supportive with a few exceptions of the FDA's proposed rule, a few important exceptions to the rule.

We would like to commend the FDA and its staff for meeting what we know was a significant challenge in reviewing, analyzing and responding to the many comments on the ANPR, and we congratulate them for the effort they have made.

At this point, we would be pleased to answer any questions you may have and either now or this afternoon in the Q&A period.

Thank you.

DR. SESSLER: We have time for one or two questions.

DR. VOLLMER: I'd just like a clarification on

the -- when you're talking about the post-marketing, and you were suggesting that you were supporting less than a one-year post-marketing if there was good European data available, and then you followed up with a comment about the lack of a need for Phase IV trials.

Could you just repeat that again because I missed it?

MR. JAMIESON: Okay. Well, our position is that the Phase IV studies are not necessary because existing processes are sufficient to make an essentiality determination. That's the position. We will elaborate on this somewhat more in our comments filed later this month.

DR. SESSLER: Thank you.

MR. JAMIESON: Thank you.

DR. SESSLER: Our second speaker in the open public hearing component is Alfred Munzer, M.D., representing the American Thoracic Society and the Medical

Section of the American Lung Association.

Dr. Munzer?

DR. MUNZER: My name is Alfred Munzer. I'm a physician specializing in lung disease. I'm a past president of the American Lung Association, and I have, as far as disclosure is concerned, to the best of my knowledge, I have no financial interest in any of the companies that are affected by this regulation.

On behalf of the American Lung Association and its Medical Section, the American Thoracic Society, I want to thank the FDA Pulmonary and Allergy Drugs Advisory Committee for the opportunity to present our views.

While many of our concerns with the previous advanced notice have been addressed in the proposed rule, there remain many important issues to be resolved. The most important issue, in the opinion of the American Lung Association and the American Thoracic Society, continues to be the need for broader public education as transition takes place.

The transition to CFC-free metered-dose

inhalers provides a unique opportunity for the entire pulmonary-allergy community to refocus attention on the proper diagnosis and management of asthma and to revitalize the relationship between physicians and other health care providers and patients with asthma.

Some people may feel that we have been dealt some lemons in this whole transition. What we have failed to do so far is to make lemonade.

The American Lung Association and the American Thoracic Society have previously commented regarding the role of patient and professional education in any transition strategy. As noted in the European Union, education needs reach a critical level when many new

products are introduced in rapid succession.

We recognize that such education efforts do not fall within the jurisdiction of the Food and Drug Administration. However, we do encourage the FDA to use its public affairs resources and to explore intraagency mechanisms to ensure coordination and collaboration with Federal Government entities having authority for educational efforts, including the National Asthma

Education and Prevention Program.

Coordination and collaboration among Federal Government agencies, non-governmental organizations representing patients and health care providers, including the pharmaceutical industry and managed care companies, must occur to ensure a consistent and appropriate level of effort as reformulated products enter the marketplace.

The American Lung Association and the American Thoracic Society look to the agency for leadership in this area.

Let me make some specific comments on the proposed rule. First, about the moiety-by-moiety approach. The American Lung Association and the American Thoracic Society concur with the moiety-by-moiety approach detailed in the proposed rule. This decision-making structure should continue to provide a range of treatment options for physicians and patients as the transition proceeds.

It is critical that any decision-making scheme is structured to ensure that physicians remain able to treat patients effectively following the National Asthma

Education and Prevention Treatment Guidelines.

Second, as to the petitions to add new essential uses, the American Lung Association and the American Thoracic Society agree that it is inappropriate to add new essential uses at a time when developed nations, including the United States, have committed to the phaseout of the production and consumption of ozone-depleting substances.

Third, as to the determination of continued essentiality, we concur with the decision-making process outlined in the proposed rule. In the first instance, the agency is to be commended for the common sense approach of removing an active moiety from the essential use list if it is no longer marketed in an ODS formulation.

Under a second scenario, the agency proposes a process commencing after January 2005 to review the essential use status of current active moieties. We believe that it is critical to fully engage the patient and health care provider communities in this process.

A notice and comment period, plus consultations with an advisory committee, are not sufficient to ensure input from a well-informed public. The agency's experience

with the advanced notice of proposed rulemaking demonstrates the need for carefully-prepared regulatory materials, patient, medical professional and public education and ample opportunity for interaction with agency advisory board bodies and personnel.

A few additional comments. First about the time frame. The American Lung Association and the American Thoracic Society are concerned that the proposed decision-making structures fail to provide a suggested time frame for non-essential use determinations beyond the market review after January 1st, 2005. We note only a time frame of one year for the collection of post-marketing studies.

The agency must provide patients, health care providers and the public with detailed time frames, including an estimation of time, for any anticipated regulatory proceeding, in addition to the content of information required.

While there is no consensus at present on what constitutes an appropriate time frame, the agency should seek public comment on this important part of the transition.

The overall monitoring process. The American Lung Association and American Thoracic Society previously commented on the need to establish a mechanism to monitor the overall transition to non-ozone-depleting substance

products.

At a minimum, such a mechanism should include an expert panel appointed to assess baseline information from which to monitor all aspects of the transition. Panel members should include medical experts, other members of the health care team, including nurse educators, pharmacists, and respiratory therapists, epidemiologists, and patients and patient advocates.

Thank you very much.

DR. SESSLER: We have time for questions.

(No response.)

DR. SESSLER: Thanks, Dr. Munzer.

DR. MUNZER: Thank you.

DR. SESSLER: Our next speaker is Mary E. Worstell, with a master's of public health, who is Executive Director of the Asthma and Allergy Foundation of America.

Ms. Worstell?

MS. WORSTELL: Good morning. I'd like to restate my title as Executive Director of the Asthma and Allergy Foundation of America. I'm a health educator by training.

The AAFA is headquartered in Washington, D.C.,

and I have no known conflict of interests as I present to you this morning.

I want to thank the committee for the opportunity to express our opinion this morning, and I also want to compliment the FDA in what I believe has been a very open and inclusive process over the last several years in seeking patient input on this very critical issue.

The position of the Asthma and Allergy Foundation of America on this issue has been stated repeatedly over the last several years in our written comment to the FDA in 1997, in a number of hearings in which we have participated on Capitol Hill over the last several years, and I can tell you that we have not wavered in our support for the transition to CFC-free metered-dose inhalers.

We believe that this transition needs to move forward. We believe it offers multiple benefits for patients. We believe that a plan for transition in this country is essential, and we would agree with what Dr. Munzer just presented on the importance of an oversight for

this process as it moves forward.

We believe that the transition to metered-dose inhalers, CFC-free metered-dose inhalers needs to be seamless for the patient, and when I talk about seamless, I'd like to emphasize certain points.

One is we do need to ensure that patients are educated in this transition, the need for this transition,

the elements of the transition.

As ALA has just presented, you have multiple new products that are coming on the market. We have new mechanisms in these products for patients. We are asking patients to change, and we are all health care consumers, and we all understand that for us to be active, responsible participants in our medical care, we need to be educated and understand what and why we are being asked to make these changes. So we will be working in patient education.

We believe strongly that education of the health care provider is key to this, that health care providers understand this process, understand the benefits of the new products, understand the special characteristics of the new products and can communicate those to their

patients. There is an integrity of the communication process between the provider and the patient that we must use.

In addition, if new information, new technology is communicated with confidence by the health care provider to the patient, the patient is steps ahead in terms of a positive attitude in looking at adopting or adapting to new characteristics of a product.

As Dr. Munzer said, we believe that there is a tremendous benefit in this transition to once again focus on proper diagnosis and management of asthma and to

revitalize the communication between patients and their health care provider. This has been lost, and we need to go back. This is critical to overall patient satisfaction and adequate management of their asthma, and we are concerned about the cost issue, and that the costs of the new products be accessible to patients.

The Asthma and Allergy Foundation of America has a task force of members of our volunteer board of directors and chapter leaders who have reviewed and

participated in the statement of position of the Asthma and Allergy Foundation since 1997.

This task force has reviewed the proposed rule, and there is initial consensus support for this rule. We are now in the process of reviewing the stakeholder consensus comments that we will be presenting to the FDA later this month, and we will be developing a short individual statement for the Asthma and Allergy Foundation congruent with this.

I would really like to say, in addition, that we will be working with the EPA next year to do some preliminary market research to reassess where the health care provider knowledge and attitude focus is on this issue so that we can better target educational messages to these critical health care providers as the transition moves forward.

We will continue to be an active participant in this topic and work as we have in the past with other groups for a consensus position moving forward.

Thank you.

DR. SESSLER: Questions or comments?

DR. GROSS: May I ask a question? I should know this, but I take it most of the membership of the foundation consists of patients and their relatives?

MS. WORSTELL: That's correct.

DR. GROSS: Have you received any individual expressions of concern from patients about not being able to use their regular inhaler because it's not considered non-essential?

MS. WORSTELL: I have not received those kinds of complaints from patients because I'm not sure that the patients understand the politics behind this transition in general.

My experience with communication with patients in principle has been that they have been provided a new inhaler, different from their old inhaler, without any advanced notice and without any information about the new inhalers.

So some of the characteristics have surprised them and disappointed them, which is why I believe that education is so important.

I think that it's simplistic when you just say, as we heard a couple of years ago, that your metered-dose inhaler may be changing, and if you don't want that to change, contact the FDA. It's very simplistic. It's much more complicated, and I believe that when you're looking at the introduction of new medications or change in medications, that provider/patient relationship is where the sense of communication needs to reside.

DR. SESSLER: Thank you.

Our final scheduled speaker is Dolores Libera, who is speaking on behalf of Nancy Sander, President, and Ms. Libera represents the Allergy and Asthma Network and Mothers of Asthmatics.

MS. LIBERA: Thank you.

My name is Dolores Libera. I'm Director of Publications at the Allergy and Asthma Network/Mothers of Asthmatics, AANMA.

I'm giving Nancy Sander's presentation. She was unable to be here because of illness. I don't believe that there are any conflict of interests, and I do want to thank the committee for allowing us to present.

Our comments will be short and direct. We support this version of the NPR because it affords patients every protection without slowing innovation or transition, and the stratospheric ozone is not at risk in the process.

The current NPR addressed the questions that the first one raised and takes preventive actions that patients believe are important. The language of the NPR is far more direct than the first version, and while there are areas of additional clarifications, these mostly affect issues directly impacting the pharmaceutical industry and do not appear to put patients at risk.

We do not understand, however, the specific manner in which grandfathered over-the-counter bronchodilators will be treated. There seems to be loopholes through which these products could receive permanent exemptions.

What actions will the FDA take to ensure that these medications do not slip through the cracks, that prescription-only products do not?

Furthermore, AANMA posted notices of the NPR on our web site and in several other sources. We did not undertake a survey as we did with the ANPR because we learned from the first effort that conducting the survey in a short period as given is costly and comes at the expense of other projects within AANMA.

However, we encourage those people who did visit the FDA web site to read the NPR and forward questions directly to the FDA and to our office. We don't

know what the FDA has received in the way of comment, but

we have received only one letter of concern.

AANMA's questions and concerns as patient advocates have been responded to thoughtfully. The NPR reflects a patient-friendly approach, one in which the best interests of the patients can be served effectively.

Thank you.

DR. SESSLER: Dr. Niederman?

DR. NIEDERMAN: As a representative of the patient group, is there any concern that's been expressed on your web site with regard to losing these CFC propellants?

DR. SESSLER: Ms. Libera?

MS. LIBERA: I'm sorry?

DR. SESSLER: Quite all right.

DR. NIEDERMAN: I'm trying to find out whether, from a patient perspective, you've had any comments that patients are concerned about losing the CFC propellant.

I think this issue was brought up earlier, I think by Dr. Meyer, that patients frequently complain when their inhalers are changed, maybe not really based on any

reality, but has there been a concern expressed by any patients that they're worried about losing their CFC propellant inhalers?

MS. LIBERA: I think originally, when this whole issue began to be publicized, there was a lot more

concern. As the transition has occurred, as we've been able to educate our members through our newsletter and magazine, and as more products have become available that do not have CFCs, there seems to be less of a concern.

As I said, apparently we have only received one letter of concern after it was posted this last time.

DR. GROSS: To what extent do you think your members understand the situation?

MS. LIBERA: Well, I guess I can't speak definitively, but I think we've gone through a very extensive process using the materials that have been available through posters, through specific articles.

We don't receive a lot of phone calls on the issue at this point.

DR. GROSS: You have publications, of course?

MS. LIBERA: We put out a newsletter.

DR. GROSS: Has there been any coverage of this subject in your publications?

MS. LIBERA: I'm sorry?

DR. GROSS: Has there been any coverage of this particular subject in your publications?

MS. LIBERA: We have discussed this extensively, especially since the original ANPR came out.

MS. CONNER: I have a question, also, and, Mary, you may want to address this as well. Have the

patients noticed -- and I don't know whether -- maybe the majority of patients now are covered by pharmacy cards, and out-of-pocket cash is not as much an issue as it used to be.

Have you noticed that the change in the devices or the change in inhalers has increased the costs? Have you seen patients complain about that? Does that appear to be an issue? Have they had difficulty with technique or -- I mean, it just seems that there's not the uproar that I would have expected, and maybe it's because it hasn't impacted that many patients yet.

MS. LIBERA: We just have not had the -- when this originally came up, we had a lot of discussions, but the transition seems to have been fairly smooth in terms of bringing attention to the efforts that are available and assuring that there will be options available.

MS. CONNER: Right. I don't doubt that there will be options. I just don't know if they are aware of maybe the financial impact that may be coming, but like I said, it depends on formularies and what managed care companies will allow them to have, so that that directly doesn't come right out of their pockets, but if they're limited not only in changing what they're familiar with to maybe something that's not a direct replication of that, but yet a total different device because of the formulary

limitations of a managed care company, I just don't know what -- it seems awfully quiet. I don't know whether this is the calm before the storm or --

MS. WORSTELL: I would have to get more specific information from our members than I have right now, but I can tell you anecdotally that the issues of

formulary are real in terms of options.

I have not heard the complaint so much in terms of cost to date as I have in terms of options, and those would go back again because, for example, with Proventil and Proventil HFA a couple of years ago, when it was first coming on the market, the products, the HFA was made the only Proventil available in some formularies, and the switch was made without any kind of education of the patient, and that was the issue.

I did not hear about costs at that time. Certainly, I think there are concerns, particularly, for example, some of our board members, some of our patient advocates, because of changes in employment and changes in health care, they have stayed with their regular physician, and they don't have the same kind of insurance reimbursement, and they're paying the costs of their medication out of their pocket. Those costs are real to those patients, and that is an increasing issue, and I think as we see more products come on the market, the costs

will become more of a topic.

MS. CONNER: And I have to commend both of

these organizations. I don't know if the other committee members are familiar with them, but it's going to be organizations like The Asthma and Allergy Foundation and the Asthma and Allergy Network/Mothers of Asthmatics that are going to play a pivotal role in this education that's going to be so necessary in the transition because their newsletters get to the public and to the population that's most affected by this type thing, and they are sort of an unbiased resource of information, and I think they do a great job.

DR. SESSLER: Thank you.

Dr. Meyer, the over-the-counter bronchodilator issue was raised. I don't know if you would care to speak to this at this time or later on.

DR. MEYER: Well, I think I would like to make one point in that regard right now, and I think perhaps the committee may choose to raise it again later, and we could talk further, but I think the main issue I'd want to clarify is that right now, epinephrine is being treated the same as every other short-acting bronchodilator, meaning that it would be considered on a moiety-by-moiety basis, and we would anticipate that it will have sort of the same paradigm as the prescription products.

Obviously it is somewhat of a different issue in terms of when you get to the broader discussion of the asthma armamentaria in the 2005 and beyond range. It has perhaps a different role from the prescription products arguably, but there's certainly no -- it's not carved out as having essentiality forever.

For one thing, the Montreal Protocol doesn't allow that, and that was not our intent. Our intent was to include it in this rule as any other moiety and treat it as any other moiety.

I gather that some of this question about whether it's got more protection is because of its market niche more than anything else, but we're not intending to treat it differently.

DR. SESSLER: That concludes our scheduled speakers for the open public hearing component. I'd like to now open the floor, if you will, to any other individuals who wish to speak before the committee in this area.

