DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE (DSaRM) COMMITTEE MEETING

Wednesday, May 5, 2004

8:18 a.m.

CDER Advisory Committee Conference Room.
5630 Fishers Lane
Rockville, Maryland

P A R T I C I P A N T S

DSaRM Committee Members:

Peter A. Gross, M.D., Chair
Shalini Jain, PA-C, M.B.A., Executive Secretary

Michael R. Cohen, R.Ph., M.S., D.Sc.
Stephanie Y. Crawford, Ph.D., M.P.H.
Curt D. Furberg, M.D., Ph.D.
Jacqueline S. Gardner, Ph.D. M.P.H.
Arthur A. Levin, M.P.H.
Henri R. Manasse, Jr., Ph.D.
Robyn S. Shapiro, J.D.
Annette Stemhagen, Dr.PH
Brian L. Strom, M.D., M.P.H.

GI Advisory Committee Members:

Alexander H. Krist, M.D.
Maria H. Sjogren, M.D.

Consultant:

Leslie Hendeles, Pharm.D.

FDA Participants:

Carol Holquist, R.Ph.
Marci Lee, Pharm.D.
Paul Seligman, M.D., M.P.H. [a.m. and p.m.]
Vibhakar Shah, Ph.D.
Eugene Sullivan, M.D.

Mark Avigan, M.D., C.M.
Julie Beitz, M.D.
Robert Justice, M.D., M.S.
Ann Marie Trentacosti, M.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

DR. GROSS: Good morning. I'm Peter Gross. I'm Chair of the Drug Safety and Risk Management Committee, and starting with the person at my left with that famous laugh, Brian Strom, would you please introduce yourself?

DR. STROM: Thank you. I'm Brian Strom from the University of Pennsylvania.

MS. JAIN: You know what? Before we go on, Brian, Peter and the rest of the committee as well as the division wanted to say a warm thank-you for serving on our committee. You've been a great asset for a year and a half, and we realize that you're going to continue as consultant, and we just wanted to say thanks.

DR. STROM: It's been a real pleasure, and it was a hard decision to let the rotation happen. I've enjoyed it, but given other commitments back home--but it's been fun.

MS. JAIN: Thank you.

DR. GROSS: You've been great, Brian. We will continue to take advantage of your skills.

DR. MANASSE: My name is Henri Manasse. I'm chief executive officer and executive vice president of the American Society of Health-System Pharmacists, a membership organization that represents about 32,000 pharmacists practicing in hospitals and organized health systems.

MS. SHAPIRO: Robyn Shapiro. I'm a professor and director of the Center for the Study of Bioethics at the Medical College of Wisconsin.

DR. STEMHAGEN: I'm Annette Stemhagen. I'm Vice President of Strategic Development at Covance, a contract research organization, and I serve as an industry representative to this committee.

DR. GARDNER: Jacqueline Gardner, University of Washington, Department of Pharmacy.

MR. LEVIN: Art Levin, Center for Medical Consumers, and I serve as the consumer representative.

DR. FURBERG: Curt Furberg, professor of public health sciences at the Wake Forest University.

DR. HENDELES: I'm Leslie Hendeles. I'm a clinical pharmacist at the University of Florida, and I've done research on the bronchospastic effects of preservatives in nebulizer solutions.

DR. CRAWFORD: Good morning. Stephanie Crawford, associate professor, College of Pharmacy, University of Illinois at Chicago.

DR. COHEN: Mike Cohen, Institute for Safe Medication Practices.

DR. SELIGMAN: Paul Seligman, Director, Office of Pharmacoepidemiology and Statistical Science, Center for Drug Evaluation and Research, FDA.

DR. SULLVAN: My name is Gene Sullivan. I'm the Deputy Director of the Division of Pulmonary and Allergy Drug Products here at FDA.

MS. HOLQUIST: I'm Carol Holquist. I'm the Director of the Division of Medication Errors and Technical Support in the Office of Drug Safety, Center for Drug Evaluation and Research.

DR. LEE: Marci Lee, a pharmacist and safety evaluator in the Division of Medication

Errors and Technical Support.

MS. JAIN: Thank you, everyone. My name is Shalini Jain. I'm the Executive Secretary for the Drug Safety and Risk Management Advisory Committee. I'll now read the conflict of interest statement for the meeting today. The meeting issue is low-density polyethylene vials.

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

Based on the agenda, it has been determined that the topics of today's meeting are issues of broad applicability, and there are no products being approved at this meeting. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions.

All special government employees have been screened for their financial interests as they may

apply to the general topics at hand. To determine if any conflict of interest existed, the agency has reviewed the agenda and all relevant financial interests reported by the meeting participants. The Food and Drug Administration has granted general matters waivers to the special government employees participating in this meeting who require a waiver under Title 18, United States Code, Section 208.

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

Because general topics impact so many entities, it is not prudent to recite all potential conflicts of interest as they apply to each member, consultants, and guest speaker.

FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussion before the committee, these potential conflicts are mitigated.

With respect to FDA's invited industry

representative, we would like to disclose that Dr. Annette Stemhagen is participating in this meeting as an industry representative, acting on behalf of regulated industry. Dr. Stemhagen is employed by Covance Periapproval Services, Incorporated.

In addition, we would like to note that Karen Stewart, FDA's invited guest speaker, is participating as a representative of the respiratory therapists in the United States through the American Association for Respiratory Care. She has no financial interest in or professional relationship with any of the products or firms that could be affected by the committee's discussions.

With respect to the three invited industry guest speakers, we would like to disclose that Mohammad Sadeghi is employed by Holopack International, Richard Schindewolf is employed by Cardinal Health and is vice president and general manager of Biotechnology and Sterile Life Sciences. Patrick Poisson is employed by Cardinal Health, and he serves as Director of Technical Services at the Biotechnology and Sterile Life Sciences division.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants' involvement and their exclusion will be noted for the record.

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

Thank you.

x DR. SELIGMAN: Good morning. On behalf of the Center for Drug Evaluation and Research, it is my pleasure to welcome members of the Drug Safety and Risk Management Advisory Committee and members of the public to today's meeting. As always, we greatly appreciate the time and efforts devoted by the committee members and all participants in providing advice to the FDA on important public health issues.

We have two topics on the agenda for discussion today--the first related to the

prevention of medication errors and the second providing an update on a risk management program that was considered by this committee two years ago and was implemented in 2002.

The first topic will focus primarily on minimizing the incidence of medication errors with drug products packages in low-density polyethylene, or LDPE, containers. The package is intended to preserve drug product purity and quality. However, current techniques used to label the product create problems related to legibility of the product name and strength. Additionally, various products are packaged in containers that look similar. We've found that these difficult-to-read labels and look-alike containers have contributed to medication errors involving the administration of wrong dosage strength or wrong drug product to the patient.

Today, we would like to discuss what other solutions or alternative packaging designs exist that could improve the legibility of the label, prevent ingress of chemical contaminants, and in

the process reduce or eliminate medication errors. Then later this afternoon, we will receive an update on the Lotronex risk management program.

With that brief introduction, I look forward to our discussions today and, again, I also want to personally thank Dr. Strom for his service on this committee.

With that, I guess we may proceed with the first speaker. Dr. Gross?

DR. GROSS: Dr. Sullivan will be the first speaker on the Permeability of LDPE Vials: A Clinical Perspective.

DR. SULLIVAN: Good morning. As I mentioned, my name is Gene Sullivan. By training I'm a pulmonologist, and I'm the Deputy Director of the Division of Pulmonary and Allergy Drug Products in the Center for Drug Evaluation and Research here at FDA.

This morning, I'm going to spend about 15 minutes or so providing some background for the discussions today. I'll be conveying some clinical observations regarding issues raised by the use of

LDPE vials in the packaging of inhalation drug products, particularly as it relates to the permeability of the vials.

This slide provides an overview of my presentation. I'll begin with some introductory remarks which will put my presentation into the context of today's discussions and will serve to introduce the remainder of the talk. Next I will discuss the inhalation drug products that are involved, providing some examples and a brief description of the nature of these drugs. Following this, I will discuss the patient populations for which these drugs are used, emphasizing aspects of these populations that put them at risk for adverse effects of chemical contaminants. Then I will discuss the potential sources of chemical contaminants, their potential adverse effects, and the difficulties that exist in terms of adequately monitoring for them. Finally, I will summarize the issue and current state of affairs in order to set the stage for the remainder of today's discussion regarding minimizing the

potential for medication errors.

The topic for discussion for today's Advisory Committee meeting is how best to minimize the potential for medication errors associated with LDPE containers, particularly given the clinical concerns related to their permeability and the resulting move away from the paper labels that have previously been used to identify the products. My presentation is intended to review the nature of these clinical concerns in order to provide background for the remainder of the discussions today.

This slide summarizes the clinical concerns that I mentioned. Many inhalation drug products are packaged in LDPE containers. LDPE is a material that is permeable to volatile chemicals, and there are numerous volatile chemicals that exist in the immediate packaging environment. Volatile chemicals that find their way into inhalation solutions may have a number of adverse effects on the airways, and because these adverse effects may be poorly tolerated by patients,

efforts should be made to minimize the potential for contamination of inhalation drug products. Such efforts have included minimizing the content of volatile chemicals in the immediate packaging environment.

For instance, the practice of using paper labels, which are applied directly to the LDPE containers and which contain numerous volatile chemicals, is not recommended. However, as you will see in subsequent presentations, the use of alternative labeling approaches has raised the issue of medication errors.

Now, I also want to point out that my presentation is focused on the clinical concerns related to chemical contamination of these products. In the next presentation, Dr. Shah will also talk about product quality concerns. For instance, ingress of volatile chemicals might adversely affect the stability of the active drug substance in a particular drug product.

This slide provides some examples of inhalation drug products that are packaged in LDPE

containers. They include bronchodilators, such as Albuterol, Ipatropium, Metaproterenol, and Levalbuterol; also a mass cell stabilizer, cromolyn sodium; an inhaled steroid, Budesonide; and an antibiotic, Tobramycin.

These products are inhalation solutions, or sometimes suspensions, that are intended for oral inhalation using a nebulizer. One thing to keep in mind is that the manufacturing processes and materials for inhalation products are very carefully controlled in order to maintain a very high standard of product purity. That is, a significant amount of attention is paid to the manufacturing processes and the materials used so that the content of contaminants is minimized. This would include contaminants that arise during the manufacturing processes, so-called process of synthetic impurities; contaminants that arise due to degradation of components of the formulation; or the subject of today's concern, contaminants that enter the formulation from the packaging materials, so-called leachables.

These drugs may be used in a regular dosing schedule or may be used as an as-needed basis, and the bronchodilator products in particular are common used in the inpatient and acute-care settings, including emergency departments and intensive care units.

These inhalation products are used by patients with a variety of pulmonary disorders, most commonly patients with asthma, COPD--which is chronic obstructive pulmonary disease, a category of lung disease comprised of chronic bronchitis and emphysema--and cystic fibrosis. Although these diseases are distinct, in general they are characterized by fixed or variable obstruction to airflow and a variety of patterns of histologic abnormalities, including various patterns of airway inflammation. In addition, asthma in particular is associated with an underlying propensity for allergic responses. And most of the diseases are associated with a sensitivity to nonspecific irritants which result in acute bronchospasm, a feature known as airway hyperresponsiveness.

To focus specifically on asthmatics for a moment, asthmatics may react adversely to both nonspecific chemical irritants and to allergens to which they have developed specific immunity. Irritant reactions are characterized by symptoms of wheezing and shortness of breath. It is well known that patients with severe asthma may react to very low levels of exposure to irritants. Clinically, this is often related to perfumes, cleaning agents, or smoke in the environment. In fact, we commonly make use of this feature of asthma to help establish the diagnosis using methacholine challenge testing. In the methacholine challenge test, patients with suspect asthma are exposed to successively higher concentrations of this irritant in order to elicit bronchospasm.

