DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PULMONARY-ALLERGY DRUGS

ADVISORY COMMITTEE

Thursday, July 14, 2005

8:10 a.m.

Gaithersberg Hilton
The Ballrooms
620 Perry Parkway
Gaithersburg, Maryland

PARTICIPANTS

Erik R. Swenson, M.D., Chairman
Teresa Watkins, R.Ph., Executive Secretary

COMMITTEE MEMBERS

Mark L. Brantly, M.D.
Steven E. Gay, M.D., M.S.
Carolyn M. Kercsmar, M.D.
Fernando D. Martinez, M.D.
I. Marc Moss, M.D.
Lee S. Newman, M.D.
Calman P. Prussin, M.D.
Michael Schatz, M.D.
David A. Schoenfeld, Ph.D.

SGE CONSULTANTS (VOTING)

Karen Schell, RRT

SGE PATIENT REPRESENTATIVE (VOTING)

Nancy J. Sander, Virginia

FDA

Robert Meyer, M.D.
Badrul Chowdhury, M.D.
Eugene J. Sullivan, M.D., FCCP

C O N T E N T S

P R O C E E D I N G S

Call to Order and Opening Remarks

DR. SWENSON: Good morning, everyone. I am Erik Swenson, Professor of Medicine at the University of Washington, and chairman of this meeting of the Pulmonary-Allergy Drugs Advisory Committee.

We are meeting today to discuss the continued need for essential use designations of several prescription drugs for the treatment of asthma and chronic obstructive pulmonary disease under 21 CFR 2.125. This is an issue surrounding the use of CFC propellants in inhaled drugs for the treatment of lung disease.

To begin with, I would like the members of the panel to go around and introduce themselves and where they are from. We will start with Dr. Meyer.

Introduction of Committee

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

DR. CHOWDHURY: I am Badrul Chowdhury,

Director, Division of Pulmonary and Allergy Drug Products, FDA.

DR. SULLIVAN: My name is Gene Sullivan. I am the Deputy Director of the Division of Pulmonary and Allergy Drug Products.

DR. SCHOENFELD: David Schoenfeld. I am a member of the Committee. I am a Professor of Medicine and Biostatistics at Harvard.

MS. SANDER: I am Nancy Sander. I am President and founder of the Allergy and Asthma Network, Mothers of Asthmatics. I am here as a patient advocate.

DR. PRUSSIN: I am Calman Prussin, Clinical Investigator, Laboratory of Allergic Diseases, National Institutes of Health.

DR. SCHATZ: Michael Schatz, an allergist/immunologist from Kaiser Permanente, San Diego.

MS. WATKINS: I am Teresa Watkins, the Executive Secretary for this committee.

DR. GAY: Steven Gay, Assistant Professor and Medical Director of Critical Care Support

Services, University of Michigan.

DR. MOSS: Marc Moss, Associate Professor of Medicine, Emory University, Atlanta.

DR. NEWMAN: Lee Newman, Professor of Medicine and Preventive Medicine Biometrics, National Jewish Medical and Research Center, and University of Colorado School of Medicine, Denver, Colorado.

DR. BRANTLY: Mark Brantly, Professor of Medicine, University of Florida.

DR. MARTINEZ: Fernando Martinez, Professor of Pediatrics, University of Arizona in Tucson.

DR. KERCSMAR: Carolyn Kercsmar, Professor of Pediatrics, Rainbow Babies and Children's Hospital, Case Medical School in Cleveland.

MS. SCHELL: Karen Schell. I am a consumer representative. I am a respiratory therapist from Emporia, Kansas.

Conflict of Interest Statement

MS. WATKINS: I will now read the Conflict of Interest Statement.

The Food and Drug Administration is convening today's meeting of the Pulmonary-Allergy Drugs Advisory Committee under the authority of Federal Advisory Committee Act of 1972. With the exception of the industry rep, all members of the Committee are special government employees or regular federal employees from other agencies subject to federal conflict of interest laws and regulations.

FDA has determined that all members of this advisory committee are in compliance with federal ethics and conflict of interest laws including, but not limited to, 18 U.S.C. 208 and 21 U.S.C. 355, Subsection (n)(4).

Under 18 U.S.C. Section 208, applicable to all government agencies and 21 U.S.C. 355(n)(4) applicable to FDA, Congress has authorized FDA to grant waivers to special government employees who have financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Members who are special government employees at today's meeting, including special government employees appointed as temporary voting members, have been screened for potential conflicts of interest of their own, as well as those imputed to them including those of their employer, spouse, or minor child related to the discussions regarding the continued need for the essential use designations of prescription drugs for the treatment of asthma and chronic obstructive pulmonary disease under 21 CFR 2.125.

These interests may include investments, consulting, expert witness testimony, contracts, grants, credos, teaching, speaking, writing, patents and royalties, and primary employment.

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

Dr. Carolyn Kercsmar, for activities on a speakers bureau. She receives less than $10,001

per year for two grants which are valued at less than $100,000 per year, and for a grant for which the firm supplies products worth approximately less than $100,000 per year. Dr. Kercsmar also owns stock worth less than $5,001. A waiver under 18 U.S.C. 208(b)(3) is not required because the de minimus exemption under 5 CFR 2640.202 applies.

Dr. Fernando Martinez, for his membership on a speakers bureau. He has not lectured or received remuneration for membership on the related advisory board. He has not participated or received any remuneration to date.

Dr. Michael Schatz, for activities on a speakers bureau. He receives less than $10,001 per year, and for a grant for which the firm supplies the product worth approximately less than $100,000 per year.

Ms. Nancy Sander, for ownership of stock currently valued between $25,001 and $50,000, and for unrelated advisory board activities for which she received less than $10,001 per year. Ms. Sander also owns stock worth less than $5,001. A

waiver under 18 U.S.C. 203(b)(3) is not required because the de minimus exemption under 5 CFR 2640.202 applies.

Dr. Steven Gay, for speakers bureau activities with five firms, three of which he receives less than $10,001 per firm per year, and two of which he receives from $10,001 to $50,000 per firm per year.

We would also like to disclose that Dr. Marc Moss' spouse owns stock worth less than $5,001. A waiver under 18 U.S.C. 208(b)(3) is not required because the de minimus exemption under 5 CFR 2640.202 applies.

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

Lastly, the industry representative Dr. Theodore Reiss was invited, but due to a family emergency he was unable to attend today.

DR. SWENSON: Dr. Robert Meyer of the FDA will give us some introductory remarks.

FDA Introductory Remarks

Plaque Presentation

DR. MEYER: Thank you very much.

Before proceeding with the formal part of today's agenda, I did want to take a moment out for I think a very nice activity, which was that Ms. Schell, Karen Schell, has served our committee now for four years, actually officially from November 2001 through May 2005. We have continued to call on her services in a special government employee role for this meeting, and I think a meeting just a few weeks ago, as well.

But she has served for these four years as the consumer representative, which is a very important role to these committees, where she brings the patient perspective, which I think she has done admirably.

Her background is, as she said earlier, as a respiratory therapist in Emporia, Kansas, and she has got a very broad background in respiratory therapy including being a registered polysomnographist and also has certification in

disease management of asthma, so she is very well qualified for representing the concerns of patients, and we have really benefited from having her on the committee.

In recognition of that, we would like to present her with this plaque and I will walk over and do so.

[Applause.]

FDA Presentation

The Montreal Protocol and the Status of Essential Use Process (21 CFR 2.125)

DR. MEYER: I would like to extend my thanks again in advance to the committee for being here. This will be a very different session from yesterday and, indeed, a very different session I think from most every advisory committee I have ever been involved in, because this is not really asking you your opinion of data, but it is really calling on your expertise as practitioners to let us know whether some of the remaining medicines that are listed as essential uses are indeed essential uses under certain criteria that I will

discuss shortly.

[Slide.]

I realized in black and white that this depiction of the earth's ozone layer over the Antarctic was a little bit of a Rorschach test. People were asking me why I was placing a picture of eyeballs or tracheas or other things in the document, but that is indeed the ozone hole over the Antarctic taken by one of NASA's environmental satellites.

I think it serves as background to the reason we are here today, which is the very serious environmental issue of the thinning of the ozone layer.

So, during this talk, I would like to briefly touch on some ozone science. I am not an ozone scientist, but I will briefly touch on that as a prelude to talking about the Montreal Protocol, which is the international treaty that is in place to deal with the preservation of the ozone layer and hopefully, the restoration of the ozone layer, and also the FDA regulations and the U.S.

laws pertaining to these. This will all serve as background to the discussion that we hope will ensue from that.

Just to start off with the general background on the ozone science, the ozone layer, as it is called, is actually a region of relatively higher ozone concentration in the stratosphere.

On this graphic that is depicted here, we have ozone amounts in parts, I think it is actually in pressure, milliPascals, and on the y axis we have altitude in kilometers. You can see other than a blip in what is really a smog ozone, which is, as asthma doctors well know, a bad thing down in the troposphere where we live. Otherwise, the ozone is fairly limited in terms of its representation in the environment until you get to the stratosphere, which begins at about 15 kilometers high and reaches a peak just at about 24 kilometers or about 16 miles up.

[Slide.]

This layer, as it is called, reduces the amount of ultraviolet radiation, UV-B in

particular, reaching the surface of the earth from sunlight.

As a result of loss of ozone from this layer in recent times, there has been an increase in the UV-B radiation that reaches the earth, and that has resulted in numerous health consequences, perhaps the most important of which are skin cancers, both melanoma and non-melanoma types, as well as other consequences, such as increase in cataracts. There is actually data that show that this increase in UV-B can lead to impaired immunity.

Besides the human consequences, there are other deleterious effects on the environment, as well, on animals, on flora and fauna of all types, and actually, on non-biologic materials, as well, like plastics in dashboards, and so on.

So, this protection from the UV-B radiation that the ozone layer affords us is important.

[Slide.]

Now, because the development of the U.S.

laws, FDA regulations, and indeed the Montreal Protocol itself have proceeded in overlapping timeframes, when I continue this talk, I will overlap these discussions and go back and forth to do this in as time-related fashion as I can.

[Slide.]

In 1974, there was a paper published in Nature by Molina and Rowland that was the first paper to tie the depletion of ozone, which had been recently detected and defined, to stratospheric chlorine from degraded CFCs, so these are the first scientists to put together the fact that the emission of CFCs could lead to this phenomenon.

At that time, CFCs were very widespread in use in the United States. They were used, for instance, in refrigerators, both in terms of the coolant itself, as well as the foam insulation in air conditioners in cars and homes, and other chillers, foams, and in many consumer and medical aerosol products. So, they were ubiquitous in use at that time.

CFCs have many wonderful properties. They

are incredibly inert and very stable, which in some respects is their downfall in the ozone, because as they migrate up to the stratosphere, their half-life up in the stratosphere is measured in decades.

[Slide.]

Now, very shortly in government time, after the science was published by Rowland and Molina--which I forgot to mention did receive a subsequent Nobel Prize--very shortly after that work was published, in response to the growing evidence of CFCs harming the ozone layer, CFCs were generally banned in spray cans and aerosols by the U.S. Government. That was through actions of the EPA.

So, since 1978, consumer aerosols, such as hairsprays and spray paint, and other such aerosols, bug sprays, have not contained CFCs, so they have actually been gone from such products for nearly 30 years.

At that same time period, FDA first published our regulation, which is 21 CFR, this is

our chapter of the Code of Federal Regulations, and the specific citation for that is 2.125, and that also banned the use of CFCs in FDA regulated products including drug products, but did allow for essential exemptions.

[Slide.]

Now, we skip forward to 1987, and at that time 27 nations, including the United States, initiated a global ozone treaty in Montreal, Canada, and that has subsequently been known as the "Montreal Protocol on Substances that Deplete the Ozone Layer," and I will call it from now on in the talk as the "MP."