(No response.)

DR. SESSLER: There appears to be no other speakers. So what I'd like to do is we've got about 35 minutes or so left, and what I'd like to go forward with is really to start the discussion of some of the discussion points that we are scheduled to address in the afternoon,

and the first of these, I think, is an important one.

The order that was created by Dr. Meyer and company, I think, is on target, in that I think some of the issues that are basic issues, specifically comparison of the different devices, I think, is a useful starting place, and particular questions that I have, and what I would like to do is invite commentary from the committee as well as from FDA individuals about some of the comparison between dry-powder inhalers and propellant-driven types of inhalers, such as the HFA formulation, with the specific limitations in mind.

In other words, not so much does this meet the needs of the general population, but really how about some of the other members of the population, such as children or the elderly or those who have limited air flow capacity, or environmental issues, such as excessive moisture in the environment and things of that nature.

Are these products really comparable? The follow-up point within that bulleted point is really what about novel devices?

So I'd really like to toss it open. I don't

know, Dr. Meyer, if you want to make any opening comments in that regard or if there are other individuals here who have data or established expertise. We'd be interested in their comments as well and then open comments by the

committee.

DR. MEYER: I think I covered sort of our concerns on this discussion point earlier. So unless people had any questions going into it right now, I'd throw it open to discussion.

DR. JOAD: I think my biggest concern about alternatives is that there should be something in the regulation that should specifically address anyone who cannot cooperate in any way with an inhalational device. So that's young children who use an MDI with a spacer and a mask or older people with cerebral palsy.

Anybody who can't actually cooperate in any way, there should be an alternative for that group, and I don't think the moiety-by-moiety approach may work for that. I'd be happy to have it work that way, but that might be a place where you needed a class-by-class suggestion, that at least within each class, there need to

be -- if we don't use the word "MDI," and I understand why you didn't do that, but there needs to be some sort of phrase for a type of portable inhalation device that requires no cooperation.

DR. SESSLER: Dr. Fink?

DR. FINK: Yes. Well, in use of the alternative devices, such as one, the budesonide Turbuhaler, I think initially I was concerned about it

being a pediatrician, and one of the things that had been very helpful there that I think the FDA could encourage is the fact that Astra made available a whistle that would show whether a child could reach adequate air flow to use the device properly has been very reassuring in introducing the device as well as reassuring parents, and the only improvement on it I could see is that if the whistle were actually built into the actual device, that the dry-powder inhalers could potentially have incorporated into them some kind of patient feedback mechanism to ensure that you've reached adequate peak air flow to deliver the dry powder, that this would really be helpful.

It's nice to have the whistle separately, but if it were actually integrated into the device, it would be even nicer.

DR. NIEDERMAN: I just want to reiterate a comment I had made earlier, and that is that we're focusing a lot on alternative MDIs and on dry-powder inhalers, but there are other types of devices that are out there. I've seen one demonstrated that's a breath-actuated nebulization in a portable device that's electric and takes liquid and would be very easily used.

So I think we have to, first of all, hope that this regulation is going to encourage through the free market system development of products like that, and,

secondly, I think if we're going to make a specific requirement in a moiety-by-moiety analysis, that we have to have an MDI specifically available that may turn out with better devices coming to be unnecessary.

We may have devices coming that are easier to use than MDIs, easier than dry-powder inhalers, and we may not want to be constrained to specifically require that an MDI alternative to an existing MDI, if we can find through

the development process that there are better devices out there.

DR. JOAD: Just briefly, to really make sure it's clear that I really don't care if it isn't an MDI, but I do care that it should be something that requires no, absolutely no cooperation from the patient, that there be such a thing for that group of people.

DR. NIEDERMAN: Or at least that it be not any more cumbersome than the current MDIs. I mean, I'm not sure that you can totally take out cooperation with the current MDIs even with a spacer device. I think you need some cooperation.

So I think the standard has to be that it's no more patient cooperation-dependent than the current devices.

DR. JOAD: I'm talking about a spacer with a mask.

DR. GROSS: I'd like to extend those concerns. I think the biggest concern that we should have, one of the biggest concerns from the patient point of view is that in

five years' time, there are going to be 25 different ways that patients have available, doctors have available to prescribe for treating airways diseases, and we don't really realize how fortunate we are at this particular time that pretty well everything we want to administer through the airways, we can do with the same device, and once you know how to use a device to inhale albuterol, you don't need to be taught again how to use the same device to administer some other drug.

But that obviously is all going to go away, and I have concerns that I'd like to address to the patient advocates and particularly to the two members that we heard from this morning that one of the biggest educational tasks that they're going to be facing is that all of their membership is going to have to learn how to use not just one new inhaler but a different new inhaler probably for every drug they have.

Unless one drug company is fortunate enough to come up with an idea that's so good, that it simply waves the other alternative agents away, and everybody wants to deliver their medication through that one new device, I don't think that's very likely to happen.

So I think that we have to get used to the idea that everybody who wants to use a drug will probably have to use it through -- every manufacturer who wants to make a drug available probably will have to do it through a different agent. That's really just an aside because I think it's really a matter for the patient and their family organizations to arrange to make sure that the education is there, and obviously the FDA can't do that for you, but you and your cooperation with other organizations, like the Thoracic Society, and certainly with the pharmaceutical industry, who are very interested, I know, in promoting education and how to use their product well, I'm sure that will have to be done very quickly.

But I would like to ask the FDA. Are you confident that the industry is moving appropriately in terms of the speed? Do you think that we will have all the agents that we need to use by the year 2005 in CFC-free form?

DR. MEYER: I think the industry has certainly been tremendously responsive to this in general. I think that it is clear, in fact we've publicly discussed in congressional testimony and other places, that we're fairly well aware that there are some products, you might call them more minor products in the armamentarium, that we do not have any evidence that they're being considered for

reformulation.

So we know there are some products that the sponsors are not attempting to reformulate, and so I guess in general, it seems like the industry's being very, very responsive, and there will be perhaps alternatives for most of the major players.

There clearly will be some that are either straggling or perhaps not reformulated at all, and they will present some, I think, challenges in the transition process.

MS. CUSUMANO: The only thing I would add to that is that 2005 is when we might start looking at those products that haven't been reformulated. So it's not necessarily a date when everything that's CFC's going to go off the market.

DR. SESSLER: Dr. Kelly?

DR. KELLY: I guess the question that comes up is on the approach that Dr. Joad talked about, was what do you do for the existing non-approved uses of the CFC MDIs?

Dealing in pediatrics, we've been using them for non-approved uses for a long time, and that has to do with the face mask and spacer devices, and if you look from a regulatory point of view at the moiety-for-moiety in just

looking at the approved uses, you might be missing some of your patient population, and have you thought about how you

are going to approach it in terms of all the unapproved uses as well?

DR. MEYER: Certainly, I think the way the notice of proposed rulemaking is written, there's sort of an upfront expectation that we're talking about a product that has a moiety, a product that has a moiety with the same indication as the CFC alternative.

But we clearly wrote the rule having in mind that there are going to be other uses, other than the approved indications, that we need to consider, and I think that that will be part of the discussion that occurs at the time of notice and comment rulemaking or any other approach that we are taking in the future when we go to delist a specific moiety. We will need to consider such uses.

I would add that the agency, through a recent revision in our Act, has much more authority now to really upfront expect pediatric trials specifically, and I think that we are very anxious to even look at some use that we

know is going on, even if it's not approved, in terms of the safety and efficacy of that, and that could include things like the use of spacers and masks and so on.

So there's perhaps not a neat answer for that right now, but I think we're building in ways in our notice of proposed rulemaking to address this, and the agency also has other ways that work at least for the pediatric

population that we're going to be getting such data that will be helpful for our ultimate assessments.

DR. SESSLER: One of the questions that I have relates to the impact of moisture on the dry powder. That was mentioned, I think, in the original presentations, and I guess I don't have a good feel for the magnitude of that.

Is it really a substantial barrier in regions or locales that have extremely high humidity or what are the real limitations? I don't know if you have data or if a member of the division is an expert on DPI and perhaps familiar with the European experiences and so on. If you could comment.

DR. MEYER: Well, our chemistry staff is most intimately involved with these issues, but they require

testing during the development of any of these products, including the dry-powder inhalers, of exposures to certain conditions, including high humidity conditions, and I might add that those high humidity conditions are perhaps even perhaps a little bit lower humidity than might be experienced in some regions of the United States. You know, Louisiana in the summer, for instance.

DR. SESSLER: Richmond.

DR. MEYER: Yes. Even Washington, D.C. But I think the other side of that is the chemistry staff is also very realistic about wanting to make sure that these

products hold up under those high humidity conditions, and really they pay a lot of attention to those sorts of issues.

But it is the reason why some dry-powder inhaler products are overwrapped, come in sort of a foil pouch, or in fact, others have deskins actually in the device, and it's the reason why some of the ones in the overwrap, for instance, have an in-use period.

In other words, they have instructions that

after it's been taken out of that pouch for a certain amount of time, they're no longer considered as within their expiration date, and because the particle size does shift over time due to humidity, and so we're fully confident that when used as directed, that they will perform safely and effectively.

But I think the industry knows, and we know, that some of these are susceptible to moisture and that changes the way they need to be handled.

DR. SESSLER: I guess as a follow-up, is the magnitude sufficient that this should be an additional consideration in terms of -- and I know it has been in a therapeutic class, that I believe you mentioned the original proposal included two different approaches to drug delivery at a minimum.

I don't know if that disappears with the

moiety-to-moiety approach. For example, for inhaled corticosteroids, is it possible that they would all be dry powder, and is our concern overstated about the moisture problem or is it something that if we feel confident that every single delivery system was similar, would that put us

in to difficulty for certain patient populations?

DR. MEYER: I think for just the issue of an adequate alternative on a moiety-by-moiety basis, that, for instance, if there were a dry-powder inhaler approved for a moiety that was delivered in CFCs, but there was no alternatively-propelled MDI, if that DPI's approved, then we are confident that it will perform sufficiently well in all the circumstances that are likely to occur.

I mean, there's always surprises, and I'll come back to that in a second, but if it's used correctly in all regions of the United States, according to the labeling, that it will perform adequately.

The question is if that means that after it's taken out of the overwrap, it's only good for three months, is that an adequate alternative? I mean, issues of inspiratory flow aside, is that an adequate alternative, knowing that perhaps some people keep their CFC inhalers in their gym locker at the Y for a couple of months, and if they need it, they go grab it, the gym locker room being a fairly moist place.

So I guess that's the question. We know that they will perform sufficiently when used as labeled. I alluded to there being surprises. I don't mean from some sort of a regulatory standpoint. Patients sometimes will do things that you can't anticipate to, but that's true of MDIs as well.

DR. SESSLER: Dr. Jenkins?

DR. JENKINS: If I could just follow up on that as well. Moisture is not only a problem for dry-powder inhalers, it can also be a problem for the metered-dose inhalers. It seems counterintuitive that moisture can make its way into those canisters, but I've been surprised to learn since I've come to the FDA that it can, and it does.

So you may even see in the future some of the alternatively-propelled metered-dose inhalers may have protective foil overwraps and may have dating periods after you've taken them out of the overwrap, how long they might be in specifications.

So it's a big problem for the dry-powder inhalers, but it's not unique to the dry-powder inhalers. It can affect the metered-dose inhalers as well. Moisture, it's everywhere, and it manages to get to wherever you don't want it to get.

DR. SESSLER: Thank you.

Any comments from the pediatricians here? I

know we've heard already a little bit. That seems to be again one of the special populations that we want to be sure that the device issue is adequately addressed, given the important differences between kids and adults.

Any further comments from the pediatric folks?

DR. FINK: Well, what's currently on the market doesn't meet the needs terribly well, and hopefully there will be some better novel devices out there.

The spacer/mask combination is usable, but you don't know how much it's delivering, and it sure is not the kind of thing you like to do repetitively to an infant. It's not usually a good maternal/child interface.

So I think that there's real room there for something novel. I mean, something that was a liquid, electrically operated or battery operated liquid device or that a dry-powder device that created a cloud. I mean, I don't know what people are going to come up with, but definitely some better devices for the minimally-cooperative patient would be appreciated and needed.

DR. JOAD: Well, I just had a concern when you mentioned that when they reformulate, they may not have to reformulate in the same doses, and just getting at our use in very young children, I wouldn't want all of those doses to be higher than what's presently available.

25 MS. CUSUMANO: That's what Bob had referred to,

to a degree, but with the 1998 pediatric rule. When a company files an NDA or a supplement, if there's pediatric use for the product, they'll have to do a pediatric assessment, which could include the development of a new formulation.

DR. JENKINS: Actually, one of the positive benefits, if you want to view positive benefits of the transition, is that it has spurred a lot of innovation. So we're no longer in a scenario where everything is just focused on CFC-based metered-dose inhalers.

There's a tremendous amount of innovation going on within the pharmaceutical industry, not only for the HFA MDIs and the multidose dry-powder inhalers, but there's also a lot of innovation going on on other unique and novel delivery systems.

So we may get a side benefit from this transition that we actually get better devices, and in many ways, they're being stimulated by the need to reformulate where maybe they would not have been so incentivized in the past. So that may be a plus.

DR. SESSLER: Any other comments related to delivery devices?

DR. FINK: Just one comment that has been an improvement in some of the newer devices, like the Diskus or the Turbuhaler. It would also be the opportunity that

as MDI replacements come along, there has for a long time been a problem of deciding when it's empty and requiring manufacturers to have some kind of built-in feature in the device so that when drug is no longer available, the device somehow indicates that it's not delivering drug any further.

DR. SESSLER: I'm going to move ahead to the second bulleted point, and this will probably finish up the morning session. The question is posed: how can FDA best determine the medical needs of patients who previously have relied on CFC MDIs are being sufficiently met?

So this is kind of, certainly, how can we do it? Yes, we need to do it, but the question really is what suggestions from the committee and others do we have as to the how?

DR. NIEDERMAN: I think that this is going to be a key issue, and we're certainly going to need to rely on patient reporting and post-marketing surveillance, but I guess the amount of data that's available now through insurance companies and Medicare and so forth probably would allow access to monitoring general admission rates for asthma, ER visits and so forth, and I think that that's going to be certainly one important end point to look at.

If we saw an upturn in the amount of emergency visits for asthma during a transition period, I think that

would be very important data to have. So I think there's going to need to be multiple levels on which this is looked at, but I would encourage that part of the program involve some of the larger databases that will be available on a community-wide level to be looking at general use of emergency services for asthma.

DR. APTER: I guess I would most like to see randomized clinical trials in patients. Those data are very useful, but they can also be flawed. For example, sometimes outpatient prescriptions by the physician are not linked to pharmacy bases or not linked to emergency room

visits and hospitalizations. So it can be useful but very difficult.

DR. NIEDERMAN: I think that's good, but --

DR. APTER: So ideally randomized trials comparing head-to-head, the old with the new, would be most ideal.

DR. NIEDERMAN: But I think if we require that in order to license a new product, it's going to discourage some of this innovation and development, and I don't know how much licensing you're going to require or how much demonstration of efficacy you're going to require before, say, a novel device gets licensed for the delivery of, say, albuterol.

DR. MEYER: It, I guess, depends a little bit

on the moiety in question. If it's an already-accepted moiety, there undoubtedly would be some streamlining to the number of trials and the types of trials that might be required, but we certainly would expect adequate demonstration of safety and effectiveness in the intended population and then perhaps, in some respects, a long-term

trial to both look at the safety of the formulation but also how the new device holds up over time in terms of performance in patient hands.

DR. NIEDERMAN: Well, as a matter of just understanding, when the albuterol HFA was released, what type of data was needed in order to get approval?

DR. MEYER: There is some pre-clinical data, some toxicology data to look specifically at the reformulation that would be expected for that sort of product. There are dose-ranging trials which, for bronchodilators, generally can be single-dose cross-over trials to compare it to the CFC product, and then there generally would be at least one, and I'm forgetting now that with Proventil HFA, whether it was in fact more than one 12-week adequate and well-controlled randomized trial in comparison to the CFC product to see how it performs, and then the one-year safety study to look at in an open-label fashion how the patients tolerate it over time.