In addition to the nonspecific irritant reactions, asthmatics may also develop bronchospasm from inhaled allergens. This allergic reaction is associated with both an acute early-phase broncho-constriction and a delayed late-phase response characterized by airway inflammation and airflow

limitation.

So what are the potential sources of contaminants in inhalation drug products packaged in LDPE? In general, these are from volatile chemicals found in the labels and secondary bulk packaging. These chemicals may be found in the various glues, inks, and lacquers that are used. One thing to point out is that the specific chemical nature of these inks, glues, et cetera, may, in fact, change after approval due to changes in the sources of these packaging materials.

The FDA conducted an analytical survey of approved inhalation solutions marketed in LDPE containers and found that 29 of the 37 samples tested positive for various volatile chemicals that were presumed to have originated in the packaging materials. Dr. Shah will describe this analysis in much more detail in his presentation later this morning.

Chemical contaminants in inhalation drug products may be associated with a variety of adverse effects, including irritant and immunologic

effects, leading to acute bronchospasm and airway inflammation and hyperresponsiveness, other toxicologic injury, or even potentially carcinogenicity.

In terms of monitoring for adverse effects that might be attributed to chemical contaminants in these products, it is important to note that appropriate attribution may be very difficult because the expected adverse effects--bronchospasm and airway hyperresponsiveness--mimic the symptoms for which the drugs are being used. This is a very difficult circumstance and makes it quite likely that adverse effects would not be recognized and reported. For instance, modest bronchospasm related to chemical contaminants might lead to reduced efficacy of the drug, but this would likely not be identified. Even if the adverse effect were more significant, the findings would likely be attributed to refractory underlying disease.

So, to summarize, many inhalation drug products are packaged in low-density polyethylene containers. This material is permeable to volatile chemicals. Numerous volatile chemicals exist in

the immediate packaging environment.

Various volatile chemicals have, in fact, been identified in these products. These volatile chemicals may have irritant as well as other toxicologic effects. And because these effects may be particularly poorly tolerated by patients, efforts should be made to minimize the potential for contamination of inhalation drug products.

It was this line of reasoning that in part led to the development of the Draft Guidance entitled "Inhalation Drug Products Packaged in Semipermeable Container Closure Systems." Among other things, the Draft Guidance recommends that measures be taken to limit chemical contamination of these products. One such measure would be the use of alternative approaches to paper labels, such as direct embossing or debossing of the containers.

However, as will be discussed in subsequent presentations, the move away from paper labels has introduced a new concern, that of medication errors due to difficult-to-read and look-alike packaging. The issue of how best to

minimize the potential for medication errors will be the topic for today's discussion.

DR. GROSS: Thank you, Dr. Sullivan.

The next speaker will be Shah.

MS. JAIN: He is not here.

DR. GROSS: Okay. Later for Dr. Shah.

Dr. Marci Lee will now talk about medication errors and low-density polyethylene plastic vials.

DR. LEE: Good morning. My name is Marci Lee. I am a pharmacist and safety evaluator in the Division of Medication Errors and Technical Support in the Office of Drug Safety.

The purpose of this presentation is to describe medication error reports and feedback from patients and practitioners involving products packaged in LDPE containers. I will focus on some factors we identified that may contribute to confusion and errors with these products. Finally, I will describe packaging and labeling approaches for your consideration.

Our error analysis included in your

background package was from 87 relevant reports. These came from patients, caregivers, and practitioners, such as respiratory therapists and pharmacists, who reported to the programs listed. These reports were received between January 1993 and August 2002. Many reports involved difficulty reading embossed product containers. Some reports were actual errors where the wrong medication or the wrong dosage strengths were dispensed. Although some of these were detected before the medication was administered to the patient, some were not. The outcomes of these reports ranged from no harm to difficulty breathing, which can be life-threatening. The remainder of the reports described the potential for confusion and errors with these products. Subsequently, as of April 2004, 51 additional relevant medication error reports were identified for a total of 138 reports.

In addition to our analysis, FDA received correspondence from ISMP, USP, and Senator Harkin regarding the safe use of products packaged in LDPE containers.

Several themes emerged from the narratives of the medication error reports as factors that can contribute to errors. They include difficult-to-read containers, look-alike packaging, and routine handling of LDPE by patients and health care practitioners.

Some of the slides for this portion of the presentation will include direct quotes from the error reporters. The first contributing factor to consider is the difficult-to-read labeling. Concern was expressed in a medication error report because it is difficult to see the name of the drug and its ingredients. Another person noted that if the lot and expiration date are on opposite sides of the same area of plastic, it is even more difficult to read. In addition, practitioners described how the vials needed to be angled in the light to read them. For some, the text is difficult or impossible to read.

In addition to difficult-to-read containers, another concern from the medication error perspective is the issue of look-alike

packaging. Often there is very little on the container itself to help people distinguish these products.

This photo accompanied one medication error report. It highlights the potential for confusion from look-alike vials from just a few of the products available in these containers. Almost all of these vials contain a different drug product. The paper labels and the unique round vial shape help to differentiate three of the vials from the rest. However, these two can be difficult to read.

In addition, this problem spans various drug classes and routes of administration. This complicates the picture for practitioners and creates the opportunity for errors to occur among inhalation, injection, ophthalmic, and oral products.

In this case, heparin is an injectable medication. This photo was included with the report of potential for confusion between heparin and Tobramycin due to look-alike containers.

Pharmacies may store a variety of these products, and the potential for confusion will likely increase as we see more products other than inhalation solutions packaged in the LDPE containers. This increases the likelihood for administration of the wrong drug product by the wrong route of administration.

Another example of an injectable drug product with similar packaging is Naropin. These ampules are specially design to fit both Luer lock and Luer slip syringes. Although this feature may minimize the likelihood for confusion with the other LDPE containers, there is still potential for confusion between the dosage strengths within the Naropin product line. This vial includes black type on a clear background. Again, for some this may be difficult to read.

Timoptic OCUDOSE is an example of an ophthalmic solution packaged in an LDPE container. This image shows that the tip of the container has been extended to allow for a label. However, there may be potential for contamination despite the

placement of this label.

Gastrocom is an example of a product for oral administration that is packaged in an LDPE container. This image illustrates the instructions for use.

In summary, there are least four different routes of administration for products packaged in LDPE containers. Again, this complicates the picture for practitioners and creates the opportunity for errors to occur among inhalation, injection, ophthalmic, and oral drug products.

We have discussed several issues that contribute to medication errors with LDPE containers. We have seen examples of containers that are difficult to read and difficult to distinguish from one another. We have noted that the look-alike contains look-alike containers are not from a single drug product category or associated with a single route of administration. Now we will explore how routine handling of LDPE containers by patients and practitioners can contribute to errors.

The foil overwrap serves to protect the containers from light and the environment. It is recommended that the containers are stored in the foil overwrap until time of use. However, the reality is that the foil overwraps are commonly discarded. Once discarded, the clearly labeled portion of the packaging is often eliminated.

One reason noted in our analysis for the overwrap to be removed is an effort to fit the products into a medication cart. The foil overwrap and carton for many inhalation solutions use color to differentiate the dosage strength. Most foil overwraps contain multiple unit dose LDPE vials. For example, the foil overwrap for Xopenex contains 12 vials.

Carol, if you'll pass the sample?

This image includes the 12 vials which are contents of a single foil pouch of Xopenex. All of the vials in this image are the same dosage strength. However, Xopenex is available in three different dosage strengths. The vials for all three strengths look alike when they are removed

from the foil. Although the foil helps to differentiate them, it is possible that these vials may not remain in the foil pouch until their time of use. These individual LDPE containers can be stored in a variety of places once removed from the foil overwrap.

It is a common practice for LDPE containers to be stored in the pockets or pouches of the practitioners who administer these medications. In summary, while it is possible for various products to have clearly marked foil overwraps, as long as the containers themselves are poorly marked there is still potential for confusion.

Once the container leaves the foil overwraps, it no longer matters how well labeled the foil pouch is. This is a concern, regardless of the number of vials contained in the foil overwrap. However, a single container in the foil pouch may minimize the likelihood for the vial to become separated from the overwrap.

At this point we would like to stimulate

ideas for discussion about how to address the issues that have been raised so far. The remainder of this presentation will include a series of photos. These images will highlight various packaging and labeling approaches to consider. Remember to keep in mind who will be using the products and how they will be used. Our goal is to identify packaging that will resolve our concerns but not introduce any new problems for those who manufacture or use the products.

The paper label approach allows for use of color to distinguish look-alike vials. For some, these may difficult to read due to the small font size of the text. The reports in our analysis demonstrated that some people may identify these medications by the color of their label alone. Based on the earlier presentation, we learned of the potential safety and product quality concerns with this approach for inhalation solutions.

Although this packaging no longer appears to be used for Timoptic, this image illustrates another approach with paper labels. The paper

label is applied to the tip of the container. The packaging allows for use of color to differentiate the containers and dosage strengths. However, it may not address the potential for ingress.

Again, consider the size of the label and the potential font size issues which may make the text difficult to read.

We have a sample of this also going around.

Here is an approach that extends the tip of the container to allow for the text to be embossed in the flange instead of the body of the vial. This approach allows for more space for printed text; however, if both sides are embossed, they tend to interfere with the readability of the text.

In contrast, this approach includes an embossed container without an extended flange. In addition, the container is topped with the letter V-shaped tip. In this case, V is for Ventolin. This approach allows for use of the unique vial shape and possibly texture to help differentiate

the product.

Another approach used to differentiate the various products in LDPE vials is the use of the embossed letters A, I, and R at the tip of the container. In addition to a visual cue, the vial makes use of texture to distinguish the products. A is for Albuterol, I is for Ipatropium, and so on. Again, for some this is difficult to read.

One approach that has contributed to medication errors with acetylcysteine is the use of a glass vial. The packaging has led to medication errors where practitioners inject the product instead of administering the drug via inhalation because the vials look similar to those that contain an injectable product. According to the May 30, 2001, ISMP newsletter article, these error occur despite warnings on the label that state "Not for injection" or "For inhalation." In addition, they have a target area on the rubber stopper similar to the injectable products.

Another approach used to distinguish these products includes the use of a uniquely shaped

container. Although these round vials distinguish Pulmicort from other drug products, it is difficult to differentiate between the two dosage strengths of Pulmicort once they are removed from the foil. The image on the right illustrates what the containers look like once the foil overwrap is removed.

Some products, such as sodium chloride inhalation solution, utilize a tinted vial as a means of differentiation. This approach allows for the use of color to help differentiate the containers from other products. However, this particular packaging has not been evaluated by CDER at FDA. These vials also include embossed text.

Another approach is the shrink wrap approach which allows for the combination of embossed information on the end of the vial and the use of black print on a clear background. Again, for some this may be difficult to read. The printed portion of this label clings to the vials without adhesives, eliminating one potential source of packaging contamination. However, there are

still sources of volatile chemicals with the shrink wrap approach.

There's also a sample of this going around. The individual foil overwrap approach was described in the Draft Guidance that Dr. Sullivan referred to in his presentation. This method will protect the drug product from contamination from the environment and minimize the opportunity for contamination from the packaging itself.

Each foil overwrap contains a single vial. This is thought to increase the likelihood of the pouch staying with the container and minimize the risk for errors. The overwrap allows for the use of color and other means of differentiation to help distinguish these products.

At this time we are seeking other ideas and approaches to consider. What other materials could we use? What has been done for other products? What will meet the needs of those using the products in both the inpatient and outpatient setting? How should FDA evaluate any proposed changes?

Also ask yourself, Will it prevent contamination from secondary packaging in the environment? Will it be difficult to read? Will it look like other containers? Will it create new problems? Will it be difficult to use? And, finally, should inhalation products be handled separately from products with other routes of administration? We look forward to hearing your ideas and suggestions.