That original protocol has grown in terms of the number of signatory parties, and it now has well over 180 signatory parties to the original protocol and is regarded as one of the role models or models of successful environmental treaties.

There have been some recent bumps in the road, but this has really been a very successful effort and has led to the near elimination of CFCs from the developed world.

[Slide.]

When original written, the phase-out of CFCs was slated for 2000. It was actually decided in London in 1990, but that was moved up to the end of 1995, so that phase-out in the developed countries was targeted for January of 1996 at a meeting in Copenhagen, because there was increasing evidence at that time of ozone depletion, particularly over the Antarctic, as I showed you in the opening slide. This has been known ever since as the ozone "hole," but it is really a relatively dramatic thinning of that ozone layer in the stratosphere.

Now, it is important to point out, though, that while there is a lot of attention paid to this ozone hole over the Antarctic, the depletion is prominent over a lot of the southern hemisphere, Australia, for instance, is quite affected by this ozone hole, and, in fact, I believe there is a law in Australia now that schoolchildren on recess need to wear hats, so this is not a trivial issue, and the depletion besides being prominent in the

southern hemisphere, is global.

The other thing I should point out that although we are here to talk about chlorofluorocarbons because of their role as propellants in many important asthma and COPD medications, the Montreal Protocol controls many ozone-depleting substances, and there are many others other than CFCs, such as halons, HCFCs, methyl bromide, and carbon tetrachloride.

[Slide.]

With regard to CFCs, however, as of January 1, 1996, all use of CFCs has been banned in industrialized countries and is targeted for this ban to go into place in the rest of the world in 2010, so just in another five years.

MDIs for asthma and COPD currently--and I underline that for a reason--are exempted from essential use processes. There has been an essential use process in place since January 1, 1996, but it was always the intent of the Montreal Protocol that this be a temporary process and that all such uses would be phased out over time.

Nominations for essential uses in medications are reviewed annually and generally, they are reviewed two years in advance, so, in other words, in 2005, the parties would ordinarily be reviewing 2007 nominations. In fact they are. I put the word "ordinarily" in there because there are some issues with that this year, that are not germane to today's discussion, but we are doing everything really in anticipation of two years down the road, and that is to allow the countries that make these nominations to go through their own processes of then taking what is allotted to them and allocating it out and making sure it gets to the products that they have deemed essential.

[Slide.]

Now, the Montreal Protocol has a number of stipulations that are worth me highlighting for you, and let me just talk a little bit about the designation here. When it says Decision IV/25, the IV refers to the fourth meeting of the parties, and the 25 means that it was the 25th decision taken there.

To draw an analogy, if the Montreal Protocol was a law, these decisions would be like a regulation, so they don't really amend the protocol, but they basically help interpret the protocol.

So, the Decision IV/25 stated that all essential uses of CFCs should be based on products being necessary for public health without adequate alternatives, and they defined adequate as either technically adequate or economically adequate.

This determination at that time was really viewed macroscopically, in other words, you could make the determination here that all CFCs and MDIs for asthma and COPD could be considered essential. You weren't saying albuterol versus beclomethasone, and so on. It was that the use of CFCs broadly in MDIs for asthma and COPD were considered essential. But again that was fairly early on in the Montreal Protocol being at the fourth meeting of the parties.

[Slide.]

Decision XII/2 stated that any product

approved after December 2000 must individually meet these criteria under IV/25, so, in other words, this really took it from the macroscopic to the microscopic, so any new product at that point must meet the criteria of having no technically or economically feasible alternatives to have that essential role in the treatment of society or in society.

This product-centered determination of essentiality really precluded new CFC generics or other new CFC products because of this high hurdle.

[Slide.]

Decision XV/5 stated that essential use nominations are now specific. In the past, a party, such as the United States, would go and say we need 2,000 tons for our essential uses. Now, we have to say we need 2,000 tons and of that 2,000 tons, 1,000 tons will be for albuterol, for instance, and those numbers are not meant to be accurate, they are just meant to be representative or used as an example.

This decision also said no quantity of

essential use CFCs will be authorized for albuterol specifically beginning with 2005's meeting of the party unless a plan was in place for the phase-out of albuterol and submitted to the Open-Ended Working Group. This is an earlier working meeting of the parties by the summer of 2005.

I would just point out that the FDA final rule published earlier this year on the phase-out of albuterol, which stated that we will consider albuterol no longer to be essential in the United States after December 31st, 2008. We regard this final rule as meeting this stipulation for the U.S.

[Slide.]

In response to the Montreal Protocol and the U.S. signing of that protocol back in the late '80s, the Clean Air Act Amendments included changes to the Clean Air Act that essentially implemented the Montreal Protocol into U.S. law.

The EPA regulations that then implemented the amendment to the Clean Air Act refer to the Health and Human Services and FDA through citing our specific regulation of essentiality for

determining medical essentiality. Again, this rule, 2.125 was published before the Montreal Protocol and, in fact, before we really had much experience with the phase-out or even the prospects of the phase-out since it was published in 1978.

[Slide.]

Now, at the time that that rule was published, it stated that CFC-containing products would be misbranded or adulterated, in other words, illegal under the Food, Drug, and Cosmetic Act unless deemed essential, and the determination for "essential" use under that rule was that there was there was not technically feasible alternatives available, that the product provided substantial benefit, be it health, public, or environmental, and that the release of CFCs from the product was small or justified given this important benefit.

[Slide.]

Importantly, that rule, when it was promulgated, had no mechanism to determine when uses were no longer essential, so it had ways to add to the list, but it had no way to determine

when products were no longer essential and then to take them off the essential use list.

The other thing that was notable about it is most important drugs were not listed as separate entities, but they were actually listed in very broad classes, such as there was a class of adrenergic bronchodilators for human use that included albuterol, pirbuterol, salmeterol, and so on, so things were not individually listed. Although there was some individual listing, many things were put into broad therapeutic classes.

So, to deal with both of these issues, in 1996, FDA published an Advanced Notice of Proposed Rulemaking, so the very early stages or rulemaking to revise 2.125.

[Slide.]

That publication led to a very large number of public comments. We had close to 10,000 public comments, which to folks not perhaps involved in regulations may not have sort of a goalpost to measure it by, but this is a large number of comments. Many of these were sparked by

lobbying efforts of concerned entities.

In 1999, taking several years to consider carefully all the comments that we received and the changes in the Montreal Protocol and other factors, FDA published a Notice of Proposed Rulemaking, which is the first formal step in rulemaking.

That Notice resulted in far fewer substantive comments and much less controversy than the original action in 1996. So, we were able to complete a final rule, revising 2.125, in July of 2002, and that rule went into effect in 2003.

[Slide.]

Just to highlight some of the revisions, then, one of the things that this rule did was it listed individual moieties as essential uses rather than classes, so, for instance, I had mentioned earlier that albuterol was under the class of adrenergic bronchodilators for human use, was taken out and listed separately within the essential use list under Part (e) here of 2.125.

One of the reasons we did this was because in 1996, when we published the Advanced Notice of

Proposed Rulemaking, one of the things we said was that it made sense to us, or at least we wanted to float the idea that you could do this two ways.

You could say, okay, albuterol will only be considered in and of itself, and after there are adequate alternatives, then, we could say albuterol CFC is no longer essential.

On the other hand, you could do what is called a therapeutic class determination and say if you took the inhaled corticosteroids, for instance, you could say, well, if we had two or three inhaled corticosteroids with adequate alternatives, we might say all the rest are no longer essential, and that would a therapeutic class approach.

The attraction to such an approach is that it allows products that are not being reformulated to be dealt with if they are in that therapeutic class, but the public comments were very strong against the therapeutic class approach, and in response to that, we no longer had a therapeutic class approach as 2.125 came to finalization.

So, it was important then to list every

moiety separately, and I will get back to the implications of the lack of a therapeutic class approach in a second.

These revisions also added a higher hurdle for new IND use or investigational new drug use of ozone depleting substances. I guess I should also pause here and say we changed the terminology here to be consistent with the Montreal Protocol, and what we are essentially talking about for the purposes of this meeting remain CFCs, but because the Montreal Protocol talks about ozone depleting substances, we have changed that to be consistent with that and the Clean Air Act.

Besides adding a higher hurdle for new IND use, it also raised the bar for new listings of essential uses, and, indeed, I do not believe there has been any new essential list listings certainly since the time of this publication.

[Slide.]

Importantly, then, the changes to 2.125 listed criteria for determining when individual uses would no longer be essential and the moiety

would come out of the essential use list that is contained in 2.125(e).

Let me just go over those criteria quickly. The non-essentiality criteria essentially stated that at least one non-ozone depleting substance product with the same activity moiety, the same indication, the same route of administration, and about the same level of convenience would need to be available.

In addition to that, we would need adequate post-marketing data to be available for the non-ODS product.

We would need to be assured that production capabilities and supplies were adequate or would be adequate at the time the de-listing becomes final, and finally, there was a requirement to be assured that patients who require the CFC product are adequately served by the alternative.

Now, there is an asterisk here stating that this is for products with only one marketed brand or strength, so there would be sort of a 1 to 1 here. For products with more than one strength

available, such as fluticasone, for instance, is a product with numerous strengths, or for products where there is more than one NDA or more than one source of that product, such as albuterol, which had not only two branded products, but numerous generic products.

We stated that there would have to be at least two non-ozone depleting products with the same active moiety, the same indication, route of administration. So, all the other criteria were the same, but the difference here was that there would have to be at least two.

[Slide.]

Now, as I mentioned earlier, one of the advantages to a therapeutic class approach is that it can help to deal with products that are not being reformulated, but because of important and well-taken public input, we did not include a therapeutic class approach in the finalization of the revised 2.125, but we did put in a pathway for dealing with products that are remaining on the market, and not represented by any kind of

alternatives in the marketplace, and we stated in that rule that FDA has therefore revised 2.125(g)(2) to permit the agency to undertake an evaluation of all ozone depleting products after January 1, 2005, not just those products without a non-ODS replacement.

[Slide.]

So, what this means is that beginning in 2005, beginning now, FDA can convene public meetings, that is, an advisory committee meeting, such as today, to discuss those products still listed as essential to determine if changes in the medical practice and availability of alternatives render these products as no longer essential.

Under the revised 2.125, kind of harkening back to earlier language, that essential is based on there being no technically feasible alternatives, provides substantial health, public, or environmental benefit, and release of CFC small, or justified given that benefit.

These reason this is in yellow and I have got some things grayed out here is because this

bullet is really what we are here to discuss. This is your expertise. I think we are not asking you to justify CFC amounts and we are not asking you about technically feasible alternatives because that expertise I think lies elsewhere, but your expertise lies in this bullet, providing do the products that remain on the market and do not have available direct alternatives with that same moiety, do those continue to provide substantial health benefit considering the practice of medicine and the availability of other products.

[Slide.]

Please note that as we go through this discussion, and we will discuss a list of the moieties that are involved, that if you recommend that Drug X is no longer essential, there is then a process that would play out from here.

If FDA were to follow the advice, we would need to publish a Notice of Proposed Rulemaking stating that we had preliminarily determined that Drug X was no longer essential, and I am sure we would cite as our basis for doing that the

recommendations coming out of this meeting.

But what that means is that the public would then have a chance to comment on that proposed rule and we would consider those public comments prior to going to final regulatory action.

So, your recommendation would not precipitously lead to any of these products disappearing. They would lead to a process being played out where we would get further public comments.

[Slide.]

Now, I have got a couple of slides that really get to the same thing. This one is a little busy, so I spend a little time on it, but then I will get to a cleaned up version, but what I wanted to show is that these are the original classifications that were included, some of these implicitly, in 2.125 back in 1978 and added subsequently.

So, at that time that the revisions to 2.125 occurred, we had this kind of universe of products listed as essential uses, and those that

are in red here are already no longer essential, so that includes things like isoethrane, isoproterenol, nasal steroids, contraceptive foams, rectal foams, polymyxin, nitroglycerine. Those products have either been discontinued, some of them have been reformulated in non-pressurized sprays.