DR. NIEDERMAN: So presumably any new product,

no matter how it's delivered, HFA or novel device, in order to get approval as a replacement is going to have to go

through a head-to-head comparison with the CFC product?

DR. MEYER: For a product that's essentially a new formulation, contains a previously-approved moiety, one of the paradigms there for the sponsor to do an abbreviated program is for them to compare it head-to-head to show how it compares to the prior products, and we can rely on our previous finding on safety and efficacy to help label the new product.

They have the option of doing a full new program and not comparing it head-to-head, but again in an abbreviated program, we would expect some level of head-to-head comparison to allow us to rely on our previous findings.

DR. NIEDERMAN: And if, hypothetically, an HFA version of a generic albuterol were to become available, would that be immediately accepted or would it also have to be tested and compared since there's a branded albuterol HFA available?

DR. MEYER: Well, it would be like any other approval of a generic, and basically they have to show bioequivalence. So it has to be the same in terms of its pharmaceutics, and then they have to prove bioequivalence, which, for the albuterol products, basically means doing a

very rigorous single-dose cross-over comparison to the innovator product and showing that it acts the same.

So in some ways, that particular study is more rigorous than we're asking for, like Proventil HFA did not have to show bioequivalence, but, on the other hand, for a generic, that's all they have to show. They have to show that they're pharmaceutically the same and then bioequivalent, and then they're done.

DR. NIEDERMAN: So if those trials aren't adequate, then I would still think monitoring some sort of larger databases will give you some general trends, maybe not accurate but certainly you're going to have these comparative data, and you're going to want the reassurance that the asthma field hasn't changed because of the availability of these new products.

DR. MEYER: I think clinical trials, well-controlled clinical trials tell you a lot, but they don't tell you certainly everything, and particularly they're very well-groomed patient populations that are taken into them. They're the only the patient populations for which the drug is indicated, and I think we're very much interested in the post-marketing period about what happens in the patients who are using it for other indications off-label or more severe patients than were the clinical trials or younger or older, so on.

And then, finally, just due to some of your statistical limitations, if you have a database of a thousand patients, you're not likely to pick up a very rare event. So if there was some rare reaction to the formulation, we wouldn't pick that up in clinical trials, unless we were quite lucky, either. So.

DR. SESSLER: Dr. Kelly?

DR. KELLY: Yes. Actually, I think the clinical efficacy and safety trials are the easiest part, as you alluded to, and it's the clinical effectiveness studies that we all struggle with on how do you get that, and I'm not sure large databases from, say, Kaiser or something like that on emergency room or hospitalization is even sufficient.

What I'd be more interested in is, you know, how many school days missed in a patient population because of less patient acceptance of a particular device, how much work days are missed.

Can we somehow get to those types of populations through employer data, and I don't know whether that's possible or not, but I think you're looking at using

the current things that we use now, you're just looking at the tip of the iceberg of asthma.

You can define clinical efficacy, but in terms of the acceptance by the patient population, what you want

is the effectiveness.

DR. MEYER: Let me make a statement in that regard and then invite you to comment back or invite anybody else to comment back, because I think if we're effective -- we being the FDA -- in gaining communication with the patient community, either through their advocacy groups or otherwise, I think the patient community, perhaps knowing that they've shifted a product, will be pretty good about coming forward and saying, you know, since I switched on this, I don't think I'm doing as well.

I think that we're probably more worried about specificity than sensitivity from that kind of data. So I guess if we do our job in terms of communication with the patient community, I suspect we may at least get some handle on important differences. That's perhaps not the ideal way to approach it, but I think that that will be one thing that will be available to us.

So I offer that as a comment and see what you think. It's not rigorous, but certainly again I think patients are quite sensitive to switching products, and if they do, and they detect a deterioration in their treatment, as long as there's a way for that to be transmitted back to us, I think that we'll at least have a signal there.

DR. SESSLER: I think one of the important

questions, also, is availability, moving away a bit from the specific characteristics of the drug and safety and efficacy, but availability in particularly the underserved populations and the risk for them perhaps having less in the way of asthma control.

Are there ways of coordinating efforts in terms of epidemiologic studies and funding for those studies with other government agencies, such as NIH, to look at this not so much as it relates to a single drug product but really the care of asthma in transition? Is there a way of having our voices heard and the FDA's voices heard as far as enlisting their financial support and so on for actually

doing good epidemiology?

DR. MEYER: I'm sure there are ways that that could be approached outside of the FDA's normal paradigm, and we do have access to managed care databases and such for doing some of our post-marketing assessments, and obviously that's not what you're talking about, and I know that those populations are of substantial interest to many groups, including the NAEPP.

So I think there are opportunities for that kind of partnering. I think that's something we'll need to consider as we move ahead.

DR. SESSLER: Two more comments, and then I think we'll break for lunch. Dr. Fink, and Dr. Joad.

DR. FINK: I would just be very concerned about the use of epidemiologic data and large databases because there are multiple transitions occurring in the care of asthma.

There's the NAEPP guidelines. There's the use of the leukotriene modifiers. We may soon have interleukin modifiers and other products that are not traditional CFC-containing devices that are going to modify the spectrum of

asthma treatment, and these are going to be reflected in any large database, and I don't know how you're going to separate out the CFC transition from all of these other undercurrents in the treatment of asthma that are occurring.

The fact that we're now getting asthma-friendly schools is an accepted concept. I think some of these are going to have much bigger impacts on what we see nationally or even locally than the switch or phaseout of CFCs.

DR. SESSLER: Did you have a comment?

DR. JOAD: Yes. In your head-to-head comparison of the alternatives, are you going to have a required measurement of convenience to the patient as part of that? Did they think of that since that's one of your criteria?

DR. MEYER: I don't think we really envisioned convenience as being something that we would gain a feeling

for out of the controlled clinical trials because, for one thing, most of those trials are done in such a manner that patients are instructed heavily and told how to use it, and

you don't really get a good feel for how convenient they are.

That being said, there are many manufacturers that do sort of ask a general questionnaire at the end of the study of what do you think of this device and often will present us that kind of data for, say, a dry-powder inhaler that's a reformulation of a CFC.

But I think we were talking or thinking more in line of us sort of, from our scientific standpoint, perhaps using input from the committee, where appropriate, on what the level of convenience seemed to be, and any signal or any information that came from the clinical trials would be additional to that but not the primary way of assessing it.

DR. SESSLER: Dr. Vollmer?

DR. VOLLMER: I've been puzzling over the various issues around this question. It seems to me that you're inevitably going to be doing a mix of both clinical trials certainly in the pre-approval phase as you're looking at head-to-head comparisons and how things shake out.

I would concur that taking account of more patient focused outcomes, such as quality of life and sick

days and days lost from work for parents, are going to be relevant outcomes to be looking at, but once the drug is approved, you're going to have certainly access to it and an enormous amount of post-marketing data, and even acknowledging the difficulties that were raised about secular trends and what else is going on, I think it's going to provide useful information.

As I thought about the way this talking point was phrased, how can we best determine the medical needs of patients who previously relied on the CFC MDIs are being sufficiently met, it seems to me there's two issues buried within that.

One is a suggestion that there may be adverse effects associated with the new devices in particular populations either because they're not able to use them properly or whatever, and that's going to have to be looked at closely, and to the extent that there are anticipated concerns, I think a lot of the patient advocacy groups in particular are going to have to be important spokespersons as these drugs are being brought forth in the development process so that we take the time to look properly at their use in those groups.

The second issue is even if there are no adverse effects from their use, there just may be populations that are unable to use them, as was pointed

out, and so that issue about patients being underserved needs to be looked at and monitored probably in post-marketing data or whatever of who's really using these, and that's going to inform the process of dropping the essential classifications from the CDCs that are currently being used for this population.

So it seems it happens in two stages. First, often the original approval, if there are concerns, you're going to have specific head-to-head focus comparisons to look at what happens. Are there potential adverse effects or problems in using these medications?

If that doesn't surface, you still have the opportunity in the post-marketing data to find out whether certain populations really wind up using them for whatever reasons, and if not, then it's going to be important to keep the alternative CFC formulations available for those populations until something else comes along that does work for them. So you have a little bit of both things going on.

DR. SESSLER: Thank you. I'd like to thank everybody for their comments.

When we start back, we'll be heading right back into post-marketing. So it's related, and so if you have

additional comments related to this issue, I think it will fold in nicely with that.

We'll meet back here at 1:00 and start on time. Thanks.

(Whereupon, at 12:02 p.m., the meeting was recessed for lunch, to reconvene at 1:00 p.m.)

AFTERNOON SESSION (1:04 p.m.)

DR. SESSLER: Good afternoon. I'd like to go ahead and bring the afternoon session to order. I hope everybody got fuel for a lot of good discussion in the afternoon and not too much fuel so you fall asleep.

Before we start, Dr. Meyer had something he wanted to address, I believe. We'll come back to that, I guess.

The afternoon is devoted to addressing a number of the talking points that were raised by FDA for committee discussion, and we've already gotten well into that with some good conversation on the first couple of points.

The third point really ties in with the second, I think, in terms of a nice segue from patients' needs to

post-marketing data, and I think some of the conversations that we were having just before lunch can easily be carried right into how this might translate into post-marketing data discussion as well.

So I'd like to read that and then just toss it open for comment, and then when Bob gets back, we'll ask him to make a comment about one of the other points.

What kind of post-marketing data will be most helpful to ensure patient needs are being met, and that the product is proving to be reliable and acceptably safe in broader use?

I know there has been some discussion already about post-marketing data with, I guess, differing views to a certain extent. I'd like to toss it open for comment from any committee members.

DR. FORD: I'd like to concur with some of the comments that Bill made and the two Bills, Bill Kelly and Bill Vollmer, about the need for studies that assess clinical effectiveness, and I would also suggest that there, it would be appropriate to really look at some

process measures because one of the issues that's going to really come up is, you know, how good is the education that's going in, and in interpreting effectiveness data ultimately, part of what we will have to know is whether or not the message is breaking down at some point in the chain, although I would expect that with increasing experience with a product, that that issue would be addressed, but it might be worthwhile monitoring whether or not -- you know, how much confusion there is in practice, let's say, in terms of the different maneuvers that patients have to learn to do effectively.

DR. SESSLER: Anything specific that you or anybody else would like to add? I think one of the things that FDA is always interested in are specific approaches. If we have any experience with it or any particular ideas?

DR. FORD: In studies, just to follow up on

that, if it were possible to in fact have data about whether or not, one, providers are communicating properly to patients in terms of how to use those devices should be a no-brainer.

I would think these devices are easier to use

than the MDIs, but on the other hand, it's probably worthwhile to look at that and that's just built-in process measures in general, and this would be one of them.

DR. NIEDERMAN: Curt, I guess I'm confused about one thing. If there's a new product that becomes available without a CFC, will the CFC product be available, say, during the first year while the product is being trialed or has FDA decided?

DR. SESSLER: I think the answer is yes, but Dr. Meyer can comment.

DR. MEYER: Yes, unless the company chose to do otherwise.

DR. NIEDERMAN: Because I think that that provides an immediate opportunity for post-marketing studies, to see with different products the ease of acceptance compared to the CFC and what the usage patterns are, because I'm not sure how you're going to mandate that.

In other words -- and I'm not sure how you would regulate that. I think that may be an important issue. If you get an HFA version of an inhaled steroid,

and you have the CFC version on the market, particularly if the costs are different, how do you get shifting from one to the other, and depending on what the answer to that is, then the monitoring of that shift may be one post-marketing way to look at the efficacy and the acceptance of that product.

DR. FINK: I think if the pharmaceutical companies are as aware of marketing as they usually are, a company's going to be faced with the decision that they either come out with both at the same price or they're going to price their new product lower because if they price their new product higher, then they've got to stop production of the CFC-containing device, and people aren't going to switch to a new product if it's significantly more expensive if you leave the low-priced alternative on the market.

DR. NIEDERMAN: Yes, but I think the problem might be if there's a generic version of it or a CFC alternative to it. You're right. For the one company that does it -- I mean, I think you take the example of albuterol HFA. Schering, I guess, eventually stopped making Proventil in favor of Proventil HFA, but --

DR. FINK: They still make Proventil, I think.

DR. NIEDERMAN: I'm not sure. I'm not sure you can get it, but you can certainly get the generic

albuterols with CFCs, and we talked earlier, but I don't know whether it's the product or it's the price that accounts for the fact that the uptake was so low.

At least it's something you can monitor. The question is, it probably will tell you different things about different products, depending on what products are remaining with CFCs in that moiety department or that class.

DR. SESSLER: Dr. Fink?

DR. FINK: One comment that's really not post-marketing, but as the newer products come out, one thing that I think would help, particularly for post-marketing surveillance and for general medical care, is if FDA could come up with some kind of standardized recognition of packaging, i.e. that inhaled steroids had to share a blue stripe, and then they could be any other color, because as a clinician, I can tell you that if you look at the various color array of MDIs out there right now, and you talk to a patient who's using two or three different MDIs, trying to get a straight history of what they're taking of which drug is difficult.

I don't know whether it should be moiety-by-moiety or class-by-class, but using some coloration of packaging to help physicians identify what kind of drug

you're dealing with would actually potentially be very

helpful both for the physicians and for the marketing.

DR. SESSLER: Let me just ask a follow-up to that. Are there requirements that have been -- is there precedent, I guess, for anything like that, either in pulmonary drugs or in other areas?

DR. MEYER: I think I may need to defer at least part of this to Dr. Jenkins from a broader center perspective because there may be some areas -- it strikes me that there might be some paradigm like that for some of the ocular medications, but I'm not entirely sure on that, and I don't know whether Dr. Jenkins knows either.

But it's not something that we have historically looked at in the Pulmonary Division. I know the U.K. does something very similar to that, where I believe the short-acting relievers are blue and the corticosteroids are brown or something like that, make color coding up tomorrow's product interesting, but --

DR. JENKINS: I don't think there's been any effort to do that with pulmonary products. There have been efforts in some other parts of the agency. For example,

there's some standardization of insulin labeling so that they have the same nomenclature and the same symbols for regular insulin versus other types of insulin, and I think there's an international working group that's working on trying to come up with standardized colors and labeling for

the various types of insulin, but that's not been something that's been considered or done in the pulmonary side of drugs so far.

DR. SESSLER: Along the lines of post-marketing surveillance, there's certainly a body of data from Europe and from other places where some of these products will have been approved and in use for some period of time, and this was alluded to by Mr. Jamieson as well.

What is the value of the European data, do you think, in terms of should it impact on the type or the amount of post-marketing data that we collect here in the States?

DR. MEYER: I think there is certainly value to non-U.S. data. That can be somewhat limited by the type of question we're asking here in terms of what kind of data we

actually can glean because we're asking some questions different from the usual regulatory questions.

The other thing I think that I should point out is that the non-U.S. versions of these products are not necessarily the same product as the U.S. version. So there would be, I guess, in theory, instances where the non-U.S. data clearly would not directly apply to the U.S. product if the products were different.

DR. JENKINS: Curt, maybe to stimulate some discussion, one of the parts of this question that we've

discussed internally, and I think Mr. Jamieson actually touched on also, is whether, when we talk about post-marketing data, should we be happy with the passive surveillance type of data that we've been talking about around the table or do you see a role for actual studies that, you know, have a protocol and have a design, maybe some sort of large simple trials or real use type of trials?

There was a trial of that nature that was done with the Proventil HFA product. It's actually called Airomir in the U.K. There was a post-marketing

surveillance type of prospective study that was done in general clinical practice, and I guess we're interested in hearing the committee's thoughts about are those types of studies worthwhile? Should they be required? Should they be requested? Where do you see those fitting in to the overall schema of collecting this post-marketing data, really getting to the issue of are patients' needs served?

DR. JOAD: Could you just explain a little bit more what that is? What post-marketing large study is?

DR. JENKINS: Well, if you go back and look, remember that the pre-approval clinical trials are very rigorously controlled. They have very selective entry criteria. So you actually generally end up with mild to moderate asthmatics who are fairly compliant with their

medications, and they're in a rigorous 12-week clinical trial with a low of follow-up.