DR. GROSS: Okay. To round out the presentations, Dr. Shah will talk about the perspective for chemistry, manufacturing, and controls.

DR. SHAH: Good morning. My name is Vibhakar Shah, and I'm a chemist in the Office of New Drug Chemistry for Pulmonary and Allergy Drug Products. Before I start, I would like to apologize for my delay. I was stuck in traffic for almost one and a half hours. Let me tell you, it's not a pleasant experience. But, in any case, that's life. And I'm sure when we move to White Oak it's going to get worse.

[Laughter.]

DR. SHAH: You were supposed to hear this talk before Marci's talk, but, anyway, here it goes.

You already heard from Dr. Sullivan the clinical concerns arising due to the permeability of LDPE vials, especially when used with paper labels for inhalation drug products, and also you heard some of the medication errors which are caused because of legibility issues with the paper labels. And I'm going to talk about in the next 20 minutes regarding the problems and issues with product quality concerns arising due to the use of LDPE containers, with or without paper labels and with or without overwrap, for these drug products.

In the context of today's discussion, my presentation will also focus on how best to minimize the potential medication errors given the quality concerns associated with these container closures.

With that, this slide gives you the outline of my talk. I'm going to start with a

brief introduction to the type of inhalation drug products that are packaged in LDPE containers, and after that I'll be overviewing the current container-closure systems that are used. Following that, I would like to discuss the results of an analytical survey conducted by the agency for several inhalation drug products under the Drug Product Quality Surveillance Program. This survey particularly identified the clinical concerns as well as the quality concerns arising from the drug product contamination by packaging components because of the permeability of LDPE.

Following that, I would like to discuss some of the quality concerns arising with the use of LDPE vials, with or without paper label and foil overwrap. I will discuss the agency's current approaches to control and minimize the product contamination from packaging components and discuss current recommendations for packaging of inhalation drug products as provided in the Draft Guidance. And I will end my presentation with summarizing the quality concerns, what I have discussed so far.

This slide lists the inhalation dosage forms administered by oral inhalation, and these drug products include inhalation solutions, suspensions, spray, inhalation aerosol, and inhalation powder. However, for today's discussion, the remainder of the talk will focus on inhalation solutions and suspensions as they are the only two dosage forms that are packaged in LDPE containers.

This slide you have already seen in Dr. Sullivan's presentation. It just shows the type of drug products which are packaged into LDPE containers.

Currently, inhalation solutions and suspensions are packaged in LDPE vials, and there are three components, basically: LDPE vials, vial labels, and foil overwrap pouch. Not all the inhalation solutions and suspensions may have foil overwrap pouch or adhesive paper label. But in any case, the unit-dose vial--that is, the LDPE vial--is made up of low-density polyethylene by blow-fill-seal or form-fill-seal process. The

labeling information on a vial is conveyed either by a self-adhesive printed paper label or by embossing or debossing the labeling information on the LDPE vial itself during the fabrication of the vial.

Foil overwrap acts as a protective secondary package and may contain anywhere from one to 12 vials per pouch. The labeling information may be conveyed by a self-adhesive paper label on the foil overwrap, or the foil overwrap may be printed. Furthermore, different colors for foil pouches may be used to differentiate the multiple strengths of the drug product.

Now, let me go over the container-closure components of the LDPE vial, paper label, and foil-laminate. I'll start the LDPE vial.

The unit-dose vial, which is made up of low-density polyethylene, is chemically a polyethylene homo-polymer resin. The polyethylene resin is made by polymerization process and may contain several chemical additives in addition to the reactant polymer. They include chain transfer

agent, chain initiator, antioxidant, so on and so forth.

Furthermore, it is available in different grades for different applications. That indicates that the composition of the LDPE may change depending upon how it is being used. There are many manufacturers and suppliers of this LDPE.

T1B This slide lists some of the characteristics and properties offered by LDPE or LDPE vials which probably makes it a material of choice for packaging of inhalation solution and suspensions from a manufacturer's point of view. These include: they are flexible and malleable; stress crack, impact, and tear resistant; they are considered chemically inert at room temperature; or it may be used at elevated temperature for extended periods of time; or it can be sterilized. They are used on high-speed production lines and, aesthetically, they can be clear to translucent in appearance.

However, it is permeable to volatile chemicals and gases, and because of this

permeability, there are several quality concerns which I'll be discussing later in my talk.

The next I would like to talk about is the paper label, the components of a self-adhesive paper label and how it may contribute to the quality concerns of inhalation solutions and suspensions.

Typically, a paper label consists of a base paper, adhesive, inks, pigments and dyes, varnishes, over-lacquer, et cetera, and depending upon the application, the base paper may contain or may be treated with all or many of the chemicals that I have listed here.

Adhesive is the layer which comes in immediate contact with the LDPE vial when it is use with self-adhesive paper labels. This slide lists typical chemical composition of an adhesive. This is not an all-inclusive list. There are many more proprietary chemicals used in the formulation of these adhesives. Depending upon the physical chemical properties of these chemicals, that is to say, volatility, they may permeate through the LDPE

vial into the drug product.

I have listed here some of the over-lacquer components. Over-lacquer is an evaporative(?) coating which is typically comprised of chemicals such as plasticizers, resins, (?) solvents, diluents, surfactants, and many more. Some of these chemicals are proprietary in nature. Over-lacquer, or varnish, may be used for a transparent glassy appearance of the label, also a stabilizer for the print work and art work, or it can be used as a protective barrier to the moisture and overall to extend the longevity of the label. Again, in this case also, depending upon the physical chemical properties of some of these chemicals and their constituents, also the concentration and storage conditions, these chemicals may have a potential to permeate through the LDPE vials into the drug product.

These are typical ink components. One may think that ink might be just a single-component formulation. However, if you look at it, there is more than one chemical included into the ink

formulation. And, again, these are also propriety formulations.

These ink formulations may be (?)-based or organic solvent-based, and depending upon the brand of solvents which are used in the formulation, they may have a potential to permeate through the LDPE vials into the drug product.

The last I would like to talk about is the foil-laminate. Primarily, foil-laminate is used as a protective secondary packaging for the drug formulations that may be sensitive to light and react to gases such as oxygen.

Typically, foil-laminate is a flexible packaging composed of multiple layers of various types of plastic films which are fused together either by heat or pressure-sensitive adhesives applied to one or both sides of an aluminum foil. In this cartoon, aluminum foil is represented by layer D, and as you can see, the whole foil overwrap surrounds the drug product vial on an automated packaging line.

The thickness of aluminum foil, which is

D, and the number of pinholes per unit area are crucial for ensuring the consistent barrier to permeability. Furthermore, each of the composite layers may contain volatility chemicals, organic solvents, as they are used in adhesives, which may permeate through a LDPE vial into the drug product, especially the adhesive layer that is closer to the drug product. In this case, that is shown by G. So the composition of these are very critical. One has to really have a knowledge of its composition before they can be selected for the foil overwrap. Alternate approaches to adhesive can be considered, such as fusion of the multiple layers of foil-laminate by heat-set process.

In addition to the clinical concerns discussed by Dr. Sullivan, the permeability of LDPE raises several quality concerns, and these are listed on this slide, mainly the drug product contamination through ingress of volatile chemicals which may be originating from the environment that may be irritant or toxic to the respiratory tract and may sensitize individuals; drug product

degradation because of the reactive gases and light that permeate through the LDPE vial and cause degradation of the drug product; and change in product concentration because of the water evaporation through the LDPE vials. This in turn can accelerate the drug product degradation because of the concentration of the drug product.

Now, let me share with you the results of an analytical survey of approved NDA and ANDA inhalation solutions marketed in LDPE vials without protective overwrap. The basis for this survey was a large-scale voluntary recall of inhalation solution by a firm due to contamination of the drug product with 1-phenoxypropanol. This is a known component present in the packaging components. This recall was conducted with FDA's knowledge and followed by a health hazard evaluation. It was later found out that the source of this chemical was the varnish or over-lacquer that was used for a shelf carton.

Alarmed by this incident, the agency was concerned that there may be other inhalation drug

products with such contamination from packaging components. As a result, it was decided to conduct a product quality survey of some of the marketed inhalation solutions.

This was initiated by the Office of Generic Drugs in consultation with the Division of Pulmonary and Allergy Drug Products and in coordination with the Office of Compliance, Office of Regulatory Affairs, field offices, and Pacific Regional Laboratory. Seven ANDAs and one NDA for inhalation solutions covering five different drug substances were selected.

There were 38 samples representing 37 lots of various drug products in LDPE vials without a protective overwrap foil pouch. The samples were screened for potential volatile chemicals which are known to be present in the packaging components, such as vanillin, 2-phenoxyethanol, and 1-phenoxy-2-propanol by sensitive analytical techniques such as GCMS and HPLC methods. Let me share the results of this survey.

Twenty-nine out of 38 samples tested

positive for chemical contamination originating from packaging components. Five known chemical contaminants, as listed below, were detected originating from packaging, such as benzophenone, polyethylene glycol, 2-(2-butoxyethoxy)ethanol, 2-(2-ethoxyethoxy) ethanol acetate, and 2-hydroxy-2-methylpropriophenone.

A health hazard evaluation was conducted at the levels these components were detected in these drug products. However, it was indicated that the levels of these components did not raise sufficient safety concern in the intended population to warrant a recall of these drug products. Nonetheless, the following issues were of concern:

It was indicated that potential for these chemicals to cause bronchospasm at levels detected is unknown, especially in patients with respiratory diseases.

It was also indicated that concentration of these chemicals might be grater at the end of expiry than what was detected at the time they were

tested.

It also showed that permeation through LDPE vial is a real phenomenon.

It was also concluded that additional chemicals may be present, but may not get detected because the analytical techniques which were used may not be suitable, not knowing what components might be present into those solutions.

And, also, future changes in the materials used in labeling and packaging may result in contamination with different chemicals.

So, in a nutshell, product contamination can occur because of the formulation component degradation or by leaching of chemical constituents from packaging components, such as resin components I have listed, paper label components, foil overwrap components, cartons, and environment.

These are the typical extractable or leachable components which have been found in the drug product from packaging components. Some of them are irganox 129, 2, 2, 6-trimethyloctane, which is coming from resin components. Some of the

paper label components that we have seen is benzoic acid, ethyl phthalate, benzophenone, danocur 1173, cyclic phthalates. From the foil overwrap, we have seen methacrylic acid, 2-phenoxyethanol, and some of the organic solvents such as acetone, 2-butanone, ethylacetate, propylacetate, heptane, and toluene. And from cartons, methacrylic acid and 1-phenoxy-2-propanol.

So this raises a significant quality concern, and there are several other factors. These are the factors. Because of the proprietary nature of components and composition of this packaging material, we may not know what is present in the solution. The composition of these components which are present in the packaging may change without the knowledge of applicant and the agency. And you cannot detect if you don't know what you are looking for. As a result, there is no one analytical procedure to detect unknown chemical contaminants. And there is incomplete toxicological data or information available for many of these identified chemical contaminants.

And as the environmental conditions change, that may introduce new contaminants.

So what are the potential approaches the agency has taken to minimize and control the contamination from packaging components to the extent possible? Our approach has been and we have recommended that characterize or identify all possible extractables and establish a profile for each packaging component, for resin, vial, paper label, foil-laminate overwrap.

What I mean by extractable is extractable is a chemical compound, which can be volatile or non-volatile, that gets extracted from a packaging component in a suitable solvent by utilizing optimum extraction conditions, such as time and temperature.

Extractable profile for a given packaging component typically can be a chromatogram representing all possible extractables.

After that, establish a correlation between extractable and its leachable potential, and what I mean by leachable is leachable is any

chemical compound that leaches into the drug product formulation either from a packaging component or a local environment on storage through expiry of the drug product. An extractable can be a leachable.

And to ensure batch-to-batch consistency of the drug product, appropriate specification for a leachable is established based on its qualification and observed levels in the drug product on storage.