In the case of nasal corticosteroids, those products were not considered essential under the Montreal Protocol and therefore no new CFCs could be obtained for the production of those, and besides that aspect, we had the aqueous formulations, the pump sprays that we thought were adequate alternatives. Indeed, now, we have some HFA products which have been approved as MDI nasal steroids.

[Slide.]

The products in yellow here are potentially or could be de-listed soon, many of these because they are no longer marketed. For instance, as GlaxoSmithKline spoke to yesterday, they chose to discontinue the marketing of

salmeterol inhalation aerosol, marking instead their dry powder inhaler, because of their own initiatives with regard to the CFCs phase-out. So, since that is no longer marketed, we could de-list that shortly. The same thing with beclomethasone.

So, what I would like to do here, and I believe in the handout today, I am not sure it is in the agenda, but in the handout of my slides today, there is a List B. This is that list. So, if you need the List B, and you don't have it, it's on the back of the slides that were being handed out today. I am not sure that the Advisory Committee folks have it or not, but it was not on the actual agenda that I had.

[Slide.]

This is the List B. There are available non-CFC inhaled respiratory medications, and I would note that I did not try to include nebulization products here.

So, for albuterol, we now have Proventil HFA approved since 1996, Ventolin HFA approved I believe since the year 2000, and IVAX's albuterol

sulfate HFA was approved last year.

Levalbuterol was more recently approved, Xopenex HFA in an MDI. We also have salmeterol, which I just mentioned is being marketed as a dry powder inhaler, a multi-dose dry powder inhaler called Serevent Diskus, and formoterol is available, as we also heard yesterday, in a dry powder inhalation, single capsule at a time form called Foradil Aerolizer.

We have numerous choices with regard to inhaled corticosteroids. We have budesonide, which is Pulmicort Turbuhaler, fluticasone, which is available in a diskus or approved in a discus formation, and Flovent HFA, which is a marketed HFA alternative to Flovent MDI.

Recently approved was mometasone, which is known as Asmanex. It is a multi-dose dry powder inhaler, and finally, beclomethasone, which is known as QVAR, which actually is approved in two different dosage strengths, unlike the MDI that was formerly available in the United States.

[Slide.]

For the cromones, we actually have no alternatives approved at this point no direct alternatives certainly in that classification.

The anticholinergics, ipratropium has been approved as an HFA metered dose inhalers known as Atrovent, and there is a dry powder inhaler also a single capsule at a time device known as Spiriva. That did not, of course, have an MDI predecessor.

Finally, I think as you are all well aware, too, there is long-acting beta-agonist corticosteroid combination known as Advair Diskus that is available in several dosage strengths, also, that had no MDI predecessor.

[Slide.]

So, that gets us to what I believe is designated as List A in your background documents, which is the moieties currently listed as essential for which there is no current reformulated or direct alternative product approved or marketed.

Under the beta-agonist classification, we have metaproterenol or Alupent. We have pirbuterol or Maxair. One thing I would point out with Maxair

is Maxair is approved both as a press and breathe, although I prefer to say breathe and press, a metered dose inhaler, and as an autohaler device or a device where, in essence, the patient's breath actuates the spray.

Under the inhaled corticosteroids, we have two products that are in that classification, flunisolide marketed as Aerobid, and triamcinolone marketed as Azmacort.

For the cromones, we have cromolyn or Intal, and nedocromil or Tilade.

Finally, there is a combination product of beta agonists and anticholinergic that while available as a nebulizer, which would not have the same level of convenience as an MDI, is not available in a sort of portable, hand-held device at this point, and that, of course, is albuterol/ipratropium also called Combivent.

Note here, too, I am not sure how legible this is, but I have not included epinephrine in the discussion of the beta agonists. We will need to have a separate discussion of epinephrine at a

later Advisory Committee meeting, because it is important, since that is an over-the-counter medicine, to include colleagues from the Non-Prescription Drug Advisory Committee, as well, so folks can look forward to a future timely discussion of epinephrine.

[Slide.]

Well, bringing this all back towards the Montreal Protocol process, what has been the history to date of the Montreal Protocol?

Although this say global, I believe this is actually restricted to the developing countries, which, of course, count for most of the use of CFCs in inhalers, but this is the pattern of the amount asked for from the Montreal Protocol parties, the amount actually used, and the amount in stockpiles within the developing countries.

You can see that in the early years of the essential use nominations, about 14,000 tons, metric tons of CFCs total were requested. At their height, about 9,000 metric tons were used, and that is now down, as far as this graph goes, down in the

4,000 range, and will continue to fall.

I would just state as sort of an educational point that the stockpiles are closely matched here to the amount used and that is by design. The Montreal Protocol, it is felt that because of uncertainties in the supply of CFCs, it is to the countries and companies within those countries' advantage to keep stockpiles that would allow for one year's worth of production.

[Slide.]

So, to conclude my talk, the U.S. Government moved proactively to address the issue of ozone depletion, and, in fact, has had a key role in the implementation and the conduct of the Montreal Protocol.

The Montreal Protocol is a successful treaty and it has led to important reductions in CFCs and other ozone-depleting substances, and, indeed, there is evidence now that the destruction of the ozone has leveled off and it is hoped and projected that under the current provisions of the Montreal Protocol, that the ozone layer will

recover to pre-1990 levels or mid-1980 levels by the mid-part of this century.

The Montreal Protocol is increasingly moving towards control in specific essential uses, notably albuterol, and the U.S. has acted accordingly.

[Slide.]

I think you can also see from the List B that I provided, that the U.S. is progressing in the CFC transition, and there are many non-CFC products available and in common use now. In fact, many of the CFC products that were formerly listed even at the time of the revision of 2.125 are no longer marketed.

However, some CFC products and moieties remain on the market and have no currently approved or marketed alternatives. So, the question for the day, and the question for you folks to ponder and to give us advice on is do these products individually remain essential.

[Slide.]

So, your charge today will be as per the

revisions of 2.125, we are convening this meeting to discuss the products listed as essential to determine if changes in the medical practice and availability of alternatives render these products as no longer essential.

Remember that that definition of "essential" is that there are no technically feasible alternatives, that the drug provides substantial health, public, or environmental benefit, and that the release of CFCs is small or justified given the benefit. Again, I think your particular expertise lies in that second bullet.

[Slide.]

Yet another depiction of the ozone layer, this being picture from 1983 and a similar vantage point in 1993 showing, indeed, the expansion and the further depletion of the ozone particularly over the Antarctic region.

With that, I will stop and than you for your attention.

Clarifying Questions

DR. SWENSON: At this point in the

meeting, we are ahead of schedule. We had a break planned following Dr. Meyer's presentation, but I think, given as early as it is already, we might move into the next session denoted by clarifying questions and take a break after that.

So, at this point, if there is no problem with proceeding, I would like to start with that and open it up to any members of the panel here to ask for clarifications.

Dr. Schatz.

DR. SCHATZ: Just one relatively simple one. I was not under the impression that nedocromil was still being marketed, I mean it is still available, but I gather it is.

DR. MEYER: I actually tried to go on drugstore.com and confirm these, and I did find it available, so to the best of my knowledge.

DR. SWENSON: Dr. Brantly.

DR. BRANTLY: Dr. Meyer, in your consideration, I didn't see consideration of the economics. Is that also a dimension that we should consider particularly in the context that

oftentimes patients are on multiple respiratory medications and some of them can be quite expensive?

DR. MEYER: It is certainly a factor that we think about in terms of the more formal moiety-by-moiety approach when we say patients are adequately served. We included the consideration of economics in that. So, I think that we would certainly welcome your thoughts in that regard as you discuss the moieties today.

DR. SWENSON: Ms. Schell.

MS. SCHELL: I have a question about supply. If we take one drug out, will there be enough to fill in the gap from the other companies that already produce it?

DR. MEYER: I think the important thing with regard to that is that we do, as I said, whatever recommendation is taken today, if there is a recommendation that a product is no longer essential, we will go through a notice and comment rulemaking which will not only allow for public comment, but will allow other manufacturers perhaps

of other products that might have to increase their supply to do so.

So, I think that this changeover would not be precipitous, it would be planned and it would allow for the other products that might need to increase their supply to do so.

MS. SCHELL: I have just one more question. With the Montreal Protocol, what other countries, are they still in use of this way, or are they completely caught up with it, or are we behind?

DR. MEYER: It depends on how you define behind. Our albuterol process is slower than some other countries, notably, Canada, Australia, many countries within the EU, for instance.

On the other hand, the EU has certain provisions that make, for instance, the de-listing of beclomethasone tougher for them, because they need to have two products to do that, and in some of the EU countries they do not. We don't even have a CFC product available. We will be able to shortly de-list beclomethasone.

So, I think that in some measures, we might be behind and in some measures we are not, but it is sort of a different healthcare system, different mix of considerations at this point, but clearly, as I said, in the List B that I pointed to earlier of the alternatives available, we have made substantial progress in the transition at this point.

DR. SWENSON: Dr. Schatz.

DR. SCHATZ: I guess I have two questions. One is by taking away some medications on this list, do we improve the chances of getting what we want for the drugs that we really do think are essential. My understanding of our relationship with the parties is that we go request and they are in a position to approve.

So, my question is, by doing this, are we improving the chances that the stuff we really think we need we are going to get?

DR. MEYER: You have to understand that I will only be able to answer that from personal opinion, because I certainly don't speak for the

parties, but I think to the degree that we are showing successful transition, that helps our requests for any remaining essential uses. I think that is true.

DR. SCHATZ: My second question is, all of us I am sure will have some views based on our own personal prescribing practices, but I am wondering whether there is any information available as to how many patients are using these drugs current, that would I think help us get some sense as to at least how many patients think they are useful or essential.

DR. MEYER: We do not have those data available for you today. I am sorry that we don't.

DR. SWENSON: Dr. Gay.

DR. GAY: Thank you. Will the FDA have available to us data concerning progression of development, for example, whether or not companies have made a good-faith attempt to begin to develop MDIs, if they are well along the pipeline and very close to approval, or if there is no significant information that they have even started

development? Will the FDA have that information available to us today?

DR. MEYER: Since this is an open public meeting, some of that information cannot be discussed in this meeting. To the degree that some of this has been acknowledged and perhaps might even be spoken about in the open public sessions by some of the manufacturers, then, yes, so not fully.

DR. SWENSON: Dr. Martinez.

DR. MARTINEZ: Dr. Meyer, one of the criteria for non-essentiality is that patients who require CFC product are adequately served. I assume that that criterion is valid. We had a similar discussion a year ago regarding albuterol.

If we decide to declare some of these products nonessential, will there be potential increase the minimal possible costs for patients of inadequate means or do not have insurance, that would make them require paying more for available products, and thus, perhaps because of means, not have the products available for treatment?

DR. MEYER: I think that will have to be

considered on a case-by-case basis. For instance, if you are talking about a patient on a brand name corticosteroid where there are many alternatives available with a variety of presentations, a variety of costs, I think it is hard to say whether that patient will be significantly impacted by this.

It is clearly a different situation from albuterol, because albuterol had a generic. There are no generic MDIs available for any other product except epinephrine, and we are not discussing epinephrine today, so while there might be differences in pricing, I don't think it is of the magnitude certainly that we are talking about with albuterol, but since these are not direct replacements, it is a little bit harder to say broadly that we could say that there is no cost impact.

I would say that for the direct switches to date, in other words, the pricing of Ventolin HFA versus Ventolin CFC, so the brand name, the price of other products that have been directly

switched, where they are branded products, they have been basically on parity, they have been the same.

The companies have actually publicly committed to that kind of pricing policy.

DR. MARTINEZ: So, as a follow-up then, are you then suggesting that a decision in this case will probably not cause a significant change in potential cost of the medicine for the public in terms of, for example, if we determine that some of the inhaled corticosteroids that are in the list that we are going to make a decision about, are discontinued, none of them is of such a low cost that would have allowed a patient to receive inhaled corticosteroids, but now will not because of an issue of cost?