A post-marketing type of study that may be of a simpler design might be more of a general practice type of study, where you in some way randomize patients in practice to one therapy or the other, but you're kind of following

how the drugs are actually used and not proscribing so much up front about entry criteria, exclusionary criteria, indications, et cetera. It's kind of that type of more simple design, real-world type of experience.

DR. JOAD: I think it's an excellent idea. I think you should have something like that afterwards.

DR. SESSLER: Actually, why don't we --

DR. JOAD: Outcome, right.

DR. SESSLER: Why don't we do something a little bit differently? I haven't done this type of thing. We've had such good conversations, but I think this may be a good time to go ahead and we can go around the table and offer an opinion, because I think it's an interesting way to get everybody to voice their questions and concerns and ideas.

Jean?

DR. FORD: I think large simple trials or other kinds of approaches to post-marketing studies, but that in particular would give us a sense of what's going on in the

real world, and if the studies are designed so that they can be informative also as to why we get this or that

result in terms of clinical effectiveness, I think that that would be useful. So I would think this is a good approach.

DR. VOLLMER: I'm biased towards research since that's what I do as my bread and butter, but I'm trying to be as objective as possible in looking at this question.

Certainly the kinds of studies that you're describing would garner a lot more insight into what's going on. It sounds like you'd be doing things above and beyond what you normally do for regular drugs that are coming through.

Questions that might be of particular interest to me might be if you have access to a population-based data set, and you can look at utilization profiles in the period prior to this coming on board -- I mean, looking at what's happening, so that would allow you to address on an individual basis the extent to which their utilization or compliance with medication seems to be changing for one medication versus a different medication. To the extent that you have different groups, and you can follow them in parallel over time, you can also look concurrently at that, but you'd also want to be careful to try to stratify populations, sort of case mix that analysis, so that you

can be looking at the more or less severe segments. You can try to identify people who may be taking medications for other co-morbidities that you're particularly interested in.

So can you identify through these databases some populations who have other co-existing diseases that might make them particularly at risk here? So there's certainly quite a bit you can learn from it, but to do it right, it's an expensive undertaking.

DR. APTER: Well, I think studying post-marketing drug use will be important, too, and it might be a way to test educational programs for the new medications and in different groups with different educational achievement to see how well various programs are accepted, to help patients to use the new medications, in addition to things like quality of life and the other outcomes of patient satisfaction, plus efficacy, in terms of disease.

DR. FINK: I guess I'm not as convinced that post-marketing studies are going to be very valuable. If they are global, I think they're going provide too little control and too little data to really tell us anything.

So I would support potentially targeted post-marketing studies that are addressing specific questions, like compliance in three- to six-year-olds or adherence or medication efficacy in an age group, but I think global

post-marketing studies are really not going to probably yield much useful information.

DR. GROSS: If I understand the question, it's how are you going to make sure the patients are willing to use new devices and do actually use them, and obviously that's a very, very important question, and I don't know whether it's because it's after lunch, or I'm just generally losing my creativity, but I really can't think of a good way to do that, unless you do it in a controlled clinical trial pre-marketing, or as part of the marketing process.

I mean, it could take you an awful long time to get enough data together from kind of casual studies post-marketing, and I don't have a great deal of confidence in those studies anyway and the outcomes.

I would think probably what Andrea suggested this morning is the best way to do it, is just simply to say we have to do a randomized study where some patients get the traditional inhaler and other patients get the innovator, and you follow clinically-relevant outcomes, number of visits to the ER, number of unscheduled doctor

visits, amount of rescue medication if that's, you know, an appropriate outcome, and, you know, the usual and traditional measures, like peak flow, and things like that.

But I guess it's going to take a lot of

patients, and it will be maybe quite difficult to evaluate these studies, but I just can't see any other appropriate way to monitor whether patients are using their new devices and whether they're actually getting the medication. I just don't see any shortcut to getting that information.

DR. JOAD: I do think it's a good idea to do that kind of a study. I understand it won't be as complete as what you do for the pre-marketing approval, but I think you'd get a lot of good information, and you do have to get some sort of sense of how convenient it is and how much people approve of using it, and from what we've heard, it doesn't sound like you can count on the market to make a place for it in such a way that there's a way to evaluate it.

DR. SESSLER: I think it's an interesting area that has a lot of different potential answers to it. I don't know if we have an ability to do a more aggressive

passive surveillance, if that's something that would be useful in terms of reaching out and trying to learn about populations that are missed with this or that suffer from, you know, underserved populations and so on, or those who are having difficulty using the device.

If you're going to do prospective trials, it seems that they really have to be based on clinically-meaningful outcomes in terms of missed days of school or

work or outcomes that are, if possible, directed in that direction rather than physiologic changes.

It's an important question. I think it's a hard one to answer, though. Some of those things might be helpful, I think, some of the ideas that have been presented so far.

Dr. Kelly?

DR. KELLY: Like the other Bill, because I do research, yes, I do more research. That way, I can get more money.

On the other hand, when you start thinking about all the things that we've been talking about in terms

of different groups and trying to stratify by those different groups, those are enormous studies, very large, cost a lot of money to do, and in order to get enough patients in some of those groups that we're interested in, I'm not sure that a prospective trial is capable of achieving that because even in those post-marketing trials, you end up with patients that are willing to participate in a trial, even if it's for a year, and so it's a lot different than patient population as a whole that we're interested in.

So unlike everybody else, I have no answers, just questions. I think there are databases out there that can be mined, such as Medicaid DUR databases, databases in

large HMO populations, that can set up a relatively rigorous change, and if you could convince a very large HMO and then some state Medicaid programs, which deal with different types of populations, and looking at the introduction of the new devices in those populations, you might get a better handle of acceptance and utility in those populations than setting up a prospective trial.

DR. DYKEWICZ: Well, I've got a few thoughts.

One is that even with our conventional MDIs, we know that despite sometimes fairly aggressive efforts at instructing patients in how to properly use inhalers, if you look a month or two down the road, the patients really are not exercising very good technique, and if we're looking at some of the CFC alternative products that might have a little bit more complexity to them, to their working, there might be more of an issue with fall-off of clinical effectiveness because of problems being consistent with the device utilization, the technique of utilization.

So I think even though to some extent, this echoes the points that have been made earlier, that we may be going above and beyond what is currently required for, let's say, the CFC-containing MDIs, there is the concern that unless we do something, we may be seeing some drop-off in patient effectiveness that had not been anticipated.

The other thing that comes to mind, and I'm not

sure whether this would be pre-marketing or post-marketing, but one of the questions, of course, is going to be whether or not if you introduce an alternative innovative product,

whether all the subgroups are being properly cared for, could be cared for by using such a device, and I think if you're looking at large population studies, it's going to be nearly impossible to glean any meaningful data about that, and you really are going to have to have some active studies that will focus on particular subgroups that could be anticipated to have some problems.

For instance, those patients who have limited capacity to cooperate with device use, and so I think in that sort of a more focused way, it really would be essential to have some active studies, perhaps cross-over studies, looking to see whether patients that have some limitations of that sort could be successfully maintained on the innovative product.

DR. NIEDERMAN: I would agree that you need post-marketing data. You need to see if these drugs are effective, and you need to see if they're being used. But I think that for a number of reasons, I think it would be a mistake to talk about a prospective randomized control trial.

First of all, those are being done to get the drug approved in the first place. Second of all, if I were

a patient, I'm not even sure what the motivation for enrolling in one of those would be, and probably most importantly, it's not a real-world observation.

I think what you're really asking post-marketing is does this product work in the real world? Will people use it? You certainly can't answer that question with a prospective randomized control trial.

I think what you really need to do is you need to observe what's happening after the product's out there, and I'm not sure exactly how to best do that. I think as I was saying earlier, I think you may have the opportunity, particularly if the CFC product remains on the market, to look at the different usage patterns and look at the outcomes of patients who are using the new products, but as much as we may criticize databases, and there are multifactorial issues that may play a role, if we see that after the introduction of new products, measurable outcomes, like ER visits and asthma mortality rates or anything else that we look at, are getting worse, we'd probably know that there's a problem, and if things are getting better, whether it's due to the other new medicines or the inhalers, it probably means that things are reasonably acceptable.

I think again things like looking at technique and monitoring that doesn't seem real world to me. I think

again the bottom line is even if a patient could demonstrate to me that they know how to use their inhaler, that doesn't prove to me that they are using it and that it's effective, and it's dealing with any of the outcome issues.

And I think the other issue that to me is very important here is, I think we have to look specifically at passive, not active, databases because I think it would be an unreasonable burden to put on the industry to tell them that after they've gotten the drug approved, they now have to fund research to document that that drug's effective.

I think it's going to discourage people from getting into the field, and I think it's going to further add to the cost of these new products. So I think that we haven't talked about these post-marketing studies and who would pay for them, but I think that if we ask for randomized trials, if we ask for detailed studies of particular populations and how they're using these products, I think it would discourage a lot of people from getting involved in this field, and I think it's going to add to the cost of these new products.

So I think that probably additionally is a compelling factor for looking at available data that the

agency could pull out of existing databases and trend specific numbers, but I think it would be a very big burden

to ask the pharmaceutical industry to develop these products, do the trials to prove they're effective, and after they're approved continue to do research to document that people are using them.

MS. CONNER: Being last in this list forces one to be creative with ideas and coming up with things that haven't been said before. My tendency as a consumer representative and as a nurse educator is to think about not necessarily just efficacy and safety. I think we have proven that or it wouldn't be approved by the FDA. It wouldn't be out there.

What we need to look at is maybe some type of a survey or questionnaire before the patient ever gets the prescription about their usage habits of their current MDI, their nocturnal wakenings, their absenteeism, their parents' absenteeism from work, and then maybe a similar questionnaire six months later, 12 months later, and if it's on an office visit, you get sometimes a little better

participation than if it's a mail-out questionnaire.

The same thing with technique, and it's not just patients who have difficulty with technique. If you remember the Interiano study, nurses were the worst and doctors were just above them just a little bit. Patients were actually better at technique than some of the physicians.

So we need to reevaluate technique, and especially as we're adding more and more devices with different techniques, we all need to brush up on that and stay current with it, but every time the patient comes in, reevaluate their nocturnal symptoms, their indirect medical expense, like absenteeism, patient missed days from work, and it's patients that report data, and some of it's anecdotal, but it may be a pretty good source of information.

DR. SESSLER: Any comments from Dr. Meyer or Jenkins?

DR. JENKINS: I think we got a pretty broad diversity of comments and feedback.

DR. VOLLMER: Having listened to the group, to

stimulate some further thoughts, I think this was brought out on several of the comments. I think the biggest potential advantage of sort of outcomes research post-marketing as opposed to a randomized trial is that it does get at more the real-world situation. I mean, that's the big advantage.

Any randomized trial that we do is going to have a very self-selected population, as was pointed out, and so the generalizability of that's questionable. Also, as was pointed out, you're going to have done any number of randomized trials to get the drug approved in the first

place.

So to the extent that you're going to gather, I think, a lot of new information, other than truly long-term effects, in a randomized trial, I don't see a lot of merit requiring those.

I was wondering whether the FDA currently requires any kind of post-marketing data for newly-approved drugs. To the extent that it doesn't now, I would feel that it wouldn't make sense to require it for these new

medications coming out.

I think that post-marketing studies are going to be done. People are going to want them done. They're going to want the information, and whether it's the pharmaceutical industry or NIH or whatever, some of that work's going to get done, but as to whether it's worth changing current FDA policies regarding what they require to be done, I would have a hard time supporting that.

Again, you have plenty of work done up front to look at the safety and efficacy of this trial, of these drugs in randomized trials. So really the issue is what's happening out there in the real world.

DR. MEYER: Just to speak to what the FDA currently requires, I guess it perhaps doesn't help you in helping us because for sort of the routine drug, where there's not a particular issue going into the post-

marketing period, typically we would not require any post-marketing studies.

However, if there are questions about the drug's safety or effectiveness in certain subpopulations, there are certainly many drugs that have Phase IV

commitments that are agreed to by the agency and the sponsors at the time of approval.

So it's sort of a mixed answer, that both paradigms exist, and I think one could argue about whether an HFA reformulation in and of itself would represent such a level of scientific interest or regulatory interest, whether you'd require a Phase IV commitment, but I think when you add on the issue that this may be the product that leads to a safe and effective product that contains CFCs no longer being able to market, it may change the balance some.

DR. VOLLMER: If that's what you're currently doing, then I would suggest that much the same is going to continue to happen. With the close scrutiny that these medications are going to get, if there are concerns about special populations that may not be adequately having their needs met, you can bet that those are going to get raised, and therefore if you're requiring post-marketing types of studies in the past in those conditions, I can't imagine that you're not going to be also requiring them again in

these kinds of conditions.

If nobody's raising those concerns, it's probably a fairly safe bet that there's no large population out there anyway, you know, a special population that's likely to be affected because again there's a lot of people looking very closely at this.

DR. SESSLER: A number of the comments here have led right into the next bullet point, which really deals with subgroups. What subgroups of asthmatics or COPD or other respiratory patients need to be specifically considered in the determination that patients' needs are being met?

There really has been a fair amount of discussion surrounding this. I'd like to see if there are additional comments. Michael?

DR. NIEDERMAN: As I'm listening, I just want to caution, I guess, that we not try to solve problems that we can't solve already with these new products.

A lot of the issues that have been brought out about inability to use inhalers correctly and days lost from work and quality of life, those are issues now today with our current technology, and to think that if we can't solve them now, that somehow that's going to become the standard by which we ask these new products to meet, it's very unrealistic.

I think that there are inherent problems in asthma that can't be solved by these new medications, and I think we have to be very careful not to set standards that try to solve again all of the problems which currently exist that we're not able to solve, and I think that particularly when we address special groups, we have to ask ourselves, if special groups are having problems now, that's the baseline to which we want to compare our new technique, and we can't ask reasonably a new device to solve the problems that special groups have now that can't be solved with the current technology.

I don't think that's the purview of what we're trying to address today.

DR. SESSLER: If I'm interpreting where the FDA is coming from this is, I think if there is a change in technique or a change in availability, would that adversely affect selected subgroups? Yes?

DR. JENKINS: I think a point we all need to keep in mind is that normally, when we are approving new drugs, whether it be a new molecular entity, a new formulation of an existing drug, we're approving that thinking that it's going to go into the market and become part of the overall armamentarium for the disease.

This is a different paradigm, where these

products are being specifically developed to replace existing products. So when we approve these non-CFC alternative products, there's an intent through the Montreal Protocol and the Clean Air Act that if those are acceptable to patients, they're going to replace the old products, and part of the question we're trying to get answers from you are, how can we be certain that we're not going to make things worse?

We certainly may not be able to address some of the concerns that are out there now, but I don't think we want to make things worse by making a determination that the alternative product meets patient needs, and you declare the CFC product as no longer essential, and the CFC product goes off the market, and then you find out that maybe it really didn't meet patient needs.

So it's a very different paradigm, and that's why we're asking these difficult questions.

DR. NIEDERMAN: And I think the opportunity is presented to you by the intention of having both products on the market initially together, and I think that that allows usage studies. It allows compliance studies. It

allows outcome studies which can be sorted out by which type of device patients were using, and I think that -- I guess that's all that I'm really -- I agree. I think that all you really want to document is that you're not making things worse. As you said, your intention is to make

things better. You're simply coming up with a replacement product.

DR. JENKINS: If I could go back, the previous point that we were discussing about the post-marketing data, it seems as we went around the room, we got kind of, you know, several different opinions. Some people advocated for asking for post-marketing studies, other people thought that they weren't all that useful, and some people said yes, they may be useful, but we're not sure we should advocate for them.

I think we heard from Mr. Jamieson's presentation earlier that the industry association, their position is that the FDA should not be requiring these studies, and that we should be relying primarily on the spontaneous reporting system for adverse events and drug

product quality problems as well as any data that can be garnered essentially passively, and I guess what I'm interested in hearing from the committee is, how do you feel about that proposal?

Not specifically point counterpoint with IPAC's proposal, but to date, we have not required any of the non-CFC products that have been approved, we have not required them to do any of these large post-marketing Phase IV studies designed to help us address this issue.