As a result, the next approach is we asked them to set meaningful acceptance criteria for a given extractable in corresponding incoming packaging components based on its qualification level and actual observed data. Once that is accomplished, meaningful acceptance criteria for a given leachable based on actual observed data in the drug product also be established.

These are the recommendations we have provided in the Draft Guidance. We have recommended that adequate knowledge of composition and physico-chemical properties of packaging

components is essential for appropriate selection of these components. We discourage paper label directly on the LDPE vial and encourage alternative approaches, including embossing or debossing, in lieu of the paper label on the LDPE vial because of the reasons I discussed, because of the product contamination. This can be accomplished by extended bottom flanges to unit-dose vial that can carry essential vial labeling information and can retain the product identity.

We have also recommended use of protective overwrap foil pouch for the LDPE unit-dose vial. This in turn can minimize the ingress and leaching of chemical contaminants from the local environment provided that the components that have been selected for the fabrication of the overwrap foil pouch are appropriately selected.

The self-adhesive paper label on a foil pouch or pre-printed foil pouch is also recommended, and different color schemes to differentiate multiple strengths of the drug product is also recommended. This in turn can

prevent ingress or leaching of chemical contaminants from paper labels and may improve the legibility issues.

The last recommendation we have in our Draft Guidance is to limit the number of unit-dose vials per pouch, ideally to one LDPE vial per foil pouch. This can minimize the risk of medication error by patients and health care professionals, and it can prevent unnecessary exposure to local environment when compared to packaging of multi-unit-dose vials in a foil pouch.

So, in summary, so far I have presented to you that volatile chemicals present in the packaging components and local environment have a great potential to permeate through LDPE vials into drug product formulation on storage. The agency's analytical survey and other supportive data have confirmed ingress and leaching of such volatile chemicals into the drug product formulations.

Ingress or leaching of such chemicals into drug product formulation poses a safety concern for patients with respiratory illnesses, such as asthma

and COPD. Embossing or debossing of LDPE vial in lieu of paper label is recognized to have legibility issue. However, paper labels, although perceived to address legibility issue, overall may not be the optimum solution because of the safety concerns associated with potential leaching and ingress of paper label components in the drug product through LDPE vial.

The agency's current recommendations as stated in the Draft Guidance may serve as a first step in the right direction to address the issues that are being discussed today. And the agency is seeking other viable approaches to address these issues to promote safe product use without compromising the integrity of the drug product.

With that, I will conclude my talk, and thank you for your attention.

DR. GROSS: Thank you very much, Dr. Shah, and I want to thank the first three speakers who presented a very clear review of the problem.

We are now open for discussion. Perhaps I'll start off with a couple questions.

We talk about low-density polyethylene. Does high-density polyethylene reduce transmission, number one? Number two, would increasing the thickness of the container reduce transmission? And, number three, have other plastics been considered? I'm not a chemist so I don't know, but polypropylene, polystyrene? And are any of those possibilities?

DR. SHAH: So far, traditionally, LDPE is the choice of material by the manufacturer because of some of the properties it can offer. And I guess one can increase the thickness of the LDPE vial or may use a different polymer. However, one has to keep in mind that by nature, when you do the fabrication of the vials, it may have some kind of a permeability. But that depends on the degree of permeability. LDPE offers one side of the spectrum, or other polymers may offer a different type of permeability. But one has to conduct some of the studies to show that it does not permeate.

DR. GROSS: Michael?

DR. COHEN: Dr. Lee mentioned shrink wrap

at one point, and then added that there might still be some concern about, you know, the volatility, I guess, of the inks in the shrink wrap itself. It does not come in contact with the actual LDPE plastic, though, so I'm trying to figure out why that would be a concern. Do you think it's still possible for that to leach in?

DR. SHAH: Yes, let me answer that. Shrink wrap, again, it's a plastic and it suffers through the same thing. It comes in direct contact with the LDPE vial. So depending upon the chemical components of the ink and how it is being used, in a shelf carton or anything, it still will have the same unit problems that I discussed.

DR. COHEN: Can I ask a follow-up?

DR. GROSS: Yes, go ahead, Michael.

DR. COHEN: Have you done testing--

DR. SHAH: No, we--I mean, we have not even received--or we have not approved a drug product with the shrink wrap. There is no example of that, at least to CDER. Maybe in other divisions, another agency, but we haven't received

any.

DR. GROSS: Jackie, next question?

DR. GARDNER: I understand the problem of potentially masking the effect of contamination by the condition, but I was surprised to see only 87 reports of medication errors that you're working from. And given the excellent presentation and the potential for confusion, I'm surprised that there were so few because it looks like it would happen a lot. I wondered if we could have some perspective on why there would be so few, and maybe Mike can help with that.

And then the second thing is I wondered whether any of the potential suggested recommendations or the different packaging types have been tested in any way that we could reasonably expect that they might reduce the potential for error if they were implemented, whether the foil wrap or any of these things have been tested among the people who would be using them.

DR. GROSS: Next question, Leslie?

Does anybody have an answer? Marci?

DR. LEE: Thank you. As to the number of reports being few, since the review was done, there have been additional reports submitted to the agency for a total, I think I said, of 138 reports, which may still sound like a small number, but considering the problem is probably very underreported. We also had some reports that were describing errors that had to do with restocking. For example, a transport team's pouch was supposed to contain three Albuterol and three Ipatropium vials, and at this one given time it contained one vial of one drug and five of the other. So, you know, in the report the narrative says, "We suspect that at least one patient has been affected by this problem."

The same thing can happen in an inpatient setting where the drugs are getting intermixed in a bin. So it's really an unknown, the actual impact of the problem.

DR. GROSS: Leslie?

DR. HENDELES: I'd like to just respond to

Jackie's comment. Mixing these medicines up is very unlikely to be associated with a visible toxic reaction, so that might be--if anything, the adverse consequences is a lack of therapeutic effect when you're treating a disease that's involving acute bronchospasm. So the clinician can't distinguish between lack of drug effect from worsening of the disease.

But the question I had was: Is there any evidence that these contaminants in any way interact with the active drugs to either decrease their stability or to in some way inactivate them?

DR. SHAH: They may not inactivate, but they will increase the degradation of the products. They may react with the active, and then you will form an adduct. But you are not going to, you know, inactivate the drug product.

DR. SULLIVAN: The other thing t keep in mind is that the list of potential contaminants is innumerable. So what may be true of one chemical may not be true of the others.

DR. GROSS: Curt Furberg?

DR. FURBERG: I'd like to expand on that question. What are the health effects of these contaminants? Are they all toxants? And if we don't know that these contaminants have adverse health effects, is this a big issue?

DR. SULLIVAN: Well, I think the unknown is part of the problem, and being a clinician at the agency, we've been tasked with addressing the specific risk of specific chemicals that have been found in assays done, particularly--it was discussed in the analytical survey and so forth. So we get asked this question: What's the toxicologic potential of this chemical? And we don't know most of the time. There haven't been toxicologic studies done. We don't know the carcinogenic potential. We don't know the extent to which it acts as an irritant or has other toxic effects. And then we have to judge, okay, what's the risk out there, and it's very difficult.

DR. FURBERG: Yes, but shouldn't you add that to your recommendation that we find out?

DR. SULLIVAN: Well, I think that's part

of why we're saying it's best to just try to limit potential exposure, because you can't list all of these chemicals. For instance, the one that was mentioned was found in a drug product, and it was traced back to the fact that the actual carton that these vials were contained in, the manufacturer of that carton, who isn't the drug manufacturer, changed the glue or lacquer in that carton. And so a chemical that we wouldn't have previously been aware of made its way into the drug.

DR. SHAH: Again, the agency does not control the cartons. We will control to a point and look into the things. The carton is something very--and as a result, I think our approach has been--or we recommend the use of overwrap pouch. That can also limit to a certain extent. I mean, there is no 100-percent guarantee that it may not permeate or the glues which are used in the foil-laminate itself may get into the drug product.

But one needs to study these things before, you know, providing to the agency.

DR. GROSS: Okay. Henri, and then we'll

hold questions after that until later.

DR. MANASSE: I have a couple of questions. One is: Do we see the impact of the degradation on all of the active ingredients, that is, for the Albuterol and the Tobramycin and the cromolyn? Is that pretty much standard across all of the ingredients that these volatile substances do have a degrading impact?

The other question I had is: What experiences can we gain from either the food and/or the cosmetic industry? Are there experiences there since so much of this packaging is also with low-density polyethylene containers?

And my last question relates to the potential application of the bar code to packages vis-a-vis the incoming rule. To what extent will symbology printing either exacerbate or lessen this particular issue?

DR. SHAH: I kind of lost you. What was the first question?

DR. MANASSE: The first question, Is the infusion, leaching of the contaminants equally

impactful on all the active ingredients in these products?

DR. SHAH: I think some of these will stay as a degradation product. They may not impact the active ingredient, but it will be just a product contamination.

Now, itself, how it will affect the particular patient population, that is--as Dr. Sullivan said, we don't know the potential of that. So it may not probably reduce the concentration of the active into the drug product. However, that uncertainty regarding the safety is a concern.

The second question was?

DR. MANASSE: The second question relating to experiences in the food and cosmetic industry and what may be learned there.

DR. SHAH: Okay. I think by far the most--these packaging components are used also in tablets and other solid oral dosage forms. There the risk is less because you are taking it orally. Here the problem is because of the patient population, we are more concerned. And I don't

know what else can be learned from food and other industries because there is--I don't know that much scrutiny is there. The only thing that is there is whether they are adequate in terms of oral dosage use. That's it.

Does that answer--

DR. MANASSE: And my last question related to the upcoming application of the bar coding rule and the imprinting of symbologies to implement that particular rule.

DR. LEE: Actually, LDPE vials was one of the products that was exempt from that rule. It won't be required down to the vial, but any outer packaging it will be on.

DR. GROSS: Okay. We'll take a break now and reconvene at 9:45.

[Recess.]

T2A DR. GROSS: The first speaker will be Mohammad Sadeghi, who will talk about container labeling options using rommelag blow-fill-seal technology.

DR. SADEGHI: Good morning. I'm Mohammad

Sadeghi with Holopack International. I'm here to talk about container labeling options using blow-fill-seal technology, and most of all these products you've been hearing today about and packaging and LDPE, low-density polyethylene, they're all manufactured using blow-fill-seal technology.

So what I'm going to do is go over what the blow-fill-seal process is, what container labeling options you have, what are the pros and cons on each, and some examples.

Blow-fill-seal technology is an integrated aseptic technology for manufacturing aseptic products. That's an example of a machine. The way it works is you feed in raw pellet resins from one end and the (?) solution from another, and the machine will actually melt the pellet, created the container, fill it aseptically, and seal it.

The process consists of four major steps. As you see, the plastic is molten first and extruded in a cylindrical shape, and the molds are formed into the container, the needle comes in, and

there is the Class 100 in this (?) area, fills the container, and it withdraws, and then the container is sealed and ejected from the machine.

Now, labeling options that you can have with this technology consist of embossing, paper label on tab if you do not want to put it directly on the container, or printing on the tabs.

Embossing consists of a mirror--engraving mold with a mirror image of the information. You have small vacuum ports on the mold surface that actually will do this, such into the softened plastic into the engraving embossing, hence embossing the container.

This is an example of what a mold cavity looks like, and you see the surface inside the main cavity where the engraving takes place.

This is a close-up of what it's like to have as the imprint. What you see in the bottom would be replaceable magazines that you can change for lot number and expiration date.

Another option of embossing is hot stamp, which in this case instead of molding it during the

production, as the container is ejected from the BFS machine, it's actually put into a machine where it actually is a hot stamp that would actually emboss the container, again, and this is done on the tabs and not directly on the body of the container.