DR. MEYER: I am not necessarily suggesting that. I am just suggesting I can't say that as a broad generalization for this. So, again, on an individual discussion, if you get to Drug X and the discussion is, well, Drug X is priced aggressively, it is cheaper than any of

these other ones, I think again we would welcome the input of the committee if they feel like that would have an important implication on the patients being affected.

DR. MARTINEZ: Are costs available as information for us at this meeting?

DR. MEYER: They are not available at this point.

DR. SWENSON: Dr. Kercsmar.

DR. KERCSMAR: Are all the inhalers that are on this B list manufactured in the United States, and if not, who gets charged for the CFC usage, the country that manufactures them or the country to which they are being sold or imported?

DR. MEYER: The products that we are talking about today are part of the U.S. essential use process, so they are produced in the United States. There are other products that have already been dealt with, albuterol is a notable one where some of the production was outside the U.S., but these products are all produced within the U.S.

DR. SWENSON: Dr. Schoenfeld.

DR. SCHOENFELD: Is there a well-defined procedure for developing reformulating these products to a non-CFC method, and does de-listing them have any effect on these companies' abilities to develop non-CFC formulations?

DR. MEYER: That is a good question. Actually, with regard to the first part of your question, it is a very difficult task to reformulate. I think early on, the thought process by any, I think even including those in the industry who are directly involved was that this would not be so difficult a task, but the chemical and physical properties of the non-CFC propellants, the HFAs, are such that it is required a reengineering of the valves, many of the gaskets, the cans themselves, so they are really entirely new products that are being developed, and it has been challenging.

In fact, some products have not been successfully reformulated because of those challenges.

With regard to if a product were to be

de-listed, would it make it more difficult for the new product to come forward, I don't think it should have any effect on that with the possible exception of one of the things we have liked to see with these replacement products is a comparison in a study against the product it is replacing when it is a direct one-to-one replacement. So, you would need to have study medication available.

But these products have all been approved under new separate drug applications, so it is not like one of them going away would affect the path forward for the other. DR. SCHOENFELD: Does that basically mean that if they reformulated, they would have to get approval of the new formulation, not on the bioequivalence grounds, but actually on efficacy grounds, and that would be true today before they de-listed, and also true after they were de-listed?

DR. MEYER: That is true. That is true, and there is a couple of reasons for that. One is that bioequivalence in terms of an inhaled drug that is locally acting is very, very difficult, if

not impossible, to establish under currently available science, but the other issue is that there are other things introduced by having such different formulations in terms of tolerability and safety that we feel need exploration in studies beyond the small, rather defined pharmacokinetics type studies.

DR. SWENSON: Dr. Newman.

DR. NEWMAN: I just want to make sure in light of some of the questions here today, I want to make sure I understand exactly what you are asking of us today, because I think that if you are asking us whether the essential question is provide substantial health benefit, that's a little different than asking us whether it provides substantial public benefit.

This question of economics, for example, comes in if we are thinking about this in terms of public benefit, and it sounds like we are not here today to really debate that, but just to give you a perspective on the health aspect and then you decide whether to--and then those other issues will

be raised subsequently. Just help clarify that for me.

DR. MEYER: Yes, I think that is a good way to put it. Clearly, your expertise is in making recommendations or observations about the specifics of the health benefit. I think we would welcome also other considerations from you. It is not like we are focusing in and will only accept recommendations or comments based on health alone, but to the degree that the economics are not things that we were planning to get into or answer today, I think if you raise concerns about that, we will duly note those, but those would be better dealt with in the notice and comment rulemaking subsequently.

DR. SWENSON: With respect to some of the drugs for which there are no obvious replacements, the cromones in particular, but this may apply to some of the others, as well, do you have any data as to when the patents expire and if any generic options are in the pipeline?

DR. MEYER: I don't have data on those. I

could probably get that in fairly short order, but I would not be surprised, particularly for the Intal, cromolyn, for instance, it that were already past.

The challenge to the developing a generic alternative to a cromone or to a corticosteroid is establishing bioequivalence, and part of the reasons that there are not further generics outside of albuterol is because of there not being a methodology for establishing bioequivalence in a reliable fashion.

DR. SWENSON: Ms. Schell.

MS. SCHELL: I have a question about the Montreal Protocol as far as deadlines or compliance. Is the United States in compliance with the Montreal Protocol, and is there a date where they have to have this totally met, and is there a consequence if not?

DR. MEYER: We are in compliance with the Montreal Protocol. There is no firm date that has been established. Back in the late nineties when I first started my involvement with this process,

many pointed to the year 2005 for the developed countries being totally out of the use of CFCs and MDIs, and that has proven not to be the case either for the United States or many of the other developed countries.

That said, I think that as I stated during my talk, it has been envisioned that the essential use process would be a temporary process, not permanent, and clearly, there is increasing interest on the parts of the countries involved with the Montreal Protocol to effect these transitions in a timely fashion.

So, I think that the U.S. does need to move forward responsibly, and when I say "responsibly," I mean both in terms of the public health benefits of the environmental side of this treaty, as well as protecting the public through assuring that medicines are available to patients who need them.

DR. SWENSON: Dr. Schatz.

DR. SCHATZ: Two questions again. Tell me if this is fair, to try to answer the question,

because I think it's answerable, is the question do we think that we and our colleagues can adequately care for our patients if a drug is gone, in other words, a drug is nonessential, if we think that we and our colleagues can adequately care for patients without it?

DR. MEYER: I think that would be a fair way to pose the question.

DR. SCHATZ: Okay. Then, my second question is that you mentioned this would be the beginning of a process. How long would you estimate, if possible, between a decision today that a drug is no longer essential and when, in fact, it would no longer be available based on that ruling?

DR. MEYER: It is hard to say with certainty what that would be, but it is very common for a rulemaking to take a year or two to play out. I mean if, for instance, you took the albuterol rule, actually, the early process began in '96, the late process began in '99, and it wasn't finalized until 2002. There was a lot of controversy and

considerations in that.

In a more focused rulemaking, it might be considerably quicker than that, but it is not uncommon for it to take a year or two to complete rulemakings, to go from notice and comment, or opening up with a Notice of Proposed Rulemaking to the point where it is finalized.

Then, once it is finalized, it doesn't necessarily become effective the day that it's published. It may be published with an effective date of six months or longer. One of the reason you might do that is to allow patients to sort of acclimate to the new realities, as well as to allow the other manufacturers who make products that might increase in sales to account for this gap in the marketplace, to plan accordingly and increase their production.

DR. SWENSON: Dr. Schoenfeld.

DR. SCHOENFELD: I have never actually designed or ran a clinical trial of an inhaled asthma medication, so I was just wondering how difficult would it be for these things to go back

on the market in new formulations in terms of the clinical trials required. Does the fact that the chemical was previously approved make a difference? Are we talking about clinical trials with thousands of patients or clinical trials with tens of patients? I don't have a good sense of how difficult these drugs are to develop.

DR. MEYER: Yes, these have typically been relatively streamlined development programs, because we do understand a lot about the moieties, so the purpose of the trials is really to understand the specifics of the product that is delivering that moiety.

Commonly, you might have a short-term trial that looks at pharmacodynamic measures if they are available, say, for a bronchodilator, and then you might have a 4- to 12-week treatment trial which may have, say, 70 to 80 patients per arm.

Then, you might also, depending on how different the formulation is, have a longer term extension of that, an open-label extension of maybe 100 to 200 patients out to six months to a year,

for instance.

So, they are much smaller than for a new molecular entity, but it is not trivial either.

DR. SWENSON: Dr. Kercsmar.

DR. KERCSMAR: I was wondering if you could clarify the reason that products that are available that are equivalent or the same drug for nebulization have been excluded, is it really thought that the convenience factor is so overwhelming for those nebulization products that should we not consider the availability of those in these deliberations?

DR. MEYER: Well, for the direct de-listing, we did not include the nebulization products because of the level of convenience, because one of the criterion was that it had to have approximately the same level of convenience, and clearly, standard nebulization treatment does not have the same level of convenience of an MDI, for instance.

For the purposes of today, I think that you are free to consider the entire therapeutic

armamentarium available in terms of making a determination, that Dr. Schatz said, you know, would my patient suffer if this product were to be removed.

DR. SWENSON: There being no further questions, Ms. Watkins is going to read a statement regarding our open public hearing.

MS. WATKINS: Actually, it will be in relationship to communication with the press.

I would like to remind the committee that in the spirit of the Federal Advisory Committee Act and the Sunshine Amendment, that discussions about today's topic should take place in the form of this meeting only, and not occur during lunch, breaks, or in private discussions.

We ask that the press honor the obligations of the committee members, as well.

The open public hearing speakers, if you would please come see me during break, I would appreciate it.

DR. SWENSON: We will break and reconvene in 15 minutes.

[Break.]

DR. SWENSON: We will begin this next portion of the meeting, if I could ask all members to return to their seats.

Open Public Hearing

DR. SWENSON: We will now begin the open public hearing portion of this meeting. Before that, I will read this particular statement relevant to presentations.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any known financial relationship that you may have with a sponsor, its product, and, if known, its direct competitors.

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

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

Our first presentation then will be by Ms. Maureen Hardwick.

MS. HARDWICK: Good morning. My name is Maureen Hardwick and I am here today on behalf of IPAC, the International Pharmaceutical Aerosol Consortium.

IPAC is an association of leading manufacturers of metered dose inhalers for the treatment of asthma and COPD. Its current members are AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, and INEX.

IPAC is firmly committed to the MDI transition as evidenced by the extraordinary investments and R&D efforts that its members have taken. IPAC companies' use of CFCs has declined substantially over the past decade as they have launched CFC alternatives and phased out CFC MDIs, and one of our members has phase out all use of CFCs in the United States.

IPAC is grateful for the opportunity to speak today and has always supported an open and transparent process that allows for input from all interested stakeholders.

IPAC strongly believes that any consideration of the continued need for CFCs under FDA's essential use exemption and under corresponding EPA regulations in which FDA has a statutory role should take into account the uncertain future access to CFCs.

As FDA itself noted at the June 2004 PADAC hearing, each year the Montreal Protocol parties are more reluctant to grant CFCs to the United States. Last month's protocol meeting only

confirmed this point.

This potential reduction is exacerbated by FDA's choice of a December 31st, 2008, effective date for albuterol non-essentiality. As a result of this decision, the U.S. albuterol market could continue to use over 1,000 metric tons of CFC per year for the next three years if the protocol allows it.

This could result in shortages for non-albuterol products for which there is as yet no CFC-free replacement. Therefore, it is critically important that CFCs only be used for truly essential products. To better ensure that this occurs, IPAC believes there are two key actions that FDA should take.

First, CFCs should be allocated only for MDIs that do not have a corresponding CFC-free alternative and where the manufacturer is diligently undertaking meaningful efforts to research and develop a CFC-free alternative.

Given future CFC uncertainty, it is imprudent for FDA and EPA to allocate annual CFC

volumes to companies for a CFC product where there are already adequate CFC-free alternatives on the market. This is particularly true when the company has in its power to phase out sale of its CFC products and to transition its own market.

IPAC companies have done this, so we know it can be accomplished, but some companies that have CFC-free alternatives are still major users of CFCs, so action by FDA is needed.

FDA should address this in two complementary ways: (a) by eliminating the essentiality designations for such products in 21 CFR Section 2.125 via a notice and comment rulemaking; and (b) by informing EPA that essential use CFC allocations are not necessary for such products.

Secondly, FDA should advise EPA not to allocate CFCs to companies that are holding excessive CFC stockpiles. The protocol's expert panel, which includes an FDA physician, Dr. Meyer, and other medical experts, has carefully reviewed the issue of CFC stockpiles and concluded that a

one-year CFC reserve is adequate.