At the end of the day, when we have the

alternative, and we start making the determination, is it meeting patient needs, do you think we're going to be able to adequately do that by relying on the post-marketing reporting system that we have, the Medwatch Program, the quality reporting of product failures, European data, other foreign data? Is that going to be enough to address the issues about meeting patient needs, subpopulations being adequately served? I think that's the key point.

DR. KELLY: Well, I guess a half response to that, John, is I guess my problem is I don't think a large post-marketing randomized trial, even though it's not

blinded or anything, just a randomized trial, which a lot of these post-marketing studies are, is going to answer that either, and I think I would fall on the side of going after larger databases along with the self-report system that we already have in terms of going after those small entities and groups, and as long as we have the CFC available until we have that information back, the community as a whole should feel fairly comfortable.

DR. JOAD: I think what I was getting at when I mentioned the market issue is, I think barring some financial incentive to go to the alternate product, the people that will use the new products are likely to be, I would guess, people who are concerned about the environment, people who are likely to work harder on their

inhaler technique and are generally more compliant or adherent, and I think if you really want to see how something works in the real world, post-marketing, you're going to need to assign people who are similar to either get that one or get the alternative or the CFC product, and maybe a simple questionnaire at the end of a year would be

sufficient or end of six months.

It doesn't have to be so detailed, but something that looks at real people who are really randomly assigned to get the alternate product compared with the CFC product.

DR. SESSLER: Dr. Apter, and then Dr. Vollmer.

DR. APTER: Dr. Fink mentioned earlier that these drugs will be coming on the market when other things are happening, like other drugs. Well, there are other things happening in the health care world while these drugs are being changed. Less time to talk with patients, less time to educate them, and so I think it's very important to study what's going on, and especially in the high-risk groups, which are the underserved populations.

It may not be the obligation of the industry that brings these drugs to market, but I think it's important. I think that all types of designs are important, too. Looking at big databases tell you some things and randomized trials and focus groups tells you

something else, and all would be important, so that these new drugs don't make things worse.

DR. VOLLMER: I'll give you an example of a specific study that I might envision and when I might envision it, not necessarily as each new drug product comes out, but when you're at the point of removing the essential status from a given moiety, at that point, you have one or other alternative competitors that are out there. I believe by your criteria, it has to be at least two.

At that point, you could go out to HMOs or a variety of other people that have access to large databases and query them. Maybe you've got two or three years of experience with some of these things now, and you've got a situation where you have both kinds of products on the formulary because to some extent, if there are unmet needs in the population, that these aren't working, then they're going to be demanding some of the other drugs.

So you can go out there and ask who's using what kinds of drugs, and in particular ask the question of the people using a given moiety, who's using the CFC formulation versus the alternative formulation, and you can take a look to see whether its release to the population -- I would be serving this population. So I'd try to find out not only their age, sex, patterns, but their co-morbidities and actually survey the patients and potentially the

providers and find out what are the factors that are causing you to be using this product and not another product?

Is it just that they just simply refuse to change in the absence of any effects or can they give you quantitative reasons why they can't use a product or, I mean, do you have some unknown reason?

But there's a situation then that you're several years out, things have sort reached somewhat of a steady state, particularly if there's multiple different alternatives for people to be using, and then you can see, and they may not all be using Drug A, some might be using Drug B and Drug C, but who's still using the old drugs, and is that selectively one population? Is it kids under five years of age? Is it individuals over 70 who have cystic fibrosis or whatever as a co-existing disease?

So you're able to get some insight into who's still using them and why they're still using them.

DR. SESSLER: Dr. Fink?

DR. FINK: I think the other issue with marketing, there are products out there, and I think, unfortunately, when you look at post-marketing surveys, and you're particularly asking the questions you're asking, the immediate introduction of the drug is when you're going to get the patients who are either poorly controlled on

current medications or want to switch, to take up the new drug.

The group you're asking about is going to be the last group to take on the use of a new drug which is going to be to the patients who are well controlled on the current agent and see no reason to change or those patients who are wedded to the current agent and don't want to change, and they're going to be the last group to transition.

So unless you do your post-marketing studies at the end of the transition, you're not going to answer the questions you're asking.

DR. NIEDERMAN: Yes. I would just caution against looking at some of the end points that you've mentioned because you're presupposing that people are going to have equal choice about which they use, and I think a lot of this is going to be driven by cost, and I think that these new inhalers -- for example, to pick on albuterol since there's generics, I can't imagine any of the newer ones are going to be any equal in price to the existing CFC ones, and I think a lot of this is going to depend on what

type of insurance you have, whether they'll pay for the new devices, and whether you've got to pay.

DR. VOLLMER: That's a very good point, yes.

DR. NIEDERMAN: So I think that you have to at

least focus on outcomes rather than patient choice because patient choice may not truly be choice. It may be driven by cost.

DR. VOLLMER: That's an excellent point. Part of what you can do with that is you can also look at a variety of different providers as well as the fee-for-service sector, but you can go to a variety of different managed care organizations and see what's on the formulary and ask them why. If Drug A is not on their formulary at all, no CFCs, is it because they've simply said they don't -- they only choose to go with one drug and that's the way it's going to be because they don't want to be buying more than one or what have you.

So gaining insight from a variety of different providers as to how they're stocking their formularies would also be -- and what's driving that is also an important piece.

DR. SESSLER: Dr. Gross?

DR. GROSS: Yes. I want to make the same point exactly. I think probably the most potent factor in terms of willingness to require the inhaler and use it is going to be cost, there's no question about that, and I don't think there's going to be any question about the fact that the new ones are certain to cost a lot more than the existing ones, and you can get a generic albuterol inhaler

for a couple dollars, and I can't see any new devices being able to deliver the same cost per dose at less than probably between 20 and 30, if that, and so I mean, that's going to be a hugely potent factor as to whether patients actually use it.

So in real-world studies, patients will have to pay for their own medication because it's not real world otherwise, and the question really is, is the patient going to pay 10 times as much, and if they do, are they going to get as satisfactory outcomes as they can get?

So I think one should be prepared for the fact that asthma control will go down, and I don't see any way

out, and there's a huge subsidy for the medications that we use right now.

So you have to look at things like emergency room visits, unscheduled doctor visits, time lost from work, time lost from school, your real-world type of outcomes. Whatever study you're doing, that's what you're going to be looking at.

But I believe that you can't really get meaningful data unless you have a control group, you know. I mean, I think you have to figure out some way where you can say, well, is this really meaningful or how does this compare with what? You know, it's always a question of what you're comparing it with, and so I would say pretty

strongly it has to be some kind of controlled study; otherwise, you really don't know what the data mean.

I mean, just think how we're still arguing about whether beta agonists in general are bad for you or not. You know, 10 years ago, you had a very same meeting in this town as to whether beta agonists were safe or not. Well, maybe it wasn't 10 years, but it was probably eight years, and should the FDA institute some additional

controls? We're still arguing about that. We don't know because these are all post-marketing type of questions, and it's very, very difficult to do it when all these agents are available, and you're not doing a controlled study. You really can't tell exactly what it's due to, what your outcomes are due to.

So I would think before you make any drastic steps and make the conventional agent unobtainable anymore, by which time it's too late to squeeze the toothpaste back in the tube, you need to do some kind of controlled studies, looking at real-world types of outcomes rather than the traditional one, which is FEV1 and peak flows and so forth.

DR. SESSLER: I think from my perspective, if prospective randomized trials in the Phase IV type of setting were to be undertaken, it probably should be focused on patient groups for whom there is some perception

that there might be a problem, perhaps specifically related to drug delivery, which would translate into long-term drop in effectiveness and could be measured in terms of real-day

outcomes in terms of ER visits and missed days and things of that nature.

But, you know, randomized prospective trials are resource-dependent, and so by focusing perhaps on those areas that might be highest yield, the ones that are of the greatest concern, the elderly who may not be able to generate adequate inspiratory flow for some of the different instruments, or the pediatric population, something like that, might be, rather than a global general population base, make it more specifically focused.

Dr. Ford?

DR. FORD: After hearing all of the perspectives presented, including my own, I feel like saying all of the above.

(Laughter.)

DR. FORD: And the reason for it is that it seems to me that we're coming at this looking at different aspects of the question in terms of what's going to happen after these drugs are introduced, and certainly if we want to look at the impact of costs and access on efficacy, a randomized trial may indeed not be the approach because most likely it would be providing medications and so forth.

So that would not be real world.

So I am favoring now perhaps a targeted approach, that is, on the one end, that is utilizing multiple approaches, depending on what the question is. If, for example, we want to know what the impact is going to be on certain more vulnerable populations, well, not necessarily vulnerable but the very young and patients who have trouble generating peak inspiratory flow that is adequate, of course, randomized trials, carefully-designed studies, with that subgroup of patients might be the appropriate thing.

But in terms of costs and access and so forth, I think it may just be appropriate to look at large databases with the caution that even among the databases, there is going to be some variability among populations as to how informative they can be.

I mean, it's really a question of generalizability, as I think you started to mention here, because the HMO population in one city may not necessarily reflect the same kinds of challenges that my patients face in Harlem, and by the same token, I'm not even sure that the Medicaid database in New York, which by the way is not largely an HMO database, you know, our patients are primarily not in managed care right now, would be informative.

So I think what really this is coming at is the need for, I think, what Dr. Sessler is mentioning implicitly here, some really hypothesis-driven kinds of studies, utilizing either databases or clinical trials, when appropriate, based on issues that we think would have a foundation, considering what we understand about how these delivery systems work and the mechanisms by which the drugs have their effect.

DR. SESSLER: How was that, John?

DR. JENKINS: Are you ready to move off the subgroup issue?

DR. SESSLER: Yes, yes.

DR. JENKINS: Because I'd like to really make you earn your keep today by helping us define what are subgroups? We've been using that term a lot today, and we've talked about some general terms, but what really constitutes a subgroup?

I know Ms. Cusumano in her presentation talked about a subgroup of one for some of the patient comments that came in. They consider themselves to be a subgroup of one, and that it was very important to them that they not lose access to the medication that they felt was the only one that provided them benefits.

So I'd be interested in any wisdom you have about how should we define the subgroup, how large is a

subgroup, and how do you address those issues of single patient concerns?

DR. SESSLER: Takers?

DR. JOAD: I just want to repeat what I said this morning, that if you include this as a subgroup that must be served, people who cannot cooperate at all in the inhalational devices, at least for each class, that you're not going to leave anyone out, that that would include young children. It would include neurologically-abnormal people. It would include several different groups that don't need to particularly be named, except that they can't cooperate in any sort of breath-activated, put your mouth around a mouth piece, effort.

DR. GROSS: I would also state what I guess is obvious, and that's the elderly, particularly because they lack manual dexterity. They lack coordination, synchronization. Many times, they can't read very well, can't see very well, and they're particularly challenged

when it comes to using inhalation devices.

DR. SESSLER: You know, I might chime in on the elderly, echoing Dr. Gross's comments, and, in addition, I think the cost issue is substantial for some of the elderly in terms of them falling kind of in that gap, and I think that's true for the working poor as it were, that the monthly costs of medications is substantial and worthy of

consideration in terms of -- I don't know if that fits into a subgroup, but at least it, I think, brings another facet to the elderly as being a high-risk subgroup, I guess.

DR. NIEDERMAN: Well, Curt, I would agree that all these groups make sense, but I would caution again that these are groups that we have problems with today, and so if we're going to study them, we have to study them in comparison to the reality of what we've currently got as problems and not expect again these products to do better than we're already doing.

The one group that hasn't been mentioned today, and at least in my practice is a substantial group, is the pregnant woman, and I guess we haven't considered whether there are issues with these new delivery devices that have

to be specifically looked at in pregnancy.

We thought a lot about the individual active ingredients, but I don't know if the propellants would have any relevance during pregnancy and whether that needs to be studied separately. Certainly asthma's an important disease in pregnancy.

DR. SESSLER: Any information to share in that area, Dr. Meyer?

MS. CUSUMANO: That was one of the comments that we had received on the advanced notice of proposed rulemaking, that I think all but one of the currently-

approved drugs are Pregnancy Category C, is that right, or I think all but one are C? I think there's one in B.

DR. VOLLMER: What does that mean? Pregnancy Category C?

DR. NIEDERMAN: It means we don't know.

MS. CUSUMANO: Well, it means different levels of effect --

DR. NIEDERMAN: I think C means that there is not enough convincing data one way or the other.

DR. MEYER: With some hint in animals that there may be some teratogenic effects or other pregnancy effects. The X is clearly bad. Thalidomide-type. A is we have good data to say to use it. B is --

DR. NIEDERMAN: But I guess what I'm asking is even if you took a component that was Category B now and put an HFA in it --

DR. MEYER: Right.

DR. NIEDERMAN: -- is it still Category B?

DR. MEYER: Right.

DR. NIEDERMAN: And what do you have to do to reach a conclusion about that?

DR. MEYER: Right. I think that is an issue that's been raised before, and one that we certainly need to grapple with as we move forward.

I think we do have some data about the exposure

and pharmacokinetics of the HFA, and it's quite minimal as it is with the CFCs, but I guess there's both that question, and this, also, I think, in terms of the comments we got to the ANPR, we're also in the situation where we can't expect the new products to necessarily leap hurdles

that we haven't gotten information on for the current products.

In other words, if we don't know enough about to use albuterol CFC, it doesn't quite seem reasonable to make the HFA product prove that it's any better or worse.

DR. NIEDERMAN: I don't think it has to prove it's better.

DR. MEYER: Well, or even to prove that it's not different, if we don't have any reason to believe that, for instance, the HFA would be particularly risky for that population.

DR. NIEDERMAN: Okay. I guess that's what I'm asking. Is that enough to know that -- because there's two questions in pregnancy. One is the obvious one of teratogenicity, but the other one is efficacy, and if there's an inherent difference in efficacy, that can affect the outcome in pregnancy as well.

MS. CUSUMANO: The only other thing I would add is that the agency as a whole is looking to increase the information and drugs generally, pregnancy labeling. So

we're aware that it's a need, not just in this category.

DR. MEYER: Yes, and I think the efficacy issue as it would be for many of these subgroups is somewhat product specific. For instance, one could theorize if you had a large abdominal mass, a fetus or a large baby in your abdomen, that you might have impaired inspiratory flow and might not be able to use a DPI quite as effectively as if you were non-pregnant.

So in other words, I think that there might be some specific products where we might have more of a question about whether there'd be sufficient efficacy in that population in pregnant women as there would be for other subgroups. But I think that might very well be product specific because presumably, although there are some differences between the way CFC MDIs and HFA MDIs are likely to perform, I don't think the efficacy in the pregnant population would be anticipated to be substantially different.

DR. SESSLER: Any other comments? Dr. Ford?

DR. FORD: Yes. I think it's been alluded to, but I also think that perhaps we should introduce it as clearly as possible as a potential subgroup, that is, urban, low-income and minority populations, because, clearly, in terms of who is bearing the brunt of the epidemic, we all know where areas of asthma, of severe

health care utilization and so forth and other outcomes for asthma, where they map out to, and I think that on the one hand, we would want to be reassured that, you know, we at least don't do so bad as we are right now overall, but I think that by the same token, things are so bad right now, that we don't want to wait to find out that there might be issues that undermine the effectiveness of asthma therapy with these new devices.

We wouldn't want to wait too long to find out about that. So I think it's really important to look, to monitor what's going on in those populations.

DR. KELLY: I would echo that, because I think the major problem in that population is access or one of the major problems, and if we're talking about changing from CFC is going to change access, then that's a particular population that we might be very interested in.

DR. SESSLER: Dr. Jenkins?

DR. JENKINS: I'd like to continue to mine a little bit with the committee the issue of the subgroup of one because we do get that type of comment a lot in the agency, either in response to the ANPR, we got a lot of comments of individual patients who said for whatever reason, that they could not be treated with any other drug than Drug X, and we also get those comments periodically

with a company for whatever reason, either has a temporary

shortfall of their ability to make a product or they stop making a product, we get lots of calls from concerned patients, saying, you know, that's the only product that works for me. What am I going to do?