Paper labels on tabs, one of the reasons this container was developed was to avoid direct contact labels with--paper labels with the actual container body, and the secondary was the small-volume containers that required information and there was not enough surface area to put the engraving on the container. They developed a tab. Either it can be on the cap or as a tail, have the embossed information.

You can use the same tab, actually, instead of--it's a solid surface, so you can use it either to print or add paper to the label.

The pros and cons of each labeling option: Embossing has been discussed here. The pros are there is no maintenance of label inventories; ensure 100-percent labeling of containers; labels

cannot be removed; and ensure each unit is traceable and no leachables. The cons are, which has been discussed also, it is difficult to read on clear containers.

Paper label on tabs is--paper label obviously makes it clearer to read, and you can use colors. It greatly reduces potential leaching into the solution because it's not directly applied to the container body. However, there is still potential leaching of adhesive.

Direct printing on the tab, it's clearer than embossing on the tab to be read; it eliminates potential leaching from paper, adhesive, varnish and stuff that goes with the paper label; and it greatly reduces potential leaching into the solution, again, because it's on the tab, on a separate space on the container, not directly on the container body; and, lastly, allows for bar code printing on line as well. However, you still have the ink, which potentially can leach into the solution.

Now, examples of these various things,

there's a container with embossed labeling. The containers can be also embossed and color-coded because the same container can be used for different concentrations of products, or you can have color-coded and embossed to represent the same product in different concentrations or doses.

You can apply the paper on the tab, both removing the paper from direct exposure to the solution, but also it is readable. Or having direct printing on the tab for bar code information.

Also, you have traditional paper on the container, which is...

Now, the other thing is the issue of--one of the things that comes to mind is the size of the containers, is eliminating paper containers--paper labels from all outside containers or is it dependent--it is a size-dependent solution. Obviously, if you have a liter container such as viewed here and you have a paper label, is that also going to be--it's something that has to be removed, and considered this is--it should be in

relation to the size of the container. If it is a three- (?) container, you have the same treatment as one-liter container.

Another example of various container sizes.

Thank you.

DR. GROSS: Okay. Now we'll hear from the Cardinal Health team, Rick Schindewolf and Patrick Poisson.

x MR. POISSON: Good morning. My name is Patrick Poisson. I'm the Director of Technical Services at Cardinal Health Woodstock. With me today is Mr. Rick Schindewolf, who's the general manager of the Woodstock, Illinois, facility.

Just a little bit about our role in the industry. Cardinal is a diversified health care company with operations in distribution, manufacturing, research, and management solutions. The Cardinal Health Woodstock facility is a blow-fill-seal facility that produces approximately 1 billion units annually. Our product portfolio involves NDA, ANDA, 510(k), and USP Monograph

products.

Some of the advantages of why people select low-density polyethylene in blow-fill-seal is blow-fill-seal is recognized as an advanced aseptic process. There's also an immense flexibility in container design that allows various applications of the container and its use. It's also a very cost-effective approach to producing pharmaceutical products.

Now, some of the limitations: As previously mentioned, LDPE is a semipermeable material. The technology also uses heat to form the container, and there may be issues with heat-sensitive products. And based on the focus of this meeting today, there are obviously some labeling issues as well.

Now, the general industry approach has been to emboss and deboss the containers to display the necessary information, which includes product name, concentration, manufacturer, lot number, et cetera. Typically, respiratory products are packaged in a secondary overwrap in multiple units

or single units, and that provides the additional protection necessary to prevent chemical contamination.

This has already been touched upon, but these are the main highlights of the Draft Guidance, and I won't spend any time on this since this has been discussed already.

Now, what are some of the advantages to the embossing/debossing approach? It provides an immediate tamper-evident identification of the product. It eliminates the potential for contamination from labels. And it provides ease of label copy control.

Some of the limitations associated with that: It can be difficult to read on clear containers. It does not provide a very readily bar code-readable print. And the vial size affects legibility of the print that's embossed and debossed. We cannot emboss or deboss down to a very small font size that's readable that could compete with a paper label.

Now, we believe there are some

possibilities for enhancing product identification in the low-density polyethylene container, and these are listed here: reduce the content requirement to allow an increased text size; addition of physical/tactile identifiers for generic product groups; alternative label approaches such as a sleeve label; color coding unit-dose vials for generic product groups; and individual secondary overwrap.

Increased text size. There's a limited surface area on the container that is available for embossing/debossing. Due to the technology, we cannot emboss or deboss on the sides of the vial. We can only emboss and deboss on the front. The text size can be significantly increased; however, we would have to remove some of the information that's normally provided. This approach would not change any of the materials involved in the process, so there would be no impact on the current product chemistry. This could also be implemented fairly quickly, eight to ten weeks. And there would be a one-time cost for the manufacturer to

buy the appropriate equipment.

This is a drawing of what that concept would look like.

In addition to that, physical/tactile identifiers could be added to the container. This would provide an easily recognizable/legible symbol on the container that would represent a product type, for instance, A for Albuterol sulfate, I for Ipatropium bromide, et cetera. This is already currently being implemented on products manufactured at Cardinal Health. This also does not change any of the container materials or process, so, again, no impact on the current product chemistry. This also could be implemented in eight to ten weeks, depending on the regulatory approval of this label change, possibly as a CBE 30. Again, there would be a one-time minimal cost to buy the necessary equipment to do such a change.

This is a drawing of what that concept could look like. And we have some samples which we'll pass around for the committee to see. And those can also be provided in clear plastic. And

here are some photos of the same vials.

This is a picture contrasted with one of the current formats that is out on the market, so you can see that there's a definite increase in the identification of the products resulting from this type of change.

The sleeve label concept would involve a redesign of the extended tab to make that area amenable for application of a non-paper label. Cardinal has designed such a vial that has a patent pending that would be capable of receiving a shrink wrap sleeve.

This label provides a contrasted background for enhanced legibility and also provide a bar code-readable print. This would involve no changes to the product contacting surfaces of the container. The shrink of pressure sensitive label would be applied to an appendage of the container, not in direct contact with the product.

This would also involve an increased manufacturing cost for equipment, labor, and materials, and we believe it could be implemented

in 12 to 14 months following regulatory approval with associated stability testing data.

This is a picture of what that concept looks like, and we have some samples that we'll pass around. This particular product was mentioned in an earlier presentation as the catheter flush saline and heparin.

Color coding. Products could be color-coded to aid in identification. That would be a similar approach to the AAO recommendations for cap color for ophthalmic products. It provides a contrasting background to aid the legibility. A colored vial is easier to read. However, it could impact the product chemistry with leachables and extractables. There would be a slight increase in manufacturing costs for raw materials. Again, implementation time would be based on stability data and regulatory approval of such a change.

This is a picture of what that concept would look like.

Individual secondary overwrap, that has been touched upon. It provides enhanced labeling

opportunities, bar code-readable print for a single-dose vial. However, the overwrap can and will be separated from that unit at some point in time during its use, and we don't control that, so we cannot predict when that will happen. So there could be legibility/identification issues still at the time of use. There's a significant manufacturing cost increase with the raw materials, equipment necessary, and labor. If that was done with the current process, that change, the implementation time would be 12 to 14 months following regulatory approval of the packaging change with associated stability data.

In summary, we believe there are opportunities for improvement of the labeling of low-density polyethylene containers. Each alternative is a viable alternative, we believe, and it should be assessed based on impact to the product, speed of implementation, ease of regulatory approval, and cost to the patient.

Thank you--oh, sorry. Our recommendations are to increase label information font size on

individual vials. Add a tactile symbol for generic identification based on the following advantages: quick approach, no impact on product chemistry or stability, and no impact on patient cost. For hospital-dispensed unit-dose vials, add a sleeve label to accommodate bar coding.

Thank you.

DR. GROSS: Thank you very much.

Our next speaker is Karen Stewart of the American Association of Respiratory Care.

x MS. STEWART: Good morning. Thank you for giving me the opportunity to present today. I think in your packets you have my written statement, and I have a couple of slides here that I want to share with you.

I've been a registered respiratory therapist since 1971, and I am here as the spokesperson for the American Association for Respiratory Care representing respiratory therapists both nationwide and internationally.

Respiratory therapists, like all other health care professionals, are very concerned about

medication errors. In recent years, since the elimination of most paper labels on unit-dose vials of medication, it has become increasingly difficult to determine the content of the unit-dose vial. I'm going to share with you some pictures of what the therapist typically has on their person as they're making rounds.

Not only is the print on the vial difficult to read, the size and the shape of the vial contributes to this difficulty.

In 2001, the American Association for Respiratory Care completed a human resource survey, and at that time the average age of a respiratory therapist was 44. This is another contributing factor to the difficulty of reading the content of the medication vial. While I may have just emphasized that the current relative age of the respiratory therapist and the difficulty the older therapist experiences in reading the labels, I want to clarify to you that deciphering respiratory care medication labels is a problem that cuts across all age groups of respiratory therapists. The problem

is how the medication is labeled or not labeled appropriately.

The work flow of the respiratory therapist I think is probably most important for you to understand. The therapist typically includes delivering medications and treatments to a number of patients for a local geographic region in a hospital. The patients that are assigned have a very wide variety of medications that are being delivered to them. Once the medication is checked by the pharmacist for drug interactions, the therapist typically carries medication with them as they begin rounds. It would not be unusual for a therapist to carry between 14 and 15 different vials of medication. The medications must be under control so that therapists either carry the medication in a fanny pack or they carry the medication in a locked draw on a cart they carry with them.

In some institutions, medications are in a Pyxsis system. In this situation, the medication can either be placed in a single patient medication

labeled drawer or they come from stock supply. So, again, multiple vials in a stock drawer.

I just wanted to give you a view of what's in somebody's pocket typically.

Another concern that faces the respiratory therapist is the lack of bar coding on the vial. Many hospitals are moving toward the scanning of medication bar codes. The driving force for this use of technology is to identify the correct patient, identify the correct medication, confirm the correct dose of medication, confirm the correct route of medication, and record the time of the medication delivery.

I want to share with you a few comments that I picked up from some respiratory therapists in just the most recent weeks.

Staff have complained about the inability to see clearly the medication information. For this reason, we switched to a different product that is individually wrapped in clearly labeled, color-coded foil packaging. The current situation with the raised-letter labeling is an accident

waiting to happen. I know you talked earlier about underreporting. It's because we've given the dose and never know we gave the wrong one in some cases.

This is a second therapist: I complained bitterly when the look-alike vials came out. We did not leave them for any nurses to confuse. We do not know of any medication errors beck of the look-alikes. Doesn't mean it didn't happen. We just don't know.

So, again, a little bit more emphasis on the fact that we are seeing probably underreporting.

This is a third one: We have had problems with the unit-doze Xopenex and Atrovent looking alike and labeled in the same clear package. We use Pyxsis and it's still a problem.

So even moving the medication into a more controlled environment continues to be a problem for the therapist who's on the floor.

This is a fourth therapist: One encouraging thing that I have seen is differing shapes and sizes on a very few of the medications.

Since the death of the multi-dose vial of Albuterol, we have a supplier who sends us unit-dose vials of Albuterol that have a very distinctive teardrop shape and a much smaller size for medication. I give that a Bravo. A similar thing has happened with the octagonal unit-dose vials of Pulmicort.

And I think if you look at the very end of this, that small round is the Pulmicort. But this is what's in the pocket of the therapist, and all they have to read on most of those are just that clear lettering.

I was at a program, I did a program in Cincinnati last week, and I mentioned this in a patient safety presentation that I did to therapists. About 600 were there, and what was interesting about it is several of them came up to me afterward and said, Can you imagine what the night shift therapist goes through trying to read these?

Now, low light--it's bad enough, you know, with the age, but the low light.

There's a couple more comments from therapists in there. I think that you've probably got those. You get the gist of what we're trying to say. So on behalf of the American Association of Respiratory Care, I really appreciate the opportunity to share the association comments.