IPAC companies, based on decades of experience manufacturing MDIs, fully concur with the protocol panel's assessment. FDA should therefore advise EPA that it is only necessary to allocate a license for new CFC production in an amount such that the receiving company's stockpile does not exceed a one-year reserve.

In conclusion, IPAC urges FDA to proactively implement the July 24, 2002, final rule and to be proactive in exercising its joint responsibility with EPA for allocating essential use volumes by taking the actions we recommended today.

Doing so will facilitate a timely and effective conclusion to the transition and minimize the continued need to CFCs to that which is truly necessary to meet patient need.

IPAC would be pleased to serve as a resource during this process and would be happy to provide further, more detailed information relevant to the transition of non-albuterol MDIs as the

issues evolve.

Thank you.

DR. SWENSON: Thank you, Ms. Hardwick.

Our next presentation will be by Dr. Kirk Shepard.

DR. SHEPARD: Good morning, Mr. Chairman, members of the Advisory Committee, FDA participants, ladies and gentlemen. My name is Kirk Shepard. I am Vice President of Clinical and Scientific Affairs at Boehringer Ingelheim Pharmaceuticals in Ridgefield, Connecticut.

Boehringer Ingelheim appreciates the opportunity to appear before the FDA Pulmonary-Allergy Drug Advisory Committee and share the company's extensive respiratory drug research and development efforts that bear directly on the discussions of this meeting.

In the United States, these efforts have yielded a number of effective products for the treatment of COPD including Spiriva, HandiHaler (tiotropium bromide inhalation powder), Atrovent (ipratropium bromide), and Combivent (ipratropium

bromide and albuterol sulfate) inhalation aerosols.

Atrovent and Combivent inhalation aerosols contain CFCs and are identified as essential uses in 21 CFR 2.125. We hope that our comments today assist the committee in advancing the public discourse on the CFC MDI transition in a manner that will be benefit patients and the environment.

Boehringer Ingelheim is committed to improving respiratory care through the development of safe, effective, and environmentally responsible therapies. For over 40 years, Boehringer Ingelheim has been a world leader in the research, development, and the manufacture of drug products for the management of respiratory disease.

Over 8 million patients worldwide with COPD and asthma rely on our medications. Recognizing that no single drug delivery system can meet all patients' needs, the company has developed, or is developing, a variety of products that included metered dose inhalation (MDIs), dry powder inhalers (DPIs), solutions for nebulization, and propellant-free inhalers. Boehringer Ingelheim

strongly endorses a smooth, timely and effective transition of our CFC-containing aerosol products that protects patients.

Protection of the environment and public health are an integral part of future planning at Boehringer Ingelheim, as we are dedicated to the research and development of CFC-free respiratory products.

The company has taken a leading role in the global CFC transition by investing nearly $400 million in the development of HFA-based MDIs and propellant-free inhalers. Our CFC-free development programs involve the reformulation of more products than any other MDI manufacturer. We have deployed over 200 scientists in 35 laboratories around the world and enrolled 10,000 patients in clinical trials to date.

Worldwide, 13 BI products have been reformulated or are in the process of being reformulated to 4 HFA MDIs and 2 propellant-free inhalers. Our CFC-free alternatives have been introduced in nearly 50 countries that are parties

to the Montreal Protocol.

In the United States, Boehringer Ingelheim research programs have yielded CFC-free products for the treatment of COPD, including Spiriva, HandiHaler introduced in the U.S. in 2004 and the recently introduced Atrovent HFA metered dose inhaler.

Atrovent HFA, approved by the FDA in November 2004 and introduced in May of 2005, is the result of over a decade of Boehringer Ingelheim research into CFC-free alternatives. During these early months after Atrovent HFA introduction, Atrovent inhalation aerosol continues to be available in the U.S. to allow for patients to make a seamless and orderly transition to CFC-free anticholinergic therapies such as Spiriva or Atrovent HFA.

Mindful of our commitment to the environment and global transition and after consultations with the FDA, Boehringer Ingelheim has decided to voluntarily discontinue the marketing and distribution of the CFC-containing

Atrovent inhalation aerosol in the United States as of January 1, 2006.

Accordingly, we have notified the U.S. EPA to reduce our 2006 CFC production rights to account for the removal of Atrovent inhalation aerosol from the market.

Combivent inhalation aerosol is an important product for the management of COPD. Clinical studies have demonstrated that maintenance bronchodilation of COPD patients is improved with Combivent compared to each of its agents alone.

There are many COPD patients whose symptoms cannot be controlled with just one inhaled bronchodilator therapy, thus making combivent patient population significant. In 2004, Boehringer Ingelheim distributed over 3.5 million combivent MDIs, serving over 2 million patients in the U.S.

Noncompliance is a significant barrier to improving patient health. The rapid onset of the benefit perceived by the patients in taking a short-acting beta-agonist in combination with the

long-acting ipratropium bromide increases both the convenience and patient satisfaction, two important factors in improving patient compliance.

Published results of several clinical trials provide evidence that regular treatment with anticholinergics may reduce the severity of COPD exacerbations in COPD patients with moderate to severe disease.

In short, combining of these two widely prescribed bronchodilators for COPD into one product has afforded these patient benefits while at the same time achieving a 50 percent reduction in CFC emissions that would have resulted from the use of the two, single-agent CFC products.

As with Atrovent, Boehringer Ingelheim has pursued a multi-year research and development program into a CFC-free alternative for Combivent. The company has applied extensive resources to reformulating Combivent, exploring both alternative HFA propellant and propellant-free inhalation devices as alternatives.

As a combination of a suspension and a

solution formulated with an HFA propellant, Combivent has posed technical complexities that have challenged our best reformulation efforts.

However, we remain optimistic that we will overcome these challenges. Our research and development is ongoing and Boehringer Ingelheim reaffirms its commitment to continue this effort to find a CRC-free alternative for Combivent.

We share FDA's high standards for products and until a CFC-free alternative to Combivent that meets those high standards is available, Combivent inhalation aerosol must continue to be designated as an essential use under 21 CFR 2.125.

Thank you for the opportunity to address the committee and for your time and attention.

DR. SWENSON: Thank you, Dr. Shepard.

Our next speaker is Mr. Alan Krueger.

MR. KRUEGER: My name is Al Krueger. I am an Associate Director of Regulatory Affairs at Kos Pharmaceuticals.

Kos acquired the U.S. marketing rights to Azmacort, both CFC and HFA, in April 2004 from

Aventis Pharmaceuticals. Azmacort CFC, available commercially for over 20 years, continues to be actively prescribed by physicians.

Since this product was acquired by Kos, new and total prescriptions have increased. In May 2005, combined total prescriptions were 92,000. New prescriptions accounted for nearly half of this number of 92,000.

Kos is committed to conversion to HFA. Final approval for Azmacort HFA is being actively pursued by Kos, an IPACT-1 and IPACT-RS member. In a December 2004 meeting with FDA, further development and approval plans for this product were discussed. Commercialization is anticipated in approximately 2008.

Other Kos aerosol R&D projects are also underway. Four projects, including two for asthma/COPD, one undisclosed for a systemic disease, and the last for inhaled insulin, are at various stages of development.

Thank you.

DR. SWENSON: Thank you, Mr. Krueger.

Our last speaker is Dr. Leslie Hendeles. I am a clinical pharmacist in the Pediatric Pulmonary Clinic at the University of Florida, and I am here as an independent person interested in the topic, and I have no conflict of interest with a beta-agonist manufacturer.

I just wanted to point out to the panel members who don't take care of children that the breath-actuated device called the autohaler has some unique properties for kids. It enables them to get a quick relief medicine without having to use a valve-holding chamber or spacer device, so in your deliberations, not only the drug is an issue, but the delivery device might be an issue, too, that I ask that you consider.

Thank you.

DR. SWENSON: Thank you.

At this point, then, I think we can move then into the formal discussion with each of the specific agents, but before we do so, if there are further points to be raised, this is the moment.

Dr. Meyer.

DR. MEYER: Yes, I want to just take time to clarify something with respect to a question that Dr. Gay asked earlier about how much we would be able to say about things under development.

I wanted to clarify for the purposes of the discussion, I would like you to speak about the transition as it is today, in other words, whether a product is being actively reformulated or not really shouldn't factor into your recommendations to us. It should be given the current medical practice and given the current available alternatives, do these products on this list in the Charge to the Committee remain essential individually.

DR. SWENSON: Dr. Moss.

DR. MOSS: I had a question for Dr. Meyer. Maybe we can benefit a little bit from the panel's experience a year ago with the albuterol discussion. It seems to me that after the discussion a year ago, there is a lag time of about I guess 3 1/2 years before there will be no CFC

compounds for albuterol.

Do you anticipate, if we make similar decisions on these agents, what the lag time would be after the decisions are made for these companies?

DR. MEYER: That time frame was very specific to the considerations with regard to albuterol and actually reflected some of the advice given by some of the members participating in that committee that they had concerns particularly about the impact of balancing cost considerations versus availability of medications, and so on.

So, that was very specific to albuterol and again was responsive to some of the advice that we got. I think this would depend whether any of these, if they were recommended to be de-listed by you folks, would have any kind of lag period afterwards would be highly individual, but would be unlikely to always be in the 3-year time frame. It might be quite a bit quicker than that.

DR. SWENSON: Dr. Schoenfeld.

DR. SCHOENFELD: Maybe this would occur at

the public hearing, at the subsequent public hearing, but I am a little concerned about the process here in that it seems that a regulatory decision is made without really relying on evidence-based medicine in the same way that, for instance, regulatory decisions were made yesterday.

That is, it would seem a better process would be to ask each of these companies that make these products to marshal the scientific evidence in the form of maybe what they initially submitted to gain approval for these products plus subsequent papers in the medical literature that would argue that these products are essential, and then have these documents just as they are in new drug applications reviewed by your staff and a report written, and in that case, we would be making these decisions based on the usual level of evidence that we are used to seeing in making important decisions like this.

DR. MEYER: Point noted. As I said at the beginning, this is a very different advisory committee than the usual. Unfortunately, I think

there would be a paucity of direct data of the kind of substantial evidence that we normally discuss in these kind of settings because of the relative lack of comparative data that exist.

But I would point out that in the subsequent rulemaking process, I suspect that any affected company would, in fact, marshal whatever kind of data that do exist to address their argument should they choose to say that they think they continue to be essential.

So, I think we would have that kind of discussion or that kind of presentation to us at that stage.

DR. SWENSON: So, Dr. Meyer, just to reiterate, then, our charge is to give you some early guidance as to prioritizing these individual decisions, that you would take a yes or a no with that type of adding weight to then your decision as to whether to bring these forward at separate discussions.

DR. MEYER: I might say it's a little bit more than early guidance, but yes, I mean it is

just the first step of the process, so this wouldn't be a definitive, if you folks recommend--and I don't refer to one of these by name--but if you recommended that Drug X was no longer essential, there is a process that goes on from there, too, more fully in a public comment manner.

DR. SWENSON: So, for each of these agents, then, there would be a fair hearing to follow.

DR. MEYER: Yes, any advice from you folks that one or more of these was no longer essential would lead to rulemaking on our part that would lead to subsequent public discussion.

DR. SCHOENFELD: Possibly meaning coming back to us.

DR. MEYER: Possibly. In some circumstances, it might be in written form, in some circumstances, it might actually come back to the committee.

DR. SWENSON: Any further general questions? Dr. Moss.

DR. MOSS: I had a general question again for Dr. Meyer. I think I am assuming correctly that the companies that make these compounds were all told about this meeting, and if they wanted to, like two of them did, they could come and talk at the open public forum?

DR. MEYER: Yes, I just was conferring with one of our regulatory legal staff, and, in fact, just in answer to the question of a moment ago, all subsequent actions, all subsequent rulemaking would engender an open public hearing, would require of us an open public hearing, so it would not just be in written form, there would be an open public hearing.