So what I'm really looking for to mine a little bit with the committee is a lot of the things we've been talking about so far with regard to subgroups have been more access-based issues or they've been functionality issues of can't generate the peak flow, can't understand how to use the device, and what I'd really to hear you comment some on, do you believe there are physiologic differences that would make individual patients respond to one inhaled corticosteroid and not respond to another inhaled corticosteroid, regardless of what dose you might give them, and the same would be true for beta agonists.

We had this discussion some in the 1997 meeting because at that point, the agency had proposed one option being the therapeutic class approach, which said that once you had a couple of options in a therapeutic class, you could consider the other members of that class to

potentially no longer be essential, and we had some discussion about whether that was a valid assumption from a physiologic standpoint.

If you respond to a beta agonist, can you expect that they will respond to a different beta agonist

or do you think they're truly patients who only respond to one molecule?

DR. SESSLER: Our pharmacologist?

DR. KELLY: From a clinical pharmacology point of view, no. Having been around for 25 years, I think you get a different perspective, and I have a similar perspective that Bob had shared about changes in metered-dose inhalers and, you know, going for metaproterenol to albuterol. From patients, you always hear that, and you always hear of, you know, relatively well-educated patients.

We had a lawyer that, once we put him on inhaled steroids --

(Laughter.)

DR. KELLY: Speaking of subgroups. Who, even

though we put him on inhaled steroids and better control, he said, "Every time I get in trouble, I still go get my Tederol," and so there is that problem, and it's a real problem from the patient's perspective, and most of the studies that we've done, that people try to look at and find those things, you can't find those differences, and so from my perspective, those N of 1s, I think they're real problems, but I don't know how to deal with them.

DR. DYKEWICZ: Well, I'd like to flip the side of the coin, so to speak, to the, if you will,

idiosyncratic responses in terms of effectiveness, but then idiosyncratic responses in terms of side effects, and that would be an issue. There might be some people that seem to get adverse effects from one agent within a class but not from other agents in the class.

DR. JENKINS: Right. That's a valid point, and I intended, when I made my point, to include that. There are documented cases where patients may be responding to an excipient, for example, an inactive ingredient that's in one formulation that's not in another formulation. So I should have put that in as a caveat, and there's obviously

also physiologic differences between different beta agonists. Some have more selective beta adrenergic effects than others.

So I was trying to target more on efficacy, but recognizing that there are potential differences and adverse event profiles because of the molecule or because of the formulation.

DR. FINK: From a doctrine of fairness approach, I'd take a different approach to defining subgroups and throw out the number 50,000, in that if 50,000 is the number of pediatric individuals who have a use for a drug to be considered significant and require pediatric studies, I'm not sure why we shouldn't use a similar criteria for asthma and say if a subgroup is less

than 50,000, it doesn't meet the federal criteria of significance.

DR. SESSLER: And that's based on --

DR. FINK: Good pediatric rule, which says that if a pediatric use of a drug is only considered significant if there is a group greater than 50,000 who would benefit

from the use of the drug.

DR. SESSLER: Is that precedent recognized?

MS. CUSUMANO: I would just say that the flip side of that rule is it's an or, or provides a meaningful therapeutic benefit. So using the number alone maybe doesn't tell us the whole story.

DR. FINK: No, but I think the point is we're splitting down to some of these very small groups that we would not be giving credence to in development of other drugs, other classes of drugs, and just because this is a replacement -- I mean, there's part of me that says this is a replacement process or a transition process.

There's part of me that says this is no different than any other transition from injectable antibiotics to oral antibiotics, QID to oral antibiotics, BID to oral antibiotics once a day, and we didn't require post-marketing surveillance to say were people happier with an antibiotic once a day than an injectable.

You know, there's some people out there who

would say the injectables work better, and I think maybe because of sensitivity to the issue, we're almost being

overly responsive to it.

DR. VOLLMER: Yes. I don't know what the number would be, but I think that is just a restatement of the point that Dr. Niederman's made repeatedly today, which is that we shouldn't set a standard for these new compounds that we can't meet for our current compounds. You're always going to find individuals now who say they can't take a medication, they're having trouble, and so it's just unrealistic to expect that we're going to do better than what we can currently do now.

DR. SESSLER: Any other comments?

(No response.)

DR. SESSLER: Why don't we switch gears in a pretty major way? The next couple of bullet points really deal with the moiety-by-moiety approach. The first is, is FDA's proposal to utilize a moiety-by-moiety approach reasonable, given the special exception for moieties with more than one product?

The follow-up is, if a moiety-by-moiety approach -- ever tried saying that? -- is taken, how should FDA determine when remaining CFC products that are not being reformulated are no longer needed?

So I'd like to toss that open for commentary.

MS. CUSUMANO: If I could just speak for a moment to the paren there, given the special exception for moieties with more than one product, this was something I didn't emphasize in my talk, but under the proposed rule, we've suggested that for products marketed under more than one NDA or in more than one distinct strength, there would have to be at least two replacement products, and that's what that paren means; whereas, in other cases, it would just be one.

DR. NIEDERMAN: Explain what that means for, say, albuterol.

MS. CUSUMANO: Albuterol's marketed under multiple NDAs. So there would have to be at least two albuterol replacement products before we would propose removing the essential use for albuterol.

DR. KELLY: Well, beclomethasone comes in two strengths. So if it comes in two strengths, then it would require just those two strengths or two replacements period of any sort?

DR. MEYER: For sort of regulatory simplicity, we combine these concepts, but they are somewhat different. I think beclomethasone actually has both considerations.

DR. KELLY: Yes.

DR. MEYER: Just as there's two different NDAs for two different strengths. I think the feeling is that

for the multistrength products, that it would be hard, I think, to argue particularly if you were reformulating, say, the higher strength, that that was an adequate replacement for a product or a moiety that's available in two or three strengths because there could be some populations who specifically need the lower-strength product. For instance, pediatric populations.

DR. KELLY: So what that means is that you would need replacement for the particular indications or strengths that are out there, not just that you'd have a dry-powder inhaler and an HFA inhaler as two replacements?

DR. MEYER: Right. And again, that's not really explicit in the rule, but that's behind our thinking, that, you know, folded into the other criteria then would be all the subpopulations that are served, and if there were two high-strength, one being a DPI, one an MDI, alternatives available, but there was no alternative low-strength product, and it was clear that that was needed for proper treatment of asthma patients who were below the age of 12, for instance, just as a hypothetical, then we would not consider that an adequate replacement.

MS. CUSUMANO: I just wanted to add to that that it's not necessarily a one-to-one, strength-to-strength replacement because of the issue that was raised earlier, that it's possible that, you know, with the

reformulation, you might only have to take one puff versus two, something like that, but that if there are particular populations that need particular strengths, then you would want to have that available for them.

DR. NIEDERMAN: I'm not sure how you would answer that question, but I can see again, as I'm thinking about it with the moiety-to-moiety approach and the rules you've made, the following problems.

We talked earlier about how if you happen to have a CFC product that's unique, and that nobody else can make, there's virtually no motivation to develop an alternative because you'll not be declared non-essential for a long time.

On the other hand, when you take the example of albuterol, if what you're saying is as soon as there are two non-CFC alternatives, all the generics are off the market, there's a great incentive for the HFA makers to

band together, make another product and get the generics off the market, and the price goes up dramatically again.

So I'm not sure how you're going to deal with that, but I can see certainly from an industry perspective, the potential for behavior to optimize profits, which is what they're in business to do, that can undermine this whole process.

DR. DYKEWICZ: Now, as I understand it, the

second question, of course, was if a moiety-by-moiety approach is taken, how should the FDA determine what remaining CFC products that are not being reformulated are no longer needed?

Now, my understanding about the two-phase process again is that when we get up to 2005, that would be the point when that type of an assessment would be required, whether the remaining products that have not been reformulated are still deemed to be essential, and earlier this morning, I was raising the question about whether then there would be an assessment based upon whether there were other available drugs within a class which, I think, is a

reasonable type of an approach to make that sort of assessment.

If you have among, let's say, the inhaled corticosteroids three or four different other moieties that have been reformulated into a non-CFC preparation, then you could make an assessment that, well, you know, the remaining product or two, they're not to be reformulated and are no longer essential.

So I think the general thrust of making some type of a class assessment in 2005, of course, is the year, you know, time line that starts after that point, but I think that's a reasonable approach personally to look at that particular question.

DR. NIEDERMAN: But again, you could do it before 2005. In other words, am I interpreting you correctly with albuterol, that if the second HFA product came out before 2005, all the generics with CFCs would be declared non-essential?

MS. CUSUMANO: What would happen is if we had two acceptable alternatives, we would propose to remove the essential use for albuterol, and we would go through the

notice and comment rulemaking for removal of that.

DR. NIEDERMAN: Because, then, again, it's obvious that the economic incentives are clearly aligned against the cheaper products, and it's certainly going to drive up the price dramatically of albuterol if that happens.

DR. JOAD: Well, doesn't that bring up acceptable -- that could include cost, right, or not?

DR. NIEDERMAN: Again, if you start to think through the real-world ramifications of all of this stuff, it gets very, very complex because I see two cost forces, and neither of which are necessarily looking out for the patient's best interests.

One of them is the industry where we could eliminate generics by having two patented non-CFC products. On the other hand, if I'm a managed care organization, I want to have an exemption for cost because I don't want to

buy these expensive products, and I want to pretend that I'm interested in low-cost products for patient well-being, but I'm really interested because I don't want the cost of

my albuterol that I'm paying for to go up tenfold.

So I really don't think these cost issues are going to be easy to sort out, and I think that there are a lot of, as I say, economic incentives that you can see playing out very quickly that don't have patients' interests in mind.

DR. FORD: I guess the other side of the economic question -- and I think these are very important points. I haven't thought about this. The other side of it also is that once albuterol becomes non-essential, then there's a huge part of the market that opens up to those two. So potentially, there's room for competition and letting the market sort it out, but I agree. I wouldn't take --

DR. NIEDERMAN: Unless now the non-CFC device as in the HFA is patented, and it's not open to everybody.

MS. CUSUMANO: Correct me if I'm wrong, but you're saying the competition between the two products?

DR. FORD: Right. That's what I mean.

PARTICIPANT: It's still going to be more expensive.

DR. FINK: With the example of albuterol, since

it's focused on a lot since it raises a lot of issues, what is its legal status? Because if these products come in as an MDA, wouldn't they potentially then fall under the single isomer rule?

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

DR. FINK: Well, the FDA guidelines that new MDAs, if they're single isomers of the product, and it's known that only one is biologically active, only the biologically active single isomers should be in the marketed product?

DR. JENKINS: That's not really an FDA position. I think there's some misunderstanding. We have not mandated that racemic mixtures can not be approved. We simply have laid out guidance on how you would go about developing single isomer products. That's my understanding of our guidance.

DR. FINK: Okay.

DR. JENKINS: And the albuterol products that we're talking about are racemic mixtures.

DR. FINK: Right.

DR. JENKINS: They don't really get into the issue of single isomer. There is a single isomer albuterol product, but that's not where we were focusing today.

DR. SESSLER: You know, I think the moiety-by-

moiety approach is on target, but at the same time, there may be different general classes of drugs that we need to consider while we're sorting out the details with this.

It seems that albuterol is really quite different than the situation for inhaled corticosteroids, primarily because of the generic drug that occupies the majority of the market right now, and then the third class is really, I guess, the others in terms of aphatropium bromide and long-acting beta agonists and so on, that these are kind of stand-alone drugs to a certain extent.

So we may need to step back a little bit and, rather than focusing attention on the moiety-by-moiety approach globally, maybe we need to specifically discuss inhaled corticosteroids and come to some grips with what are reasonable alternatives there, and I think coming back to the idea of 2005 and the class, the therapeutic class issue, at that point, since we have more than five different active moieties within that class, and yet the albuterol issues are, I think, entirely separate and perhaps trickier in terms of the generic drug and the potentially underserved population.

So it may be that we need to step back a step and look at it with that caveat in mind, that there may be

different groups.

Anybody want to talk about inhaled steroids?

DR. FINK: Inhaled steroids or albuterol?

DR. SESSLER: Well, whatever you want.

DR. FINK: Well, the other approach to albuterol is to say that if we're looking at the NAEPP guidelines, it's grossly overused today. If we bring its usage down to recommended levels of one to two puffs two to three times a week, there's not such a great big market for it, and maybe the problem is that albuterol is just grossly overutilized today, not that we should be worried about its costs, because if asthma is treated according to guidelines, albuterol should actually be used with a frequency somewhere less than the inhaled steroids or other controller agents.

DR. SESSLER: I guess the flip side of that might be that it's the rescue drug, and that certainly it's something we want to make sure, of all the drugs, that it's one that really we don't lose to our underserved populations that Dr. Ford has spoken to, and we want to be

particularly careful there in terms of not making it more difficult for the folks who really represent the epidemic of asthma difficulty from getting drug.

DR. FINK: And how could you handle the non-albuterol albuterols, pirbuterol? Is that a different moiety, and therefore has its own category, so that it could stay CFC and cheap?

DR. MEYER: In that moiety-by-moiety approach, the other short-acting beta agonists, such as metaproterenol and pirbuterol and so on, would be considered separately. They'd be considered as their own moiety.

DR. FINK: And that potentially is a big problem in that if an albuterol replacement is more expensive than the generics, you potentially then are encouraging more production of the moieties, like pirbuterol, that are CFC-containing.

DR. DYKEWICZ: Until 2005.

DR. MEYER: Yes, I mean, it's certainly a thought that has crossed our minds, and I think that's part of the reason why we at least proposed the therapeutic

class approach in the past.

I think that there's some merit to that approach or I don't think we would have advanced it as a possibility two years ago, but I think there are some substantial concerns about it, and I think we acknowledge and understand those concerns as well.

DR. VOLLMER: I was compelled, I guess, I mean, when I read the advanced notice, I liked the recommendation for therapeutic classes. It was pretty clear that you got a lot of feedback to the contrary that came in amongst the thousands of responses that you got.

I was impressed today that all the parties that spoke, both industry and representatives from ATS as well as our consumer group representatives, all seemed to be supportive of the moiety-by-moiety approach, and so since they've had a lot more thought and energy going into it than I, it seems to me it's probably a way to go.

I'd actually like to get some clarity on an issue that Mr. Jamieson raised regarding the requirement that when there's multiple manufacturing sites, that you

have to have a product being apparently produced in multiple manufacturing sites, and they were proposing -- am I correct in assuming this is a separate issue than we've been discussing now? It's not dosing schemes. It's actual different people manufacturing it, and the industry seems to say that's not a problem for them. They're actually happy to have a looser standard. Have I caught that right?

MS. CUSUMANO: What Mr. Jamieson's referring to is actually a statement in the preamble to the actual proposed rule. All we say in the proposed rule is that there must be supplies and production capacity adequate to provide supplies to patients, and one of the things that we thought when we wrote that statement is you never know what might happen to one manufacturing site.

Like Dr. Jenkins was saying earlier, you know, if you have an earthquake in California, and your

manufacturing site's in California, and you're put off line for several months, what are you going to do? Where's the patient going to get their drug from? And it's not necessarily that in that case that there have to be multiple sponsors, just that they have to have multiple

manufacturing sites.

DR. JENKINS: And that's listed in there as a presumption. I think it's in language that says that when FDA is evaluating whether the supplies and production capacity are adequate, that that might be something we would take into account.

It's not an absolute requirement. It's not in the codified section of the proposed rule. It's just trying to explain how the agency would think about those things when we're evaluating supplies and production capacity.

There have been instances where natural disasters have impacted upon the ability of companies to manufacture inhaled products because they have one location where they inhaled the product, and the natural disaster takes that plant off line.

So that's one of the things we were putting in. We did not say it was an absolute requirement. We said it was something we would probably have a presumption that that would be better than not having to.

DR. VOLLMER: That helps. Thank you.

DR. JOAD: I have a comment with regard to my request of there being a portable device that requires no cooperation. In that instance, it seems like it would be unreasonable to have a moiety-by-moiety approach to that request, that a class request would be sufficient for that request. It wouldn't have to be such a thing for every single beta agonist out there, but there should be at least one.

DR. SESSLER: How about inhaled corticosteroids? The reason I bring it up, I think, is a lot of the discussion and examples really revolve around albuterol and around the generic question and so on, but this is, I think, a different kettle of fish in terms of perhaps the pace of development and some of the impediments that are different from albuterol.