I have one more slide that I want to share with you, and it's this one. What you're seeing here are just the different medications. One of those happens to be Tobramycin. One of them--two of them are bronchodilators. Two of them are exactly the same medication in different doses. Just to really emphasize what the packaging is doing to the therapist at the bedside.

Thank you.

x DR. GROSS: Okay. Thank you very much.

We will not have the committee ask some questions of the speakers, and you can ask questions of any of the speakers that have presented this morning.

Leslie?

DR. HENDELES: I have two questions for Karen. First, is there any Joint Commission

requirements in terms of how respiratory therapists are supposed to handle medication?

MS. STEWART: There's been--

DR. HENDELES: And I have a second question, which is: Would respiratory therapists mind carrying these single-unit dose vials wrapped in foil in their pockets?

MS. STEWART: There are recommendations around the delivery of medications from JCAHO, and most of that is surrounding the control. It is first the pharmacist's review of that medication to see if there are any other interactions, and the second being that that medication is always under control. And you'll see as you go across the country a number of different ways that hospitals are handling the medication control issue. Some of them--the folks that I talked to last week, some of them have a cart where they carry all their plastics and other things that they need with a locked drawer, and their medications are in that drawer. Other ones are using Pyxsis, and some are still carrying it physically on their person in a

side pocket or a fanny pack.

Your second question is, if they were individually wrapped, I think that therapists would use those either in any of those devices under control. The problem is that they open, for example, a packet of Xopenex with 12 vials in it. That's just too much for them to carry when they've got so many different types to carry.

DR. HENDELES: If it's just one, they would be able to?

MS. STEWART: I think they would be able to carry it, yes.

DR. GROSS: Yes, Stephanie?

DR. CRAWFORD: Thank you. This question is for Patrick Poisson, but, Ms. Stewart, don't go too far just in case you want to add to it. I thank each of the speakers for their presentations.

Mr. Poisson, with respect to your presentation, the sixth slide was talking about the advantages and disadvantages--I'm sorry, the advantages and limitations. Each of the advantages from my interpretation were in the manufacturing

process. As you presented, each of the limitations was from the clinical use. So my question is: From the recommendation--potential alternatives that you suggested, have you conducted, your company, or performed any studies using clinical groups such as the respiratory therapists to see acceptability of each of these options?

MR. POISSON: One thing I probably failed to mention is that Cardinal Health is a contract manufacturer, and the products that we manufacture are distributed by our customers. And it's difficult for us to step in front of them and ask for this type of work to be done.

Now, we have done some work with the shrink wrap sleeve label, and the feedback from that was very positive. However, that was a very unique opportunity for us to get involved with that.

In regards to the recommendations, yes, some of them are manufacturing--are good for the manufacturing process. However, one that maybe wasn't explained as well is the sterility of the

product. Using a blow-fill-seal technology to manufacture products is recognized as providing a better microbiological quality of product out to the market versus a conventional process.

DR. GROSS: Michael? I'm sorry. Stephanie, another question?

DR. CRAWFORD: Thank you. Just one quick follow-up. One of your recommendations was increase text size. You mentioned that, of course, something would have to come off if that were happening--would come off if--

MR. POISSON: I think we'd have to undertake those discussions with the agency as to what could come off.

DR. GROSS: Michael?

DR. COHEN: I've been looking at these LDPE plastics for several years, actually, and trying to come up with solutions. And actually the best thing I've ever seen is that shrink wrap, that overwrap, or sleeve, or whatever you want to call it. Is that a proprietary system, or is that available to any manufacturer? And can you foresee

the actual use across the entire spectrum of LDPE containers, even the parenterals?

MR. POISSON: Well, we're very pleased with the progress we've made on the sleeve label. It did involve some development that we regard as intellectual property. So regarding availability to the whole industry, I really can't speak on that.

There will be potentially some leachable extractables even from that system. There is ink on that label. So that has to be evaluated for each product that it's used for. It still may not work for every product.

MR. SCHINDEWOLF: If I could just make a comment on the proprietary nature, what's proprietary about that vial is the rounded end. A lot of the vials that you'll see and I think some that were presented earlier can be on a flat end as well. And we found that the rounded end helped the legibility. As the sleeve shrinks, there tends to be some--what's the word I'm looking for? The print can be--

MR. POISSON: It can be distorted.

MR. SCHINDEWOLF: Yes, "distortion," that's the word. So this was to help the readability of the bar code label itself, so that's what's proprietary in that particular design.

DR. GROSS: Yes, Henri?

DR. MANASSE: In terms of patient safety, one of the biggest issues that I think most practitioners confront is the kind of work-arounds that people utilize to make things convenient for them, and this notion of carrying drugs around in your pocket is a very good example. But it seems that the sleeve is a pretty critical issue with respect to the capacity of adding more information coupled with bar codes, symbologies, et cetera.

Have you all thought about how you can eliminate the dissociation of the sleeve from the package itself? Because the work-around, people are tearing off the sleeves and then carrying the package by themselves. And is there a way that you can avoid that other than at the direct point of care?

MR. POISSON: I'll try and address that. One of the ways that these are used is that the cap is actually twisted off of the vial. And one of the problems I see with individually foil overwrapping is the removal of that foil could potentially damage the vial in that process. So it's a difficult thing to overcome. We could tighten the foil potentially around the vial, but it just opens it up for damage in the transfer process from the location within the hospital to its use point.

You know, there are a lot of advancements going on in packaging. Certainly five years ago I don't think we would have all the options that we have now. Maybe at some point in time we can get to a better alternative with the foil.

DR. GROSS: Robyn?

MS. SHAPIRO: I have two questions. One is actually Henri's. And this is to the agency. What factors, if any, are considered currently in the approval process with respect to these problems?

And the second question is: It seems to me that this morning we have much more information about the potential error, problem, than the leachability and contamination problem, and much more potential risk. Has there been--maybe this is for Karen. Has there been litigation over this? And, if so, what has happened?

MS. STEWART: I can't speak to any litigation, and I think one of the concerns that we have as therapists is that this probably goes underreported. The therapist delivers that care and leaves the bedside to treat the next patient. So they may not see an adverse effect or, as stated earlier by Dr. Sullivan, I believe, the patient does not get the potential relief of the medication.

In other words, if you have Tobramycin and a bronchodilator in your pocket, they both look alike, you give the Tobramycin to the patient who needs the bronchodilator, you may not see the effect. So it becomes underreported.

MS. SHAPIRO: And the patient may not

either. I mean, they may not realize--the patient or the family or whomever, the error may not be disclosed to anyone.

MS. STEWART: Except the patient's therapeutic treatment regime is going to be longer with a longer length of stay because they didn't get the proper--

MS. SHAPIRO: Sure, but they may not know why.

MS. STEWART: Right.

DR. GROSS: Are there any other questions?

MS. SHAPIRO: Can I have the first question answered by Paul or somebody about what currently is considered?

DR. SHAH: You are talking about in terms of the quality controls?

MS. SHAPIRO: In the approval process for any new drugs, what, if any, is considered with respect to safety relating to this possibility for error?

DR. SHAH: Let me just try to briefly summarize.

When we get an application and we have these kind of packaging components, then usually the applicant may provide this information for all the components of each and every packaging component into the NDA, or they may choose to provide that information, if it proprietary, through a Drug Master File. Then we review the chemical composition of each and very packaging component in a Drug Master File, but we cannot relay that information to the applicant.

Once we know from the composition that there is a potential for volatile chemicals to be present in the component and they may permeate through the LDPE vials, then we ask the applicant indirectly, without revealing the other information, Have you studied any legibility or extractable--have you found any extractable, what kind of solvent conditions you have used to extract this leachable? And we encourage them to contact the DMF supplier, work with them, and develop some procedures to find out what can be present and establish a profile. Once you establish a profile,

then you may identify, okay, these are the typical components present into a component, packaging component, and we are going to use that as a basis for screening the incoming packaging material. And then you may have some kind of acceptance criteria. That may be a GC profile. Or if you have identified a particular component by its chemical structure, then you may say, okay, it is extracted at, say, one milligram per ml or something like that, okay? So then you will conduct some kind of a study for the shelf life, over the shelf life, whether that particular extractable gets into the drug product or not. If it does not, then at least you have established that if I control the amount of incoming acceptance criteria, I have established incoming packaging material, then I do not see the leachable into the drug product. So then you don't have to have a test for leachable into the drug product, but you have to establish that relationship.

So we go through a series of steps to establish that, and once we are satisfied, then we

may decide, okay, you are going to control or minimize this particular component at acceptance level in incoming packaging material. Or you will have to carry out the leachable testing.

MS. SHAPIRO: What about the analysis with respect to the possible safety problems on account of the error issues?

DR. SHAH: Okay. Once we get that, we see that, okay, it is present into the drug product at a certain level. And if we know the identity of that chemical, then we ask our pharmacology and toxicology person to review that data and decide whether that will have any safety issue. And if they decide that it may have a safety issue, then they may ask the applicant to qualify that particular material or chemical at that level.

MS. SHAPIRO: Okay. And all that has to do with the leachability question. But what about the question having to do with the confusion problems on account of the labeling and its impact on safety?

DR. SELIGMAN: For all drug products that

are approved by the agency, we look at the accuracy of the label, whether it's misleading or not, whether it's nonpromotional in nature. We look at the name for potential confusion. We look at the packaging regarding dose and frequency. And if at the time we find, either at the time of approval or even subsequent to approval, that there is such a potential for either name confusion, for misleading dose, or any kind of misleading information that might lead to medication error, we make a recommendation to the manufacturers to try to--to alter that.

I think the reason we're bringing this particular issue to this committee is that this is a particularly vexing issue. But for the vast majority of products that we review, when we find such potential for confusion or potential error, we recommend to the manufacturer that that be addressed prior to approval of the product.

MS. SHAPIRO: Have you ever, with containers like this, sent it back and said, no, this doesn't--this won't do given these sorts of

problems?

T2B DR. SELIGMAN: I'm not aware of any. Some of them go through generics.

Carol, did you want to respond to that?

MS. HOLQUIST: Yes. Actually, our office in Office of Drug Safety, we only get whatever--we only see the packaging material that comes in with new products. A lot of these products have been on the market for years and years. So if indeed one of these products came in today with this packaging labeling, yes, of course, that would be one of our recommendations in our review that, based on post-marketing reports and evidence, we wouldn't recommend this. But then the agency's hands are kind of tied because of the ingress issue. So until we find an alternative packaging, it's a conundrum we're in.

DR. GROSS: Gene, did you want to comment?

DR. SULLIVAN: Yes, I just wanted to follow up on a couple things that have been said so far: one, to just make sure the categories of harm to patients are in the right column. There's the

harm that the legibility issue brings in, so the harm that a patient suffers if he or she doesn't receive Tobramycin but instead receives Albuterol. And then what I was trying to touch on and the thing that's hard to get your hands around is the harm from the actual presence of these chemicals, and that it's well known that a patient may come to the emergency department and receive a few treatments of Albuterol and recover and be discharged. Another patient may come in and not seem to respond and end up mechanically ventilated. And to what extent that could be related to contaminants in the drug product would be anyone's guess and impossible to day. So I just wanted to make sure we consider those two sort of as they're the competing harms.

The other issue I just wanted to talk about a little bit was the issue of the use of the flange or labeling that's not directly applied to the actual body of the nebule, be it with a shrink wrap or an applied label and so forth; that there is some intrinsic appeal because it seems to be

less in contact with the LDPE, but keep in mind that if these are then put into an overwrap, a foil overwrap, perhaps for other reasons--light-sensitive products and so forth--that then you have sort of a micro environment, you know, like a little humidor with these chemical vapors that could then make their way--even though they're here on the flange, they could easily make their way into the product, and that's sort of evidenced by that case where we had the cardboard carton and that chemical made its way in. So it's not, you know, a complete solution. We have to keep that in mind.

DR. GROSS: Arthur, you had a question?