Yes, there would be opportunities at that for the companies to either--I don't know whether it would be in the open public hearing session or might even be a sponsor's presentation as a part of that meeting.

DR. MOSS: But all of the companies were informed of this meeting, so if they had information that they wanted to relay, they could

have come to this meeting for the other compounds?

DR. MEYER: This meeting was publicly announced in the Federal Register as per usual, and I believe companies are very good at surveying the Federal Register for notices that affect them.

Committee Discussion

DR. SWENSON: If there are no further general questions, I think we should move then to the specifics, and the first will be the beta-agonist. This will be on your List A page, and I think we should start with metaproterenol and ask if there are any specific comments about metaproterenol from any of the panel members.

Dr. Schatz.

DR. SCHATZ: Just a point. Are we going to actually vote, do we want to vote on each of these, or is it not that sort of decisionmaking?

DR. MEYER: I don't think we were envisioning a formal vote on these. So, I think we were envisioning much more of a discussion and allowing folks to make individual recommendations, but not a formal vote.

DR. SCHATZ: Since my microphone is on, I will just say that I do believe I could care for my patients without the availability of metaproterenol.

DR. SWENSON: Any other thoughts by panel members?

Dr. Brantly.

DR. BRANTLY: I agree.

DR. SWENSON: Dr. Moss?

DR. MOSS: I would agree also.

DR. SWENSON: I will go ahead and agree, as well.

DR. GAY: I will agree, as well.

DR. NEWMAN: I would agree, as well, and just add that given the circumstance that we are in here, and what we are being asked to do here today, and that there is going to be a public process that follows, I don't actually know why we wouldn't want to start the ball in motion for everything on this list.

DR. SWENSON: That is fair enough since we are talking about two drugs here of very similar

action and basically the same position, so what I might do is recommend in behalf of the panel that both of these not be considered for special exemption and ask if any members wish to disagree with that assessment.

MS. SANDER: I have a couple of questions. With the Alupent, I don't see--are there any plans of Boehringer Ingelheim to discontinue this product anyway, do you know?

DR. MEYER: We had a spokesperson from Boehringer Ingelheim speak just a few moments ago. I don't know whether he would like to address that question.

DR. SHEPARD: We do not plan to reformulate the decision as far as when it would be discontinued, which it probably would be, has not been made yet.

MS. SANDER: How many patients do you have using that right now?

DR. SHEPARD: I am sorry, I don't have the specifics on that.

MS. SANDER: Okay. With regard to Maxair,

do we have anyone from 3M?

DR. MEYER: I do not believe that I saw anybody from 3M.

MS. SANDER: I agree with the panel with regard to Alupent. With regard to Maxair, I think we would need to do a little more examination about its use in pediatric populations. I don't have enough information in that area, because it is a breath-activated inhaler, but I don't know the amount of people using it.

DR. SWENSON: Could we ask our two pediatricians to comment to Ms. Sander?

DR. KERCSMAR: The device in question certainly confers benefit in ease of use, and while it certainly may be relevant to pediatric patients, I would still say that probably a minority of our patients use it, but on the other hand, I would argue that it is not just for kids and that anybody who has difficulty with an MDI device certainly would benefit from an autohaler, and that could include any adult, and certainly elderly patients perhaps as well, so I don't think it's an issue

just restricted to children.

I think that the other thing that would be important to know is whether that device can be adapted to non-CFC-containing inhalers.

DR. SWENSON: Dr. Martinez.

DR. MARTINEZ: I agree. I don't have anything to add.

DR. SWENSON: Dr. Newman.

DR. NEWMAN: I guess that given the scope of what we are being asked to do here, I would agree that what you are all saying about the potential use of that delivery device is potentially important, I think there is a step beyond this for addressing how important that is and what the alternatives could be to that, and whether there is a way of making it CFC-free, et cetera.

I would again stress I think the importance of setting the ball in motion on both of these products in order to let that be aired.

DR. MEYER: I have perhaps changed my request to the panel. What I would like to do is

actually--let's call it a poll, because I don't want it to have the formality of a vote, but I think it might be helpful just to poll each person on the individual moiety after you have had your discussion about it.

I know that your comment, Dr. Swenson, was about perhaps the committee could regard these together, but I would like to individually poll on both of them.

DR. SWENSON: Before we start that poll, any further questions, comments?

Okay. Ms. Schell, would you offer your advice?

MS. SCHELL: On we are just using Alupent?

DR. SWENSON: On metaproterenol only.

MS. SCHELL: I don't qualify it as an essential drug.

DR. KERCSMAR: I would agree. I can take care of my patients without that drug.

DR. MARTINEZ: Nonessential.

DR. BRANTLY: Nonessential.

DR. NEWMAN: Nonessential.

DR. MOSS: Nonessential.

DR. GAY: Nonessential.

DR. SWENSON: Nonessential.

DR. SCHATZ: Nonessential.

DR. PRUSSIN: Nonessential.

MS. SANDER: Nonessential.

DR. SCHOENFELD: I will have to abstain since this is not my level of expertise. If somebody has data, I will be glad to look at it.

DR. SWENSON: All right. We will proceed then with pirbuterol or Maxair, and we have already had some comments, but before we do this poll, any further points to make?

Dr. Schoenfeld, I will let you start. I suspect maybe it's the same.

DR. SCHOENFELD: The same.

DR. SWENSON: Abstention.

Ms. Sander.

MS. SANDER: There is part of me that realizes that CFCs are going away and that there is holding chambers and other devices, and maybe I should abstain.

DR. PRUSSIN: Nonessential.

DR. SCHATZ: Nonessential.

DR. SWENSON: Nonessential.

DR. GAY: Nonessential.

DR. MOSS: Nonessential.

DR. NEWMAN: Nonessential.

DR. BRANTLY: Nonessential.

DR. MARTINEZ: Nonessential.

DR. KERCSMAR: Nonessential.

MS. SCHELL: Nonessential.

DR. SWENSON: We will move then to the category of inhaled corticosteroids. Let's begin just then with the opportunity for any general comments or questions of either of the two agents, flunisolide or triamcinolone.

Dr. Martinez.

DR. MARTINEZ: As I requested before, information about potential costs, cost consequences of the decision we are going to make, I would like to comment about this.

I think that as has been well said by the FDA representatives, this is I think not an issue

in this case. There is a situation with respect to inhaled corticosteroids which are as essential for the treatment of asthma as albuterol is, and it has to do with our previous discussion.

The situation for inhaled corticosteroids is not the same as that for albuterol. The discontinuation of the medicines that are in this list, I don't think will have an effect on the capacity of patients given their economic means to have access to these medicines.

So, with a sense of fairness with respect to the type of discussion we had the last time about albuterol, I think in this case, this does not apply. This not applying the issue of the atmosphere in relation to CFC exposure becomes essential.

Therefore, I think that that needs to be considered, and since there are other medicines that are equally or more effective than the ones that are on this list, I think that should be the essential consideration in this case.

DR. SWENSON: Any further questions?

Comments?

We will begin then with flunisolide. Ms. Schell.

MS. SCHELL: Nonessential.

DR. KERCSMAR: Nonessential.

DR. MARTINEZ: Nonessential.

DR. BRANTLY: Nonessential.

DR. NEWMAN: Nonessential.

DR. MOSS: Nonessential.

DR. GAY: Nonessential.

DR. SWENSON: Nonessential.

DR. SCHATZ: Nonessential.

DR. PRUSSIN: Nonessential.

MS. SANDER: Nonessential.

DR. SCHOENFELD: I will abstain.

DR. SWENSON: We will move to triamcinolone.

Dr. Schoenfeld, you abstain? All right.

Ms. Sander.

MS. SANDER: Nonessential.

DR. PRUSSIN: Nonessential.

DR. SCHATZ: Nonessential.

DR. SWENSON: Nonessential.

DR. GAY: Nonessential.

DR. MOSS: Nonessential.

DR. NEWMAN: Nonessential.

DR. BRANTLY: Nonessential.

DR. MARTINEZ: Nonessential.

DR. KERCSMAR: Nonessential.

MS. SCHELL: Nonessential.

DR. SWENSON: We move now to the third category, the cromones, cromolyn or Intal, and nedocromil or Tilade, and specific comments related to the class or to individual compounds? Dr. Schatz.

DR. SCHATZ: Here, I can think of a couple of circumstances where I think it has a unique role. One is in exercise-induced bronchospasm for people who don't tolerate beta-agonists, and the other is prevention of a specific allergy-induced episode of asthma, patients going to visit where there is a cat in the house, it really does seem to prevent those symptoms.

So, in this case, I actually would like to

still--I feel I can take care of my patients better with it available.

DR. SWENSON: Any further comments? Ms. Sander.

MS. SANDER: We don't have anyone here from the company that manufactures this, do we?

DR. SWENSON: No representatives applied for the public hearing.

Dr. Newman.

DR. NEWMAN: Could I make two comments? One is if they aren't here, that would sort of imply to me that maybe they have nothing to say on it, but we obviously don't know that for sure.

But the other thing I wanted to say is that Dr. Schatz, your comment I think is well taken, but I think of alternatives in other classes that I can use that allow me to get around whether a cromolyn type compound is available.

It is true that it seems to hold kind of a small place still in the armamentarium, but from my perspective, I think one can work without it just in my own practice.

DR. SWENSON: Dr. Prussin.

DR. PRUSSIN: I would concur with that. I mean you are right, there are uses of these drugs that are unique and I am sure there are patients who really prize them, but they are relatively ineffective drugs in terms of clinical trials in asthma, they track more or less with placebo, and when you compare cromones to inhaled steroids, they are much less active.

Now, again, I think you are right, there are specific patients who get benefit from them, but I guess the question is how many of those are there and are there really no other alternatives. I just put that out there for the group.

DR. SWENSON: Dr. Schatz.

DR. SCHATZ: I actually think this is a situation where it isn't so patient specific, as much as it is circumstance specific. I think the data are quite good for the two circumstances that I mentioned, and I actually don't think there are--I mean there are alternatives--but I don't think there are better alternatives for the patient

who is sensitive to beta-agonists taking something right ahead of time for exercise, and the patients, I don't think there are any other alternatives that do the same thing prior to a specific allergen exposure.

I would also say that if, in fact, it is limited to those uses, which certainly in my practice it is, I don't use it instead of inhaled steroids in any other circumstances, the amount of total use would not contribute a lot of CFCs, but I do believe the benefit to those patients in that category of patients would be worth it.

I still, in my sense, and by my definition, this would help me differently. I certainly understand the other views that are being expressed.

DR. SWENSON: I want to echo some of that in that as we discussed albuterol in the last meeting, that total amount relative to the vast amount of CFCs that were being used for all the commercial and industrial and cosmetic purposes that you outlined, Dr. Meyer, if we decide to keep

an essentiality to these compounds, this represents an even smaller, vanishingly small total amount of CFC, and again for the individual patient for whom, for reasons that we can't put our finger on, a certain drug works wonderfully, I think possibly given there are no alternatives, and this represents possibly a very, very small amount of the total, small amount being used for inhaled therapy, I would think that maybe we should consider an essentiality continuation.

Ms. Sander.

MS. SANDER: The request for CFCs for this product, Dr. Meyer, can you tell us is it a large amount, is it a small amount?

DR. MEYER: I don't think I can properly characterize that. Dr. Swenson just referred to that albuterol certainly accounts for approximately half of all the CFCs requested by the United States, so all the rest of these products, some of which are not on this list because they have direct alternatives, such as the Atrovent HFA, account for the other half.

So, I think you could sort of work from there. If each of these was equally distributed, you could sort of guess what that might be, but I can't really quantitate that for you.

MS. SANDER: So, CFCs are going to go away totally at some point in time in the future, right?

DR. MEYER: Yes, that's the expectation of the Montreal Protocol.