Is everybody happy with the moiety-by-moiety approach there with perhaps the 2005 reevaluation of therapeutic class? Is that what you all are kind of thinking about or really am I overstepping, and it's just moiety-by-moiety?

MS. CUSUMANO: I'm just kind of hesitant to use the therapeutic class necessarily, I mean, because what Dr. Jenkins and Dr. Meyer were saying earlier about, is that what we're looking at is the market as a whole. So about

what was said earlier about progress being made in the treatment of asthma, so that we're not necessarily looking at the therapeutic class of corticosteroids, but that if there have been several reformulated, and in 2005, there are some that have not been, but there are a number of other products out there for the treatment of asthma, not necessarily just corticosteroids, under which people are well controlled, and they're happy with their asthma, not missing work, that kind of thing, then looking at the market as a whole and not just the class necessarily, we would talk about whether the essential use was still necessary for a particular product, whether it be a corticosteroid or a bag.

DR. SESSLER: Any discussion?

DR. MEYER: Just as a specific example to sort of flesh that out a little bit, budesonide is not available as a CFC inhaler. It's not really part of this question about the CFC transition. But it could very well be that when you're considering the market, for instance, that the Pulmicort Turbuhaler could enter into sort of the consideration of how the asthmatic population in general is being managed at that time, and, you know, it's quite conceivable that leukotriene antagonist might play into that consideration, other agents that have yet to come, as

we are talking about five years hence.

So we're trying to avoid the therapeutic class terminology, not just because there were so many comments about it in the past, but more specifically because we are proposing something different from that. It's akin to it, but it is different from that.

DR. FINK: For the inhaled steroids, if there are four or five alternative devices available by 2001, would you undertake a class review at that point or would you wait till 2005? Because it's clear we probably will be in that situation by the end of next year, I would think, in terms of having four or five, at least, non-CFC products available. And do you wait another four years before you look at the remainder?

MS. CUSUMANO: Under the proposed rule, we would wait another four years. Now, the flip side of it is what happens with the Montreal Protocol, because the parties to the Protocol would look at our requests, and from that angle, they might not allocate CFCs, but under the proposed rule, we would not look at it until 2005.

DR. JENKINS: I think it's also important to

remember the process that is being proposed here because you can't just focus on the timing at which, say, an alternative product becomes available because in the proposed rule, one of the additional criteria was that we would have at least one year of U.S. post-marketing safety

data. So that takes you out at least another year.

Then the agency has to make a determination that the product adequately meets patient needs and fulfills those criteria and would issue a proposed rule to eliminate the use of CFCs in that moiety.

So we're not going to be in the situation a year from now for the corticosteroids that you were referencing, Dr. Fink, where we're going to be ready to say that things are not essential. This is a process that's going to take time, and I think everyone needs to understand the process.

Today, we're talking about a proposed rule which has no impact until it becomes a final rule, and even when it becomes a final rule, it simply lays out the process and the criteria the agency will follow in making

those future determinations.

So this is a multiyear process that we're talking about here. Nothing is going to happen overnight.

DR. GROSS: I'm trying to figure out, if I was a drug company, why would I have any interest in developing a non-CFC version of my product until the year 2005? Because it's bound to be more expensive, and I'm going to be paying the development costs anyway, but why not put them off until the year 2004, and so until I have to comply, then why would I do so?

Isn't it sort of like the situation with automobile air bags and seatbelts? You know, there was a time when some people wanted to pay a little bit more, but, in general, the manufacturers said we don't want to do this because it's going to add a lot more to the cost, and so they kicked and screamed about that, but when a deadline came, lo and behold, everybody had seatbelts in their cars, and I don't know whether we pay a little bit more for that, I suppose we do, but it just became an acceptable thing.

So isn't this almost the same situation, where basically they're not going to do it voluntarily until

there's a deadline that they have to meet?

DR. MEYER: Well, I think there are various levels of complexity to answering that, but I think the message of the international community is clear, that a date will come when these products can no longer be marketed, and there is not an absolute deadline, and certainly we don't want the message coming out of here that 2005 is the absolute deadline in the United States. So the companies have that.

There's enough vagaries in being able to conduct a good, rational and timely development program, that I'm sure companies would not want to push it off to the last minute.

Furthermore, I think there's certainly

increasing problems with getting access to the CFCs. The companies do have to go through the essential use process, and even then, they have to be able to import these and store them and handle them, and the expense is getting more to be a consideration, too.

So I think there are some clear incentives for

companies out there, but as we discussed for some products, I think that some companies have looked at the bottom line, and for, you know, considering their market, considering what they see as the future for their market, for their product, to look at that and say, okay, when the door shut on us, that's it.

So I think those who want to reformulate, there's a clear reason why they might want to do that earlier rather than later. For those who don't want to reformulate, I'm sure they'll want to take it out as far as they can.

DR. JENKINS: I would add to that that you have to understand that the development of new drugs is mainly a global effort these days. Most of the pharmaceutical companies that we're talking about who market the CFC-based inhalers that are the market leaders in the United States are global companies. So they're working on developing these formulations for the global community, and actually the transition pace may occur more rapidly in other markets

than it may occur in the United States.

For example, the Australians have already made

a determination that the use of CFCs in albuterol may no longer be essential in Australia. So you have to factor in the global nature of not only the transition and the Montreal Protocol but also the global nature of how these companies operate.

The Europeans are, I think, very close to getting to a point where they may decide that albuterol is no longer an essential use of CFCs in the European Union. So the United States may not be the fastest in the transition. So simply looking at it from a U.S. perspective doesn't give you the total picture that the companies need to address.

DR. NIEDERMAN: But again, the economic incentive is clearly there to develop a non-CFC albuterol because that will close down the generic market with CFCs, correct?

DR. JENKINS: Well, that's one way of looking at it. I can say that for the market-leading products in the United States, those products who have substantial market share, I've not seen any evidence that there's not an incentive for those companies to reformulate. Those companies have been working very actively, even in situations where they don't have competition. They're the

single source of a molecule. Companies have been working activity to reformulate.

DR. NIEDERMAN: They may do it, as you say, when they don't have to, but, conversely, specifically in the albuterol market, there seems to be a strong economic incentive with your rule of two products to develop a second product and close down the generic market.

DR. JENKINS: Right. That incentive existed even before we proposed the rule, and I can tell you that multiple companies are working on albuterol alternative products, not just one or two and not just necessarily the ones that currently market albuterol products.

It seems sometimes like every company out there must be developing an albuterol product because we get the requests for meetings from them. So there's no lack of interest in developing albuterol replacement products.

DR. NIEDERMAN: So you think that there would be enough competition of non-CFC albuterol that would not drive the price up?

DR. JENKINS: I don't want to get into speculating about what the market forces of competition may or may not do because that's way beyond my level of expertise, but I think we do have the potential that in the future, there will be multiple albuterol inhalation products, and I think there will be multiple types of

devices.

DR. GROSS: But the criterion of necessity would be met by having one HFA albuterol and one dry-powder albuterol?

DR. JENKINS: That's possible. It could be two HFA albuterols.

DR. GROSS: Right. But I mean, given that HFA is a patented substance.

DR. JENKINS: Well, there are ways around those patents, and you can enter into licensing agreements, et cetera. So.

DR. GROSS: Yes, but I mean, everybody is developing dry-powder albuterol right now. So that, I mean, is that what you were referring to when you said you see the new applications coming through? There's a lot of applications for dry-powder albuterol.

DR. JENKINS: There are also applications or development for HFA albuterols as well. So there are ways that companies can address those patent issues.

DR. SESSLER: Any other comments?

DR. FORD: I guess following up on the issue

that Dr. Niederman brought up, one practical question that would come up in the implementation of non-essential status for albuterol would be whether we would want to wait until there is sufficient assurance, even as we know what the

pipeline looks like, that at least albuterol won't become cost prohibitive even for a period of time, until the pipeline catches up.

I don't know how much of a concern that is, but I would imagine that this would be a consideration in the timing of that determination for albuterol.

DR. SESSLER: Bob, the next point is really related to the issues that we've been discussing as it relates to albuterol, and I believe you wanted to make some sort of a correction or a statement on that.

DR. MEYER: Yes. There's an inaccuracy that I need to take credit for on that, and that is that the consortium itself of IPAC has not made this statement, I think, for understandable reasons. They don't see themselves in the position to make statements about drug pricing because they are a consortium.

So it's actually been member companies not

speaking on behalf of the consortium but on their own behalf that have stated in various fora that they would see the replacement products as being priced very comparably to their CFC-branded counterparts.

So in other words, as I think I mentioned earlier, Proventil HFA is within pennies of the cost of Proventil CFC, and other companies have made similar commitments. So again not to belabor this point, but I

think the issue of cost really is perhaps the thorniest for the products where there's a generic, and right now, the status of the market is such that's only albuterol. So we're really talking about the cost issue being most important there.

I think I'd even reflect, maybe following up on what Dr. Ford just said, that I think we have to bear in mind that three years ago, there were no generic albuterols, and, you know, for better or for worse, they're here now, and I think one could argue that perhaps having cheaper medications is quite a benefit.

But I think we need to bear in mind that up

until three years ago, this was a market without any generic competition. So certainly, outside of albuterol, we're really not talking about costs being -- we anticipate a major part of this process, but even albuterol, although I think the issue is important, and we have it here as a talking point, I'd just like to have everybody bear in mind that as patients are doing reasonably well compared to how they're doing today three years ago at a time where albuterol had a very different pricing structure.

DR. KELLY: Maybe the low cost of albuterol is not a good thing. If we're overusing it, as Dr. Fink has said, maybe we want to make it costlier so the HMOs would prefer to give inhaled corticosteroids and not so much

albuterol. I mean, there are other ways of looking at costs.

DR. SESSLER: Dr. Jenkins?

DR. JENKINS: Curtis, I get the feeling that you're getting ready to discuss the specific point on costs, and before you leave the moiety-by-moiety approach, I wanted to stimulate a little bit more discussion about -- I tried to highlight a little while ago something that may

be considered to be a positive benefit of the transition, and that's a lot of innovation and a lot of attention to new devices.

You could look at another issue related to the transition that could be viewed as a negative, is it's very likely at the end of this transition, we will have fewer moieties by inhalation than we had when we started, and, for example, some of the very small market share products that are out there, companies may choose not to reformulate those products, and it may come that eventually, under this 2005 provision that we've proposed, there will be a determination that those products are no longer essential, and I'm wondering how the committee feels about that, the fact that at the end of the day, as a result of the transition, there may be fewer moieties available than there were when we started.

DR. NIEDERMAN: It seems inevitable, but not

necessarily bad. I think some of these, as you said, have such a small market share, that it's hard to justify either clinically or pharmacologically that we need as many

different moieties, and there's a lot of historical perspective as to why some of these products exist.

I think this is probably one issue that's probably not bad to cut down the number of choices.

DR. JOAD: I guess it might only be a problem with inhaled steroids, but we don't know the answer to that yet. I mean, we have very little information about choosing one over another, and when we get that, hopefully in the next several years, then it could really matter if one of them is not available, that really does matter to us more than another.

So that class, I would be more worried about than, say, the beta agonist class, short-acting beta agonist class.

DR. JENKINS: Just to follow up on that, we've talked a lot today about albuterol, and clearly there's no secret that albuterol already has an alternative, and we've talked a lot about other alternatives being developed.

As a hypothetical and not to suggest that this would be the outcome, how would you feel if, at the end of the day, when this transition was over, albuterol was the only short-acting beta agonist that was available?

DR. GROSS: I guess I just don't believe there's a lot of difference between the molecular entities, but there are other cosmetic things about different bronchodilators. There's taste and slight differences between the devices and so forth.

I mean, I think one needs to have some choices for non-medical reasons but simply because there is a preference issue there, and obviously you need it for competition as well, but I, for one, wouldn't really mind very much if all the other beta agonists disappeared of the same duration of action and otherwise similar pharmacologic properties.

MS. CONNER: Does anyone else have patient experience of patients that just absolutely -- if you've ever tried them on pirbuterol, they won't go back to albuterol because of the lack of tremor? They just don't seem to have -- whether that's real or imagined. I have patients that really, really prefer pirbuterol over albuterol, and it's something that they can detect a significant difference.

DR. JENKINS: So you're saying you would be concerned if there were not a choice?

MS. CONNER: Yes. Yes, I would. At least that choice. Some of the others --

DR. GROSS: Well, that's really hard to justify

scientifically, because tremor is a beta2 action.

MS. CONNER: Right.

DR. GROSS: It's a specific subgroup of one type of problem.

MS. CONNER: Of the others, it's the one that I've seen preferred or asked for.

DR. KELLY: It's a little less potent than albuterol, and so you'd expect a little fewer systemic side effects if you gave the same dosage.

MS. CONNER: And it may be that they're milder and use it less frequently when they do use it.

DR. DYKEWICZ: Hypothetically speaking, let's say it came to pass that it was found that albuterol had some unforeseen toxicity in some set of patients. You know, we have no evidence, for instance, that it's a particularly teratogenic agent in pregnancy, but let's say it played out that in fact that was a problem or that you got any sort of adverse effect problem, and then you had no alternative for another drug in the class being available. Again, we're talking hypothetically, but that might be an issue. There would be no alternatives to turn to.

DR. SESSLER: You know, I think one thing that's worth bearing in mind, too, is we offer the

prospective of clinicians and the like, and we don't necessarily represent the patient's perspective, and I

think Brenda brought that out nicely, that there may be a much greater outcry from a less scientifically rigorous look at the comparable drugs, and that we should value that and pay close attention to it.

So my guess is that choice is better than no choice for a variety of reasons, although it probably doesn't need to be quite as broad perhaps as we have currently.

MS. CONNER: And I have to admit I'm one of those patients.

DR. SESSLER: A personal issue.

MS. CONNER: It gets right down to it.

DR. SESSLER: Politics are personal.

DR. GROSS: Wouldn't market forces suggest that we will have more than one choice, though, for the same reason that we have six separate beta2 agonists now?

Once we cross this 2005 hurdle, and for all the new entities certainly and old entities, with very few

exceptions, have to meet the same standards of the non-CFC, wouldn't you then have the same comparative pressure to introduce or bring back a lot of well-known agents, if they had gone out of production? Am I missing an economic factor here?

MS. CUSUMANO: It might depend on current market share.

DR. SESSLER: You know, another issue that relates to choice is not so much the molecular entity as it is the delivery, which is, you know, obvious for the things in the future, but also you've got the Maxair Autohalers, something different in terms of a beta2, and you've got Azmacort with its built-in spacer and convenience of that, that has played a role at least historically in terms of drug selection for a lot of patients and doctors, I suspect.

Some of those, they're separate issues, but at the same time, from a regulatory standpoint, my understanding is that they are kind of approved as one package, that is, the drug and the device, and so that's, I guess, another wrinkle in to the number of entries into the

market and another factor, I suppose, to be considered with how many are enough.

DR. JENKINS: I didn't want it to go unnoticed that I think Ms. Conner finally answered my question about what is a subgroup. I think she defined herself as a subgroup.

(Laughter.)

DR. SESSLER: Okay. Very good. Any other moiety-to-moiety -- actually, I brought up the other topic because we're starting to move into the cost issue or all day, I guess, we've really been talking about the cost of

albuterol, but just to get that out there as well.

Anything else from the moiety-to-moiety approach? Any last comments on that?

DR. KELLY: Just a last comment on what Dr. Jenkins just talked about in terms of albuterol possibly being the only -- those are market forces which we have no control over, and they're going to happen probably anyway in the long run.

If you can't sell pirbuterol Maxair or

whatever, you'll stop making it, even if you don't make the transition to CFCs, I would think.

DR. SESSLER: We've touched on it many times, the cost issue, and Dr. Meyer clarified that second-to-the-last bullet point there.

I guess the question that was -- there was a set-up, and then the question was, would price be such a substantial barrier to access for albuterol that it should be considered in the determination of essentiality?

So this, I guess, puts the regulatory component on the question that we've really been talking about for much of the day.

Michael?