MR. LEVIN: One is just a point of information. Mike, is that the packaging with that label, that's what you are referencing when you say so far that's the best--

DR. COHEN: Not necessarily.

MR. LEVIN: Okay.

DR. COHEN: This is certainly acceptable as a way to identify a container. But the ones

I've seen have actually had a similar type of film, but it's been around the body of the ampule device. And there was a tear-off so that you would literally pull the tab and tear off the top part of the plastic. It was a total overwrap.

MR. LEVIN: But it's something more than that.

DR. COHEN: Leaving the identify, even though this was exposed.

MR. LEVIN: Okay. So the whole thing is shrink wrapped to something.

DR. COHEN: That's correct.

MR. LEVIN: Right, okay. I didn't think we had seen one of those.

DR. COHEN: We didn't.

MR. LEVIN: Yes, okay. So that clarifies that.

The second thing is we seem to be sort of entirely focusing in inpatient and, you know, the issue of outpatient is certainly significant. And I'm just wondering from, you know, what you've done to look at how well these kinds of solutions work

in the outpatient pharmacy setting as opposed to inpatient settings where it's really--making sure that the respiratory therapist who administers the drug is clear on the right drug and the dosage et cetera. What about an outpatient pharmacy?

MR. POISSON: Well, one of the reasons why--and someone may question why there's 12 vials in a pouch or even 28 or up to 60. A lot of the reason behind that is because of the use period in the outpatient--outside of the hospital. And based on feedback we've received, they view that as an advantage to have that type of packaging in that particular environment. And the possibility exists that maybe some of these options we've presented today, such as the symbol on the vial would help them in that area from using the wrong product.

So I think, you know, there's opportunities for a number of these options to be implemented based on the setting that they're used in.

DR. GROSS: Okay. Henri, you have a question?

DR. MANASSE: I just want to follow up on Art's point in terms of outpatient use. I can't imagine given the size of these containers, given the unreadability of these containers, and the obvious confusion that is brought to bear to those problems, that outpatients, particularly elderly outpatients, can manage this on their own. I think somehow we've got to contemplate where we go with that because the increasing number of people who are using these on an outpatient basis and the increasing aging of the population presents us with an incredible challenge.

DR. GROSS: Okay. Marci would like to make a comment.

DR. LEE: Thank you. I just wanted to add to that. Based on the medication error reports that we have received most recently, there are many comments about the elderly population using these drugs. There are several reports from a pharmacist saying that his patients are expressing that they're afraid to use the product because they're afraid that they're going to double their dose

accidentally because they're not sure what is in each ampule.

Then, also, the letter in the background package that was sent to Senator Harkin, that also involved a woman who was writing in about her elderly mother that was having the same problem also from a mail-order pharmacy. So in addition to a regular outpatient pharmacy where there's direct interaction with the pharmacist, you have people who are unable to get out of their home and receive their medications by mail having the same experiences.

Carol wants to add something.

MS. HOLQUIST: Also, just in relation to the letters at the top of the vials themselves, we actually have gotten some reports as well where there's a question as to what the actual letter stands for, like A, is it for Albuterol or for Atrovent. So some simple fixes, sometimes you also have to think beyond, that there's more than one product that begins with that letter.

x DR. GROSS: Okay. We are a little bit

ahead of schedule, and we will proceed at this time with the open public hearing. Dr. Eric Sheinin will present. First I need to--

MS. JAIN: We need to read a statement first.

DR. GROSS: 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 this 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 financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

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

with your attendance at the meeting. Likewise, 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.

x DR. SHEININ: Thank you, Dr. Gross. I have no financial ties or interests in any pharmaceutical company or any other company or organization that would be interested in the proceedings before the committee today, so I think I'm okay with that.

DR. GROSS: Thank you.

DR. SHEININ: My name is Eric Sheinin, and I'm here today to represent the United States Pharmacopeia. At the UPS, I am the Vice President for Information and Standards Development. We do have an expert committee that deals with safety issues, and much of what I'm going to say today is a direct result of work that they have done. But I would like to give you some background about the

USP for those of you who may not be familiar with us and also to have it in the record.

The USP is a nongovernmental organization that promotes the public health by establishing state-of-the-art standards to ensure the quality of medicines and other health care technologies. These standards are developed by a unique process of public involvement and they're accepted worldwide. Many other countries around the world recognize the USPNF standards as their own standards in terms of regulatory procedures within those countries.

USP is a not-for-profit organization that achieves this goal through the scientific contribution of volunteers, and the volunteers represent pharmacy, medicine, and many other health care professions. These individuals work in academia, they work in government, both U.S. and international. In fact, there are many FDA scientists who serve as volunteer to USP. They also come from the pharmaceutical industry and consumer organizations. In addition to standards

development, USP's has several other public health programs that focus on promoting optimal public health care delivery.

In our mission statement, it says the mission is to promote the public health, and I always liken that to the mission of CDER, which is also basically to promote the public health. So I believe we're all interested in the same types of standards.

At the USP, the volunteers, many of them serve on our Council of Experts and its expert committees. The members of these committees are USP scientific decisionmakers, and they form our standard-setting body. Council members are elected by USP's membership at our five-year convention. They're elected on the basis of their knowledge and expertise, and they serve five-year terms. So even individuals who come from industry, from their companies, when they volunteer to work with USP, they represent themselves. They do not represent their employer, their organization, or anybody else when they work on our standards.

The 2000-2005 Council of Experts comprises 62 nationally recognized scientists, academicians, and clinicians. Each one of these individuals chairs an expert committee, and the expert committees are made up then in turn of distinguished experts.

One of the committees is named the USP Safe Medication Use Expert Committee. This committee is comprised of 18 members representing pharmacy, nursing, and medicine. It includes an FDA liaison, Carol Holquist. It includes Captain Jerry Phillips, who was formerly the Associate Director for Medication Error Prevention in FDA's Office of Drug Safety.

For more than 30 years, USP has promoted the importance of collecting and sharing experiential data from health care professionals. In the last decade, particular emphasis has focused on medication error reporting and prevention as a way for USP to positively affect the public health. The data collected from two of our programs--the USP-ISMP Medication Error Reporting, or MER,

Program and MEDMARX--are reviewed and analyzed by USP staff and USP's Safe Medication Use Expert Committee.

In October of 2002, USP sent a letter to the chief of CDER's Compendial Operations staff, Yanna Mille, to inform her, on behalf of the Safe Medication Use Expert Committee, of the continuing concerns of the committee and of health care professionals and practitioners regarding both the difficulty in identifying drug products packaged in low-density polyethylene ampules and vials and the resultant medication errors from their misuse.

Plastic ampule packaging is frequently used for respiratory therapy drugs. The ampules often do not bear labels but are labeled by debossing or embossing the actual plastic container. This debossing or embossing is described by health care practitioners who have reported to the USP reporting programs as being unreadable, causing difficulty in identifying the product within. Because this packaging is now being used not only for respiratory therapy drugs

but also for injectables and oral solution, it is even more important that the subject products be easily identified and readily distinguishable from each other.

USP has provided the Compendial Operations staff, the Dockets Branch, and the Office of Drug Safety with more than 42 specific case studies where mediation errors occurred because of the use of these products. We also have submitted copies of the actual product containers involved in the medication errors that were reported through the two USP reporting programs.

In addition to providing comment on the concerns expressed to USP by health care practitioners, the USP Safe Medication Use Expert Committee unanimously voted to encourage FDA to establish an alternate method of labeling for the various drug products packaged in the plastic vials being discussed today. This would be in order for these products to be clearly identifiable, hopefully thereby reducing the numerous medication errors that have occurred and likely will continue

to occur.

The expert committee also suggested that the FDA cease approval of products in these containers because their use continues to be the subject of numerous medication error reports.

From April 20, 2002, through January 31, 2004, an additional 26 reports of actual and potential medication errors have been received through USP's medication errors reporting programs regarding the similarity in the labeling of products in low-density polyethylene vials. The problems with these containers continue, and the USP and the USP Safe Medication Use Expert Committee recommends that FDA take any necessary action to improve the labeling of low-density polyethylene ampules and vials.

I thank you for your attention and your consideration of USP's concerns. If you have any questions, I'll certainly try to answer them.

DR. GROSS: Thank you very much.

Are there any questions from the panel? Jackie?

DR. GARDNER: I would just like to ask, Dr. Sheinin, does USP have a recommendation of one of these methods over another?

DR. SHEININ: A recommendation?

DR. GARDNER: For solving this problem?

DR. SHEININ: Not at this point, not that I'm aware of. The obvious solution to me--and I actually worked at FDA for 30 years before I went to USP--would be to have a label on the containers. But there are concerns with migration through the low-density polyethylene. I'm sorry I missed the end of the previous presentation where they were describing perhaps some way to help identify these products.

DR. GROSS: Robyn Shapiro?

MS. SHAPIRO: I just have a question about these report forms. Was patient counseling provided? And then, if yes, before or after error was discovered? Does that mean about what the drug is, how to take it, how to read it? What does the counseling refer to?

DR. SHEININ: I believe that the

counseling is provided by the professional who's reporting the problem to us. I don't believe USP does the counseling.

MS. SHAPIRO: So we don't really know what that refers to.

DR. SHEININ: Unfortunately, the Safe Medication Use Expert Committee is not under my area of responsibility. But as far as I know, that counseling would not be provided by USP, and we probably do not know what the nature of that counseling was. The form is asking if there has been any counseling.

DR. GROSS: Henri?

DR. MANASSE: Good morning, Eric.

DR. SHEININ: Hi, Henri.

DR. MANASSE: Two questions. We've talked today about two major issues: one is the leaching of chemical agents from various labeling techniques and embossments; the other having to do with the readability issues and the packages themselves.

Has USP convened any technical experts on either one of those issues to contemplate what's

the existing science, what do we know, what do we not know, as well as what our reasonable solutions, given what's known, in other industries or other options for dealing with this problem?

DR. SHEININ: Not that I'm aware of. It certainly is a good suggestion, and I will take that back to the committee and to Diane Cousins, whom I think many of you probably know, and see if there is a way that we could proceed in that manner. I think it's a very good suggestion and something that should be done.

DR. GROSS: Okay. Thank you very much.

DR. SHEININ: Thank you.

x DR. GROSS: If there are no further 14

questions, since we remain ahead of schedule, Dr. Paul Seligman will now introduce the issues and questions that he has for the Advisory Committee.

DR. SELIGMAN: You should all, members of the committee, have a one-page LDPE Discussion Points. These, I believe, are in the packages as well for public distribution. Why don't we simply refer to these rather than booting up the slides.

You've heard this morning about the issue related to the ingress of volatile compounds as a problem with these particular containers and various approaches to deal with this issue as well as not only--to deal with both the preservation of the purity of the drug, as well as ways in which to improve the legibility of the label.

What we've asked in the first question is: Given the various approaches that you've heard today, including embossing and debossing of containers, the use of unit package overwraps, the elongation of the bottom tab and using that as an place to print critical information, the use of paper labels, the use of ink directly on the vial, various potential approaches including tactile recognition, shrink wrap labels, and then we actually even saw the use of glass ampules or vials, what we're interested in the committee addressing first off is to discuss the potential advantages or disadvantages of these approaches and to identify in 1b any creative solutions or alternate packaging design that would improve

legibility and address the problem of ingress of chemical contaminants and at the same time not create additional problems.

We'd also like to have you put on your thinking caps and consider if there are stakeholder groups, such as manufacturers, practitioners, consumers, and others, who might best advise FDA about possible new packaging configurations that might resolve some of these issues.

And then given what you've heard today and based on our discussion, describe and advise us on an appropriate course of action to address not only the problem of ingress of contaminants but also medication errors due to legibility and similar packaging issues.

So those are the issues before us. Peter?

DR. GROSS: We share in your perplexity.

DR. SELIGMAN: Thank you.

x DR. GROSS: This is a difficult issue.