MS. SANDER: Right. So, patients who are currently using drugs that contain CFCs really need to be thinking about, and working with their doctor, on alternatives now as opposed to waiting until later on, is that right?

DR. MEYER: Well, I think that would depend on your point of view, but I think that that is a valid way to view things.

DR. SWENSON: Dr. Newman.

DR. NEWMAN: I think absent knowing how small this contribution in and not really knowing how appropriately confined the practice use patterns are for these drugs, I don't know why we wouldn't want to go ahead and have there be a

public airing and let the cromone enthusiasts speak and map out how large or small this contribution is, and let this again be brought forward for public discussion.

I would be in favor of there being public discussion around it.

DR. SWENSON: Dr. Moss.

DR. MOSS: I would agree with what Dr. Newman was saying. I think it is important to find out why the companies that makes these cromolyn medications have not proceeded through the process of converting from CFC compounds to non-CFC inhalers.

The Montreal Protocol has been around for a while. If the other companies have done a very job of converting over, you know, it would be nice to hear from the company side why they haven't made the effort to convert their medication over.

Maybe they are not as committed to the medication as we are, and if that is an important point, then, it sort of doesn't matter in the sense if we think it is essential or not, if they are not

committed to changing over to proper inhalation compounds.

So, I agree, it would be nice to get more information from these companies before we make a decision.

DR. SWENSON: Dr. Kercsmar.

DR. KERCSMAR: I also agree with Dr. Newman. The cromones are still going to be available in nebulized form and certainly while the convenience isn't great, the efficacy will be the same for the patient with a planned known exposure, nebulization could certainly serve as an alternative for the small group of patients that have no choice.

I think there probably are other alternatives for exercise, but I think the bigger issue, the market I am sure is still very small, and this is other data that we would need to make a cogent decision.

DR. SWENSON: Dr. Schatz.

DR. SCHATZ: I would say a couple of things. I think as we all know, the difference in

convenience between a metered dose inhaler and a nebulizer are substantial, so that wouldn't make me feel better if it weren't there.

I also don't think it is our decision, I don't think it's our role to try to figure out why the company isn't here or be concerned that they are not here. I think we could conjecture that the total market, as was mentioned, for cromolyn is small, and therefore it doesn't make a difference to them, that's a conjecture, but that doesn't matter, I think, to my determination that I would like to have it available in that niche that it serves.

So, I guess those are my two responses.

DR. SWENSON: At this moment, and in an attempt to be totally fair, we have one more person that wishes to express a statement in the spirit of an open public forum, so I will ask that individual to stand.

Would you please introduce yourself, because we have no information about you, would you identify your affiliation and abide by all of the

strictures that I read at the start of this open forum.

MR. DABREZZI: My name is Carl Dabrezzi. I am with 3M. I am coming up partially because of your question of the manufacturer for Intal. That is 3M. This also goes back to the comment back on pirbuterol, and I guess the only comment I would like to make is that do not assume, the committee should not assume that activities are not going on with these molecules simply because presentations weren't here.

We are aware the public comment period will be made available to us at the time of the rulemaking process. So, I stepped up only as a manufacturer of the Intal as you were asking. So, thank you.

DR. SWENSON: Thank you.

If there are no further discussions to be made--

DR. SCHOENFELD: I am a little confused about the sort of level of proof here in this kind of meeting, which is a little bit--in other words,

is the idea that sort of anything that has a suspicion of being nonessential should go through to the next step, or is it that we should be fairly sure that it is nonessential to go to the next step?

I mean this is not for me to make the decision, but for the rest of the committee, I am not sure what--this is a question of the FDA, at what level of feeling, what level would--I mean in a way, the purpose of this meeting is to sort of save a lot of trouble because once things to on to the next step, it is going to cost the companies a lot of money, and it is going to cost the taxpayer a lot of money to go to the next step, so I am not sure what kind of burden is for our voting.

DR. MEYER: Fair enough. I would like to introduce Mr. Wayne Mitchell, who is a lawyer in the regulatory policy staff of the Center for Drugs, who has been very involved with these issues for a number of years. I would like to introduce him and allow him to speak to this.

MR. MITCHELL: The first thing is the next

step is a Notice of Proposed Rulemaking, and in that, our conclusions are very tentative or can be very tentative.

The other thing we can do in that, and I am certainly listening to the discussions on pirbuterol and the cromones, is we can ask specific questions, ask for specific comments on what sort of niche market a particular drug has, whether the Maxair mechanism presents special advantages for pediatric patients. We can ask for specific comments on these sorts of things.

That is one of the things I am trying to derive from not so much the polling, but from the discussion that precedes the polling, or what sort of comments should we be looking for, which we would be asking for.

I mean there is a certain inclination, at least on my part, to want to go ahead with the Notice of Proposed Rulemaking on as many drugs as possible. If I hear from the committee, no, that's totally wrong, that is absolutely an essential use, well, that is a different situation, but if it's an

open question, then, I would like to go ahead with this, just because it is a long, complicated administrative process.

We have this meeting. We have the Notice of Proposed Rulemaking. We have a comment period. During that comment period, we will have an open public hearing. Then, finally we have to have a final rule. We will also be consulting with other agencies - EPA, State, OMB, so it is a very long process.

So, if we can get the process started, even if during that process we are not 100 percent sure and we are still asking questions, then, I think that is probably the best way to go here.

DR. SWENSON: We will poll then with each of these drugs, and I think we will allow people to offer any further points to the needs that you foresee in any new rule policymaking.

Ms. Schell, will you begin for us then with cromolyn?

MS. SCHELL: Nonessential.

DR. KERCSMAR: Nonessential.

DR. MARTINEZ: Essential.

DR. BRANTLY: Nonessential.

DR. NEWMAN: Nonessential.

DR. MOSS: I am going to abstain.

DR. GAY: Essential.

DR. SWENSON: Essential.

DR. SCHATZ: Essential.

DR. PRUSSIN: Essential.

MS. SANDER: Essential.

DR. SCHOENFELD: I will abstain.

DR. SWENSON: Okay.

Dr. Schoenfeld, I will start you off.

DR. SCHOENFELD: I will abstain.

DR. SWENSON: For Tilade. We are talking about nedocromil.

Ms. Sander.

MS. SANDER: Are we going to have any discussion around Tilade?

DR. SWENSON: We can, certainly. This is the point. If you wish to make comments, go ahead.

MS. SANDER: I would just like to hear from people around the table a little bit of

discussion about this, about Tilade, what they see.

DR. SWENSON: Could you help us by at least asking a few questions as to why you think maybe it's different from what we have done with cromolyn, what separates them?

MS. SANDER: Well, actually, the very first question, is Tilade really still even around. It know it's not on this list, and the way this list was done, we contacted manufacturers.

DR. MEYER: It is still on the essential use list. It was probably several months ago that I looked on line to see, but I could not state with surety that it is marketed at this point, but let's assume for the purposes of discussion that it is, because if it's not marketed, we actually have a mechanism in our essential use rules right now to remove it without any recommendations of the committee.

MS. SANDER: I feel it's nonessential.

DR. SWENSON: Does anybody wish to say anything, so that your opinions might inform the other members of the panel, or should we continue

with the poll?

Dr. Schatz, go ahead.

DR. SCHATZ: As a champion for cromolyn, I don't feel the same way from clinical experience or from the data that exists in terms of the differences between nedocromil and cromolyn, and I know I can live without it because I have assumed it has been unavailable and have not been prescribing it for a long time.

So I feel that it is not the same as cromolyn in terms of its essentiality, and I think the comparative data that do exist, by and large, support that. So, particularly if cromolyn were available, I don't see nedocromil would have to be.

DR. SWENSON: Dr. Newman.

DR. NEWMAN: I can't think of the last time I picked up a pen and wrote a prescription for that particular medication, so I would underscore that.

DR. SWENSON: Ms. Sander, do you have anything further?

MS. SANDER: No.

DR. SWENSON: Let's start again then just in light of these comments.

Dr. Schoenfeld.

DR. SCHOENFELD: I will abstain.

DR. SWENSON: Ms. Sander.

MS. SANDER: Nonessential.

DR. PRUSSIN: Nonessential.

DR. SCHATZ: Nonessential.

DR. SWENSON: Nonessential.

DR. GAY: Nonessential.

DR. MOSS: Nonessential.

DR. NEWMAN: Nonessential.

DR. BRANTLY: Nonessential.

DR. MARTINEZ: Nonessential.

DR. KERCSMAR: Nonessential.

MS. SCHELL: Nonessential.

DR. SWENSON: We will move to our last agent, the combined product of albuterol and ipratropium, Combivent. I think we should just begin first with any general comments that panel members wish to make.

DR. PRUSSIN: I have a question for the

pulmonologists. How much Combivent, how often is it being used rather than, let's say, as a combination inhaler rather than somebody, let's say, being on Advair and then using ipratropium as a separate inhaler? Is this really a mainstay of COPD therapy?

DR. BRANTLY: It remains a mainstay. It is used quite frequently by many physicians at the present time.

DR. SWENSON: I would concur with that. It represents probably about 50 percent for me vis-a-vis the separate agents.

Dr. Gay.

DR. GAY: Indeed, it remains quite popular. The concern is whether or not its popularity will begin to progressively wane with the increasing popularity of Spiriva. The two drugs cannot be used together because of the interactions between the short-acting anticholinergic and the long-acting anticholinergic, so what you may see with time is if patients triage to the newer medication, the

Spiriva (tiotropium), clearly, the usage of Combivent is going to have to decrease.

DR. SWENSON: Dr. Moss.

DR. MOSS: I work at a hospital that has a very limited budget, and we do not have Combivent on our formulary. Patients are required or have to use each medication individually, and I think it is just important to point out that these medications are available individually, people can get these drugs.

It is easier if they use it in one inhaler, but if we are thinking about whether something is essential or not, I am not sure we can say it's essential if the two drugs are available independently in non-CFC compounds.

DR. SWENSON: Dr. Schatz.

DR. SCHATZ: I believe there were some recent COPD guidelines, at least I heard a presentation about that, and I don't take care of COPD, so I am not as up to date, but where does this combination fit in terms of those guidelines?

DR. SWENSON: Dr. Gay.

DR. GAY: It fits in the guidelines with the short-acting bronchodilator, so for patients with mild disease, at this time, that is where it falls. It has been used upon occasion as a rescue type inhaler, as well, not only in COPD, but in asthma, as well, but its utility, its frequency of use in that asthma population tends to be considerably low.

But at this point, it's a short-acting PRN or a short-acting inhaler for patients with mild disease.

DR. SWENSON: Dr. Kercsmar.

DR. KERCSMAR: I just have a question to clarify also. We don't take care of a lot of COPD in pediatrics. So, is what you are saying in the guidelines, is what is recommended the fixed dose, metered dose inhaler, or the two drugs given separately or simultaneously?

DR. GAY: No, you are very correct, and I thank you. It is not specifically this inhaler, but the two drugs, the two drugs.

DR. SWENSON: Ms. Schell.

MS. SCHELL: I am not sure if this is a consideration, but compliance factor of the patient taking the medication, taking the Combivent compared to taking the two inhalers, is that something that would play into this when we are looking at essential or not, because I know, as a practitioner, with patients, that I can get them to take a Combivent easier than I can get them to take two different inhalers. So, is that a factor that we look at when we are looking at if it's essential, its compliance?

DR. MEYER: I just wanted to make a comment in that regard. I think it's an important question. Both albuterol and the ipratropium in the setting of COPD are primarily aimed at symptom reduction, and not disease modification.

Compliance would be a particularly important consideration in a disease modification therapy, and a therapy aimed at treating symptoms and driven by, particularly if it's prescribed at a PRN manner by symptoms occurring, I don't think compliance is quite the issue.

So, I would just raise that perspective.

DR. SWENSON: Dr. Schatz.

DR. SCHATZ: I would still say that I think it should be an issue. I think that if the guidelines recommend the combination, there is just no question that the fact that they are available separately, I think we serve patients better by keeping the combination available.