DR. NIEDERMAN: Well, I think, again, this is an extremely complex question, and it's not what it appears on the surface, and I think if you think it through, my

answer would be that the costs should not be the reason to make it an exemption from the essential drug list.

I'll tell you the example that I worry about is, I think about my patient population, and how often I prescribe the drug that I think is better, and the managed

care prescription plan comes back and asks me to change it to a cheaper product, and I think that that will end up being the major lobbying force for a cheaper alternative.

It will not really be as much the underserved patient, which clearly will benefit from a lower-cost product, but I think in the marketplace, managed care will probably be the largest lobbyer for a cheap product rather than the underserved patient, and I think that they will work very hard, if cost will be viewed as an exemption. I think they will certainly work very hard to maintain low-cost products that have CFCs because it's a tremendous economic impact on them with all the inhalers that they're paying for.

DR. JOAD: I would just say the transition has to happen some time, and this will probably always be an issue. So that there's probably no perfect time where you could say cost was an issue now and cost is not an issue now. So probably that should not be built into it.

I also realize Dr. Kelly's point about that maybe it wouldn't be so bad if albuterol weren't quite so

cheap.

DR. KELLY: Thank you.

DR. NIEDERMAN: I think cost is an issue, but I think, as I say, it's got multiple sides to it.

DR. SESSLER: I think there are a lot of layers to this one because you've got your generic albuterol, and then you've got your albuterol look-alikes that are separate molecular entities and may hang around for their five years and be priced more cheaply and impair the overall transition of the short-acting beta agonist group, and yet I sure take care of a whole lot of poor folks, and I'm really concerned about it.

I mean, from the epi standpoint, that's the area that really we're not winning the battle yet, I don't think, and, you know, I'd hate for us to look retrospectively and find that the mortality has gone up in that subset, you know, that it's gone down for folks who can afford their meds, and it's gone up for folks who can't, and so I think even though cost, I think, is extremely complicated, and I'm not sure how to factor it in exactly, but that would be my fear, I guess, is if we ignore it, that that's the consequences that we might pay.

MS. CONNER: I've also been in a situation at an asthma camp where we had a large contingency of inner-city low socioeconomic, lower-income kids, and just in

dealing with their medications as well as the ones from the suburbs at all at one time. you can see that availability and price dictates prescribing patterns.

I mean, these kids would be on generic theophylline, not even long-acting, but they'd be on generic theophylline four times a day around the clock because it was cheaper than a long-acting theophylline, or they'd be on inhaled nebulized medications, 15-16-year old kids, because it was cheaper than a metered-dose inhaler.

So I think we can't let their care be impacted if we limit resources, but by the same token, just like you said, if it's too cheap or if the lesser-desired product is cheaper, are we doing them an injustice by making that available? I don't know.

DR. FINK: But, for the children, at least, Medicaid is done on a state-by-state basis, and all you're dealing with there really is the state as an HMO because where there are limitations -- in D.C., there is no limitation on what I prescribe. Medicaid is the best payer for drugs in D.C. It just depends on how your state functions as an HMO. So it's just 50 more HMOs to deal with, which, if you had another 250 that already exist, I'm not sure it's terrible.

MS. CONNER: That in itself is so frightening.

DR. FINK: But, I don't think it is exclusively

the underserved that have problems getting their prescriptions. They usually have less out-of-pocket expense for their drugs than other groups, unless the state has been very aggressive in limiting the choice of physicians.

DR. FORD: I think that this is a very complex issue, and there are multiple layers. I think there's the interaction between what providers actually prescribe and what's available based on cost and so forth, and even if we were to limit availability of albuterol, I think that there are other layers of complexity. You know, if people have access to other molecules, then they go for the Primatene Mist a little bit more at that point, and so whatever intervention we introduce, we're going to have to weigh very carefully.

I think it's very hard to say categorically do it this way or the other, and it requires a lot of thought. I wish I could be more direct than that.

DR. NIEDERMAN: I mean, one way to solve the problem is -- and I don't know how you do this

legislatively, but if there was some way to make it required, that anybody who needed albuterol would have it paid for by somebody, then immediately -- I think the problem is that you create a two-tiered system if you allow cost to be an issue.

I think you allow underserved people who have bad insurance to potentially get inferior products.

DR. FORD: Precisely. A lot of our patients, for example, they are uninsured or they're immigrants who are outside of any -- they fall off any radar screen.

DR. NIEDERMAN: I think, again, if this discussion were being held in Europe, we would realize how silly our American health care system is, where we're talking about potentially allowing less than satisfactory products to stay on the market because we're not providing coverage for some people with a very serious disease to get their medications.

So I mean, it's, as has been said repeatedly, it's complex, but it's complex in the context of the whole health care system that we work in.

DR. DYKEWICZ: Another layer of the complexity may be the reality that really for most patients who are using albuterol with any frequency, they should be also obtaining some other controller agent, an inhaled steroid, for instance, and so what you're really looking at is the impact on the overall costs for treatment.

On one hand, you could say, well, if they're going to have to pay a lot more for their albuterol, is that going to reach a threshold that they aren't going to be able to afford the controller medication?

On the other hand, you could make the case that if they really should be on an inhaled steroid, with very infrequent use of albuterol, that might be the better way to kind of drive the utilization or whatever limited resources there may be. But, you know, another layer of the complexity.

DR. SESSLER: So we need a generic inhaled corticosteroid?

DR. GROSS: I think the idea that you're going to get people to use more steroid by making the albuterol more expensive is frankly ridiculous.

(Laughter.)

DR. GROSS: I mean, this is the first-line treatment for people who have acute attacks. You can't simply limit their use certainly by economic forces, and I can tell you absolutely without any question of being contradicted, that if you ask a patient, particularly a poor one, which drug they would rather be able to have easy access to, albuterol or a steroid, they'd say albuterol every day of the week.

So I mean, I wish we would stop discussing the possibility of reducing the use of albuterol by increasing the price. I mean, that's gotten flippant, right?

DR. SESSLER: I hope that helped.

(Laughter.)

DR. SESSLER: Any other discussion on the cost issue?

DR. NIEDERMAN: But, Curt, I think most people do agree that costs shouldn't be a way of declaring it an essential product because it's cheap. I didn't think anybody was arguing that we should allow a low-cost CFC

compound to stay on the market simply because it's cheap.

DR. SESSLER: I think it's a question, to a certain extent, is that perhaps additional caution should be undertaken, and that some careful epidemiology work be done. If indeed that happens, that to monitor what the asthma mortality and outcomes are in the groups that we would target as being at highest risk for having a negative impact from elimination of that.

I would say that, you know, perhaps it wouldn't be something that, for my own opinion, would impact the determination of its essentiality, but I think it would certainly give us cause to be cautious with our approach.

DR. NIEDERMAN: But the answer, again, if, let's say hypothetically, you eliminated the low-cost alternatives, and in specific populations, they stopped using the medication because they couldn't get it, and mortality went up, the answer probably isn't to bring back the low-cost alternatives, if they're considered environmentally dangerous and maybe not as good.

The answer is to find a way to deliver the drugs to people who can't afford it.

DR. FORD: So I don't think anybody has a problem with introducing the new drugs and even taking off the low-cost alternatives, but I think that for public health policymakers, there is an obligation that goes along with this to make sure that at the very least, the level of access will be comparable to use your standard, and to just introduce it and think that the marketplace is going to take care of it, I think, could -- we don't want to wait for the statistics to tell us that people are going to have access to albuterol who are having asthma attacks.

DR. SESSLER: Dr. Meyer?

DR. MEYER: I was just going to make the comment, I'm not sure that these kind of data exist in any rigorous fashion, and this is confounded by secular trends and so on, but we do have several years now of albuterol being available as a generic, and I guess we could at least consider whether there are data to address whether that has had any impact on asthma morbidity and mortality since it's been available.

I would hazard a guess that it's probably not made any definable dents in either of those statistics, but I don't know.

DR. KELLY: Well, the morbidity and mortality

from asthma is still rising in the last CDC report. So I guess we haven't had an impact.

DR. SESSLER: Well, it's hard to sort out whether the rate of rise would be steeper, and it would be flatter in that one.

DR. DYKEWICZ: Although I believe in our briefing documents, we received some data which indicated that the overall number of prescriptions of albuterol before and after the availability of generics was not significantly changed, implying that perhaps the access to albuterol was not that significantly impacted.

DR. MEYER: Yes. That is actually true of what we found with the albuterol data, and it actually tends to be true of generic drugs in general, and when a drug becomes available in a generic form, most times, there is no expansion of the market. In fact, often, there's a mild shrinkage of that particular drug being used.

DR. NIEDERMAN: Which is just saying that the people who are paying for the drugs are saving more money, and these days, most of that is probably not the patients. Most of that is the third party payers.

DR. SESSLER: Let's move ahead to the final bullet point here, an entirely different topic. What are the merits/problems with a rapid elimination of CFC-based nasal corticosteroid products, given the availability of

aqueous products and other alternative treatments?

Bob?

DR. FINK: I think it's meritorious, and at least it says that the FDA has taken a stance on the CFC use, and it sends a message that at least in one product line, we are phasing it out, and it sends a reality message to anybody who didn't believe that the eventual phaseout for the other devices is coming and probably won't cause any increase in mortality.

DR. SESSLER: Yes. Dissenting views?

DR. DYKEWICZ: I would say that there are some individual patients, of course, who prefer the non-aqueous preparations. I think if you're looking at probably controlled studies indicating that there's any difference in efficacy, we really don't have anything that demonstrates that.

If you're looking at serious adverse effect profiles, I don't think there's any clear evidence that there's any difference between that. You will see the episodic patient who will say that they just can't tolerate the drippiness of an aqueous preparation, and they won't in

fact take it as a result, but then, I guess, when you try to define this in terms of is this, you know, an essential need to have some non-aqueous preparations available, I'm not sure if you can make that case, you know, in terms of

national policymaking or regulatory authority.

DR. SESSLER: Dr. Meyer, could you give us an overview on what we currently have available in terms of both aqueous and CFC products out there, so just to get a feel for the magnitude of what would change?

DR. MEYER: Yes. There are three moieties that are available and CFC-driven metered-dose inhalers for nasal corticosteroids, that being triamcinolone, beclomethasone, and budesonide.

Currently, all of those have aqueous formulations, either by the same manufacturer or otherwise. There's also other aqueous formulations available that are not available as CFC-driven MDIs, such as fluticasone and mometasone and momisamide.

I think we are safe to say that, I think, some of the industry perceives that there is perhaps some reasons to reformulate the metered-dose nasal products, and

there is some interest in that regard.

So you know, I can't really speculate about the future, but I'd suspect if there's enough of a patient need or desire for that, that that will be met.

DR. SESSLER: Do we have any data as to the frequency with which intolerance occurs with this? I mean, I know there have been some discussion, but again, is that substantial?

DR. MEYER: I think we can pretty safely say that FDA does not have any good controlled data that would really answer that question. It's much more anecdotal, and even gets to the point -- I know that one of the folks who serves on the Technical Options Committee with me in the UNEP is rather prominent in the U.K.'s transition, and he gets personal calls from people in the EU saying why are you taking away my nasal inhaler?

So it's anecdotal from him, too, I know, but in any case, we don't have any good data.

DR. SESSLER: Can we hear from the allergists here? I would like to call on you.

DR. APTER: I want to second what Dr. Dykewicz said and reiterate what I said this morning. For the patients who have difficult nasal polyps, sometimes topical nasal steroids won't even get to the right place, and you require prednisone, but I do have the feeling, and again there's not head-to-head controlled data, that the difference in delivery system makes a difference for some people, some people who have very deviated septa, you know, very different anatoma, anatomy people with polyps, and so I think it would be ideal to have a propellant formulation, but I don't know that it's life-threatening. I don't know in weighing the risk of CFC that would be worth delaying taking the nasal steroid off the market, the propellant off

the market.

DR. SESSLER: Other discussion?

(No response.)

DR. SESSLER: Anything coming down the pike in terms of non-aqueous agents or is that --

DR. MEYER: We have seen some gipicard. I don't want to be too explicit, but, yes, we have seen some interest in that.

DR. KELLY: Is there any marketing data on what portion of the market the non-aqueous is?

MS. CUSUMANO: It represents about 20 percent currently, apparently. 20 percent of the market of the CFC.

DR. KELLY: Of the market. Okay.

DR. APTER: But my experience is that the aqueous versions are very heavily marketed at the expense of the aerosol. So I'm not sure what that means.

DR. MEYER: Well, I guess the reason may be marketing, but at least we know that 80 percent of the patients at this point seem to be having that as a satisfactory treatment option.

DR. SESSLER: Other comments?

(No response.)

DR. SESSLER: I kind of share the idea that it's a good starting point, and it sounds like the impact

would be relatively minimal, especially if there's other agents that are aqueous alternatives that are coming down the pike, because I think Dr. Fink stated correctly that

this sends a good message in terms of that it's a deliberate process, but there's actions being taken as well.

We certainly have a little bit of time left, if anybody has any other closing comments as members of the committee on this process, if anybody would like to offer anything additional.

Dr. Meyer?

DR. MEYER: I actually wanted to ask the committee and the audience a question, because I think one thing that's clear is that we benefit in trying to come up with a transition policy that makes sense for patients and protects patients, and in getting some level of feedback from patients, and one of the very nice ways that we get that is through interactions with patient advocacy organizations.

It has struck me, I certainly have had this thought before, but it's become much more clear to me, that the asthma community is rather better organized than some of the other constituencies, and the one I have in mind particularly is the chronic obstructive pulmonary disease community. Even doing sort of a web search on COPD, it's

very hard to find many good sort of national organizations that address that, and I might be missing some resources.

So I'd certainly invite anybody from the committee or from the audience who really has some contacts with patient groups, particularly in the chronic obstructive pulmonary disease community, to share them.

DR. APTER: I think the place to look is in the pulmonary rehab community. There are very active pulmonary rehab groups. You can find them meeting at the ATS.

DR. MEYER: Yes. I think what I've found, and this may differ from other people's experience, but what I've found is they tend to be much more locally or regionally organized rather than nationally, so that you have support groups through local ALAs or, you know, hospital-based programs for rehabilitation or maybe regional-based programs.

DR. APTER: But they do meet nationally, too.

DR. NIEDERMAN: There is the AACVPR, the American Association of Cardiovascular and Pulmonary Rehab, but I think that's more of a physician group and not a patient advocacy group.

DR. GROSS: And there's the Alpha I community.

DR. MEYER: Right. It's quite well organized, yes.

DR. DYKEWICZ: I do have one other thought.

DR. SESSLER: Please.

DR. DYKEWICZ: This may not really have any ultimate impact on how the regulation is being articulated, but a practical matter, is that if you have a patient who requires several different classes for treatment of asthma, so they need their quick-acting beta agonist, they need their inhaled steroid, and maybe even a third agent, nedocromil or whatever, the question would be, having some uniformity of delivery technique so that a patient is not going to be confused between switching from one preparation to another, you know.

The problem that immediately has come to mind in a more restricted way with the introduction of dry-powdered inhalers has been that the inhalation technique for those requires a quick, rapid inhalation as opposed to the MDIs which are more like five-second inhalations, and then if we're looking ahead at maybe a variety of different devices, that we'd want to have some type of ideally a uniformity of technique with drugs of different classes, a long-acting beta agonist, an inhaled steroid, and a quick-relief beta agonist, so that a patient wasn't getting totally confused trying to do a switchover with different sorts of techniques.

Again, I'm not sure that that's something that has to be actually put into the whole regulatory proposal,

but I think it is a practical consideration in real life with treatment of patients.

DR. MEYER: I think that it does represent a part of the educational challenge of the entire transition because with many new products coming on, it is quite likely that patients will be on some products that differ in terms of their technique, and I think that currently, we know that many patients do not know or cannot use MDIs correctly sometimes with and sometimes without spacing devices, or that their practitioners can't instruct them correctly.

So I think that's an issue that relates to the transition but perhaps is not directly related but certainly represents a part of the educational challenges as we move forward in all this.

DR. SESSLER: Well, I'd like to thank everyone for their thoughtful comments. Thanks.

(Whereupon, at 3:19 p.m., the meeting was

recessed, to reconvene at 7:45 a.m. on Tuesday, November 23, 1999.)