DR. SWENSON: Dr. Newman.

DR. NEWMAN: I think a clarification. I don't think that there is a guideline that I am aware of that requires you to be on both of these medicines simultaneously. Dr. Gay, maybe you want to comment on that.

DR. GAY: To clarify this, each of these medications separately falls under the guideline of a short-acting bronchodilator, which is recommended for the treatment across the board for use in COPD.

There is no place in the guideline specifically for the physical moiety of Combivent. There is clearly use of beta-agonists in combination with anticholinergics as part of

symptom reduction, both as short acting and long acting agents, but no, there is not a specific place in any of the guidelines that says that Combivent alone is appropriate therapy, although there are places in the guidelines where they do clearly talk about the combination of the different bronchodilators.

DR. SWENSON: Dr. Moss.

DR. MOSS: I think if we are going to talk about compliance issues that Ms. Schell brought up, which I think are very important, I agree if you have one inhaler, it is easier to use that than if you have two, and the compliance will be better, but I think that needs to be balanced by the cost of the medication as Combivent together is more than each individual inhaler alone, at least in our practice.

So, when you are talking about compliance, there is the other side of cost that needs to be balanced with the ease of use. So, I just wanted to make that statement.

DR. MEYER: Can I follow up on that,

because that is probably true now. When albuterol is no longer available as a generic inhaler, which will happen as of December 31st, 2008, that may well not be the case any longer.

So, just to put that in perspective.

DR. SWENSON: Ms. Sander.

MS. SANDER: I have a couple of questions for Boehringer Ingelheim. Can I ask them directly?

DR. SWENSON: I think that is fair.

MS. SANDER: In your presentation, you said over 8 million patients worldwide use Combivent, or excuse me, use your medications. How many of them use Combivent?

DR. SHEPARD: We quoted that 2 million patients in the U.S. use Combivent. As far as the worldwide figure, I am sorry, I am not sure, but it's 2 million in the U.S. with over 13 million prescriptions also in the U.S.

MS. SANDER: With 13 million prescriptions did you say?

DR. SHEPARD: Correct.

MS. SANDER: In your testimony, you said

you strongly endorse a smooth, timely, and effective transition that protects patients. How would you describe that for Combivent, taking place for Combivent?

DR. SHEPARD: In other words, protecting the patient?

MS. SANDER: Right, well, in terms of you making your company strategy, to make the transition from CFC to--you know, I know that you are working on your HFA.

DR. SHEPARD: Atrovent HFA was approved. It was a comment relating to that as far as making sure the transition occurred smoothly, having the offering of both, and then the discontinuation of that product which we thought was a reasonable time for the patient and the physician to make that transition.

Did I answer your question?

MS. SANDER: Yes. So, your conclusion is that right now, in order for you to serve patients' needs here in the United States, Combivent must continue to be designated as an essential use, is

that right?

DR. SHEPARD: Correct.

MS. SANDER: Thank you.

DR. SHEPARD: I guess I shouldn't comment anymore if I wasn't asked a question about it, but when we are talking about patient care also, we are also saying that we have made available, somebody else said Spiriva in an alternative form, we now have Atrovent, but there is a stronghold of patients--that is where we gave the numbers--that still use this product, and are very loyal to it.

MS. SANDER: We see in our dealings with patients that a lot of them are using Combivent.

DR. SWENSON: Dr. Prussin.

DR. PRUSSIN: A very simple and direct point, but the word here is essential, and I think all these uses we are talking about are preferable, but not essential uses of a drug.

DR. SWENSON: Dr. Martinez.

DR. MARTINEZ: The arguments that have been given convince me that we cannot consider this an essential medication in the sense described.

The patients will have available the two other products. I completely agree with Dr. Meyer that this does not meet the requirement for compliance because here, it should be considered more relief type medication, and individuals who take this medication, one would suspect feel the relief and thus will have the stimulus to do so, which is different for a controller.

I think here we have to take into account what Dr. Meyer told us with respect to the commitments of the United States to the protection of the environment. I mean that sense and given also the fact that the company has told us explicitly that they remain optimistic that they will overcome these challenges to product this combined product.

I think by declaring nonessential will stimulate the company to pursue this even further and more aggressively because by 2008, which is when the albuterol will become perhaps more expensive, if they do so, I think we should expect that this product will be available in the form of

an HFA.

So, for those reasons, I think we cannot consider this an essential product.

DR. SWENSON: Ms. Schell.

MS. SCHELL: I have a question. If we consider this nonessential, will there be enough Atrovent available? I mean is there enough drug available to replace the 13 1/2 million? Do you see what I am saying? Will the drug be available if we don't have Combivent available, will there be enough Atrovent available?

DR. MEYER: Again, I think the important point there is that there is a process that would play out from here that would allow time, and if, in fact, we were convinced that there were not adequate alternatives available in terms of supply, we could effect a date such that it would allow for that.

I did want to make one comment with regard to Dr. Martinez's points, which is I don't think we can infer that the lack of Combivent alternative product now represents any lack of commitment on

the part of BI, and therefore, I don't think we can infer that if we said that Combivent was nonessential, that it would spur their development to be better than it is now, you know, to be fair to the company.

I think your points are well taken, but I just wanted to make that point that I think the challenges to reformulation, particularly for products with very low microgram strength, such as the ipratropium component of this product, are high, they are very high, and I don't think you could take the lack of a product being available at this point as a lack of commitment on the part of the sponsor.

DR. MARTINEZ: I am sorry, I didn't intend to infer that. I just said that--I am not talking about the past--I am talking about the future. It is obvious to me as a matter of logic that the fact that now perhaps this product would be on the list of products that would be declared nonessential, could stimulate even further efforts, because the amount of efforts that can be put may differ

depending on how much time you have available to develop those efforts.

It is just an opinion, not a definitive issue.

DR. MEYER: Understood. I just wanted to make a defense of the company, that I think that there are significant challenges, and I don't think we can infer or imply that, in fact, the fact that it is not on the market right now means they are not fully committed and working quite hard in terms of reformulation.

DR. MARTINEZ: Point well taken.

DR. SWENSON: Dr. Schatz.

DR. SCHATZ: I come back to these guidelines which I think I am remembering better. It was my understanding that these international guidelines started with beta-agonists, and granted for the milder ones, that when that wasn't adequate, then, a second inhaled bronchodilator was recommended, and that would either be then albuterol plus ipratropium, or it would be albuterol plus tiotropium.

Then, the next level up was inhaled steroids. So, for that group, if I am correct about that, for that group that we want to add that second bronchodilator, if they don't tolerate tiotropium, then, if we take away the combination, then again we are forcing these two different products, and I do come back to the fact that one product in that recommended category for patients is easier than the other.

So, I do believe that this has an important role for a substantial number of patients, and so I am still advocating for its essential use.

DR. SWENSON: Dr. Gay.

DR. GAY: Yes, I should clarify the guideline once again. No, the initial portion of the guideline is not beta-agonist. It is clearly written as short-acting bronchodilator, and that bronchodilator can be either the short-acting beta-agonist or a short-acting anticholinergic.

DR. SCHATZ: Right, and the next level is two bronchodilators.

DR. GAY: That is correct.

DR. SWENSON: Dr. Newman.

DR. NEWMAN: I think at the end of the day I ask myself can I practice good medicine without this particular combination drug, and the answer is yes. Do I think that Marc Moss' patients get inferior care because this hospital doesn't have Combivent on its formulary, I think the answer is no, they can get good care.

If a patient came to me and said, Dr. Newman, I must have Combivent, and I didn't have it available, I would say we can take care of your needs with other medications. I think for me, at the end of the day, that makes it nonessential in my view, you know, with all the caveats about yes, it is more convenient, and in the short term I think it is admirable that it's a drug that, by combining it, reducing the CFCs by 50 percent, and all the energy that BI is putting into trying to reformulate, all that being taken into account, when you ask the question is this essential, I would say no, it isn't in my practice.

DR. SWENSON: Dr. Brantly.

DR. BRANTLY: I would go back to the studies that have shown that the combination of ipratropium bromide and albuterol versus the two separate is superior in several of the studies that have been done, and I think that from that standpoint, I think it is--it has been shown in the past to be more effective primarily because of patient compliance.

I just want to remind you again that there are probably 2 million patients that are taking this, and they are taking it for a good reason. At least in my practice of medicine, I prescribe this widely, and it is used, and the patients ask for it on a regular basis also.

I believe that in the context that this company has been moving forward in transferring, I think leaving it as an essential drug for the present time is a reasonable approach.

DR. SWENSON: Ms. Sander.

MS. SANDER: What happens if the manufacturer for Drug X is making all these great

strides forward with an HFA formulation, but, you know, there is challenges that they just ultimately don't meet, they can't meet in the new formulation?

If we decide something today is not essential, how does that affect what patients are going to wind up with if a company is unable to get something through the NDA process? That is part one of my question.

DR. MEYER: Okay. Again, I think for purposes of today's discussion, you should not regard the reformulation effort. So, you should assume that if you were to recommend that Drug X is not essential, that you are envisioning a future where Drug X may not be available to your patients in any formulation.

MS. SANDER: Thank you. With that, then, I would have to say as a patient advocate and from the patient perspective, you know, I do see this as a drug that needs to remain essential at least for the time being, because of the severe anxiety and unnecessary anxiety that many families and patients, more importantly, would go through,

patients who are currently tethered to oxygen or to their homes, and really do see this as a necessary medication.

DR. SWENSON: Dr. Moss.

DR. MOSS: I have sort of a question and a comment. It gets back to the timing issue. Correct me if I am wrong, Dr. Meyer, but it is not, you know, when something is decided to be nonessential, the amount of time that the company has to try to convert over is not a uniform thing, and it would be something that the FDA could work with the company to help with that transition process, is that correct?

DR. MEYER: I think if we were aware of an impending approval, for instance, we might take that into consideration, but again, we have to some degree divorce these to some degree.

DR. MOSS: The other think I wanted to say is if we start talking about compliance issues, which are clearly important, and we combine an anticholinergic agent with a beta-agonist, and Combivent, and say that is essential, it sort of to

me raises the issue which I don't think we want to raise, well, what if you combine a beta-agonist with an inhaled corticosteroid, are those all of a sudden now essential medications because it is easier to use those two combined them, one separately, so I think it raises another issue that if you think about it that way, I am not sure we would sit there and now say that Advair is an essential medication, and they could go back to using it that way.

DR. SWENSON: All right. There being no further questions, one last chance. I think people have expressed some opinion.

DR. MEYER: I just wanted to respond to Dr. Moss' comment. I understand your comment, but I don't think the committee should really be thinking that way either. Just focus on this particular matter and don't think about the present.

DR. SWENSON: We will go ahead and begin our poll.

Ms. Schell.

MS. SCHELL: Essential.

DR. KERCSMAR: I am going to abstain.

DR. MARTINEZ: Nonessential.

DR. BRANTLY: Essential.

DR. NEWMAN: Nonessential.

DR. MOSS: Nonessential.

DR. GAY: Essential.

DR. SWENSON: Nonessential.

DR. SCHATZ: Essential.

DR. PRUSSIN: Nonessential.

MS. SANDER: Essential.

DR. SCHOENFELD: Abstain.

DR. SWENSON: Okay. I believe we have concluded business, but, Dr. Meyer, any other points?

DR. MEYER: Just again I know I started off by thanking the committee in advance, and now I would like to thank you in retrospect actually for both days. I think this has been very different considerations on day one versus day two, but I think this has been a very, very helpful discussion on both days.

I am very grateful to the talented and very intelligent folks who are serving on our committee, and thank you for your attendance. I am glad to have you dismissed a little early.

DR. SWENSON: And we thank you, the FDA, for all the work that you have put together for this and to everyone.

We are formally adjourned.

[Whereupon, at 11:00 a.m., the meeting was adjourned.]

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