Thank you very much for the questions, Paul, and we will initiate the discussion. The agenda allows two hours for discussion, so why

don't we do roughly an hour, and then maybe we can have lunch and then finish up, if that's okay.

MS. JAIN: Lunch is on its way.

DR. GROSS: Okay. Well, whenever lunch is here, we will re-evaluate our timing. But let's begin the discussion now.

Anyone have any comments? Why don't we do this in an orderly fashion and take the issues as Paul presented them, with 1a being the first. They're all sort of interrelated, but why don't we get specific and talk about 1a first. Leslie?

DR. HENDELES: I'd like to preface my comments by saying that nebulization of bronchodilators is an obsolete way of treating acute bronchospasm, and part of whatever we do needs to focus on an educational program designed at using the meter-dose inhaler through a valve holding chamber, which is far more efficient, causes fewer side effects, less expensive way, and it's the way the rest of the world treats acute asthma. The United States has a fixation on nebulizer therapy that they won't let go of, for

some reason, especially pediatricians, but there's clearly 10 to 15 double-blind, placebo-controlled trials, a Cochran review, et cetera, that indicate that there are much more efficient ways and it would, of course, circumvent this problem for asthma.

Now, having said that, I really like the idea of having that foil pack, like the Nephron, with a single unit, and I think that would solve the problem. It would allow for the bar coding. And according to Karen, respiratory therapists would be willing to carry that in their pocket. As I understand it, the reason why they carry single units in their pocket is because when they open the foil pack, there's 12 of them there. If there's only one, they would probably carry it. And, of course, that could also be addressed through professional education as well.

DR. GROSS: Leslie, for myself and anyone else who is not 100 percent clear on what you said, would you contrast the two methods of medication delivery again?

DR. HENDELES: Bronchodilators as well as inhaled steroids can be delivered by a pressurized, meter-dose inhaler that's attached to a valve holding chamber with an age-appropriate connection, either a mouthpiece for older folks or a mask for preschool kids that seals around their nose and mouth, and you fire off a few puffs, such as four puffs, into this chamber and it's equivalent in efficacy to nebulizing a bronchodilator in the emergency room. It causes fewer side effects. It takes a minute or two to give the treatment instead of 15 to 20 minutes, and it's far more convenient for patients and cheaper. They don't have to buy a compressor for $150.

DR. GROSS: Could someone from the FDA comment on whether or not they want to tackle that issue?

DR. SULLIVAN: That may not be an issue for the FDA really to address. I don't think there would be any--the evidence being what it is, that MDIs may effect just as great a degree of bronchodilation as a nebulizer, it would be

something that physicians should interpret and use in their clinical judgment. I don't think there would be any rationale for the agency to pull nebulizer solutions off the market. I think that would be very drastic. So from our perspective, we have to deal with them.

Now, if the medical community starts to learn that maybe they are overusing nebulizers through Dr. Hendeles' shaking the cage a little bit, that's just great. But the issue will still remain for us.

DR. HENDELES: And, indeed, there are patients who might be unconscious, for example, or would need the nebulizer, and there are drugs such as Tobramycin that can't be delivered by MDI.

DR. GROSS: Arthur?

MR. LEVIN: I realize it isn't within the scope of authority of the FDA to dictate clinical practice, but part of the problem here is we're dealing with a tension between an issue of potential harm, which is the leaching of, you know, substances that don't belong in the solution into

the solution and the documented potential harm of error. And we're looking at a variety of solutions, none of which is perfect and each of which brings with it some question: You know, does it solve the error problem entirely? Or by solving the error problem entirely, does it still leave us open to the problem of possible impurity?

In that context, I think the FDA does have something to say, and then when we move to the ambulatory setting particularly, where these issues I think get even more complicated--and we really haven't talked about it--that if there are better ways to deliver the product that relief us of the burden of trying to figure out the perfect solution on these two different potential harms, that's worthy of comment. I mean, nobody expects you to be able to pull the product from the market, but in dealing with improving safety of products, I don't think it's entirely out of character for the FDA to make a comment that one of the solutions here is to use a different form of delivery that obviates the need to talk about all of this. You may not be

able to say, "You can't use the other," but you can certainly say, "Moving in this direction seems to be a way to solve the problem," and I would say particularly in the ambulatory populations.

DR. GROSS: Maybe we'll have one or two more comments on this particular issue. Then we'll have to get back to the questions raised by Dr. Seligman in 1a.

Brian?

DR. STROM: yes, I'd like to in my initial start be more provocative. We're hearing, as Arthur is saying, between two safety problems, without good data on either side to quantify each of them. We're using in one case physiological chemical tests and the theory that leaching might be a problem, and it's clearly understandable why it can't be quantified more than that. And we're hearing on the other side about medication errors based on the spontaneous reporting system, which is grossly incomplete. We don't know how many there are out there other than the fact that we're seeing a number, and there are clearly many more out there

than we're seeing that could be studied more concretely, potentially. But, in either case, we don't have good quantification, and so part of the problem here is balancing two risks, neither of which are quantified.

If we're hearing from Leslie--and you're not disagreeing--that there is a better approach which is more effective and is safer, why isn't that a regulatory reason for the FDA to remove the nebulizers--this packaging?

DR. SULLIVAN: Well, I'm not actually agreeing. I'm aware of the various articles that are out there. I have not reviewed those studies myself, seen the data myself. Certainly the agency has not come to that conclusion that the MDIs have these attributes, these costs, and effectiveness and so forth. And that's an open question, I believe. Dr. Hendeles probably knows that literature even better than I.

But for the agency to come to a conclusion like that is a very significant matter, and, again, although we can make comments, it's not clear in

what context that comment will hold any water until or unless we were to, as suggested, remove them from the market. And I think that that's quite a drastic step, and I think that as Dr. Hendeles pointed out, there would be very good arguments that there may be some populations who are only served by the nebulizers, and, therefore, it would be unwise to remove them from the market.

So let me say that we haven't made that determination, number one, and that even if we made the determination that for the average patient it was efficient in some way that you would like to define efficiency, it would be hard for us to move on that.

So I understand your perspective and I understand Dr. Hendeles' perspective that perhaps the American physicians are overutilizing them. But I don't think that's going to get around the issues that we have to face.

DR. GROSS: Okay. I think that maybe the sense of the committee is that this is advice they'd like to give to the FDA to look into this

issue and decide how they want to proceed. But I would like that the issue should be brought to the attention of the national pulmonary organizations, and they in their guidelines should make this recommendation because in that setting they might have a significant clinical impact.

DR. HENDELES: It shouldn't be limited to physicians. I think health system pharmacists and respiratory therapists and those organizations play a role, too.

DR. GROSS: Absolutely. But that might be the way to begin to make the change, if that's what the scientific evidence indicates.

Okay. I know you've all been trying to avoid 1a, but we do have to address it.

[Laughter.]

DR. GROSS: And I saw Michael's hand up first.

DR. COHEN: Thank you very much, sir.

First of all, let me just ask the question: Are we talking only about the respiratory ampules, the LDPE, or are you talking

about all LDPE? Because there's a difference between the two, and the way they may be labeled might be different as well. So that would be the first question. Are there, in fact--we need to clarify that there are, in fact, LDPE ampules for injectables and ophthalmics, et cetera? Is that what we heard earlier? That's number one.

MS. HOLQUIST: Yes, and that was one of our questions, too. Should we treat the pulmonary products separately than these other products that are packaged by other routes of administration?

DR. COHEN: I guess what I'm saying is, even if we do clarify what you just brought up, Dr. Hendeles, we'd still need to address the issue of the labeling because there are other forms, if, in fact, they're LDPE. So that was the first thing I wanted to mention.

Can I make a suggestion to the Chair that we go through each of these bullets, perhaps separately? Or do you want us to comment on all of them at the same time?

DR. GROSS: I think that's a very good

idea, Michael. Do you want to begin with embossed?

DR. MANASSE: Peter, I wonder if I could just interrupt.

DR. GROSS: Yes, sure. Henri?

DR. MANASSE: I think before we jump to choosing between evils, I think we have to lift up, perhaps, to the 30,000-foot level a minute and, that is, if we're going to continue to use these low-density polyethylene containers in the sizes that we're going to use them, if that's a given, we're going to have to more carefully understand and identify both the packaging and ingress issues.

I'm a little bit uncomfortable jumping to picking what we think is the best when we don't have all the information. I don't think we're totally educated on all the potential leaching issues, all the potential chemical agents that could cause degradation, et cetera, et cetera.

At the same time, I'd hate to see us jump to figuring out packaging solutions when at least I, for one, have not been presented with all of the packaging options that might be a possibility.

We're limiting ourselves largely to pharmaceutical packaging, and I'm amazed in this country how creative packaging can become. All you have to do is look at the cosmetics industry to see some of that creativity. I'm not sure that we've exhausted the dialogue around creative mechanisms by which people can read this stuff, that they can handle it without an intervening health professional, at home, for example, and particularly relating to the elderly. And I'm not convinced that we know enough yet about what kind of package designs are utilized in other industries that might be applicable here that could solve our problem in a much bigger way.

I don't want to be interruptive, Peter, but it seems to me that we've got to look at those issues.

DR. GROSS: I think those are very critical points, Henri. I know from my point of view, I'm not sure I got an answer as to why other polymers have not been selected as opposed to polyethylene, you know, like polypropylene or polystyrene. Is there any potential there? Can

that be looked at? Is high-density any better than low-density is another issue. Should the thickness of the LDPE be made greater and that would probably slow the migration? But would it make a significant difference over a period of time or not? So there's just a tremendous amount that's not known.

But in the absence of all the knowledge that we need, which is the situation in most instances that we have to deal with in life, just read Robert Rubin's book, we still do have to address the questions posed to us.

Does anybody have any other comments before we address those specific questions? Yes, Jackie?

DR. GARDNER: Since we aren't experts on this and what you're saying is correct, and since Brian is leaving this committee and he always has one mantra, and that is, we need data, where are the data, and he won't be here anymore, so I'll take that up for him, my suggestion would be that we ask, maybe starting with Michael, of these

options which is probably the most satisfactory on the face of it given everything we've heard today, recommend that maybe starting with that, some studies be done to address the extent of the ingress using that method, and has it solved that problem? And so to that end, it sounds like either the shrink wrapping of the ampule, as Michael suggested, or the foil wrap, individual unit of use sleeve, which I happen to like because it seems like you could bar code it and also put instructions and colors and other kinds of things on it, but pick one, the best that we can come up with and ask them to study it and then tell us how bad it turns out to be.

DR. GROSS: Well, we don't even know the toxicity of the chemicals that are ingressing. We don't even have that information. Certainly a lot of products that are available commercially have low levels of toxin that are considered acceptable. So, I mean, that's another big area where we just don't have the information.

Leslie?

DR. HENDELES: Did we learn whether this foil wrap actually prevents the problem or does it add anything else to the vial, the solution?

DR. SHAH: Well, it depends.

DR. HENDELES: Yes, okay.

DR. SHAH: Again, it goes back to the question of having adequate knowledge of the chemical components which you have selected for your foil laminate and, critically, the adhesive layer which is used. Most of the time, the organic solvents which are used in adhesives, they migrate from the adhesive layer to the LDPE vial. As long as the adhesive layer is on the other side of the aluminum foil, they may not have to worry about that. You can use a sort of adhesive layer, you can use pressure-sensitive materials which can just fuse together. Then you can avoid using adhesives.

Again, that's solving one problem coming from adhesive. However, the other layers which are used inside the aluminum foil, again, the product composition, chemical composition does matter. If there are small organic molecules which have a

volatile potential, there is a likelihood that it may migrate. However, the applicant can do a one-time study and demonstrate that whatever leaches into the drug product is not significant enough to pose a safety issue. If that is being done, then that may be a possibility.

But we really don't know, I mean, in that sense that it will solve the problem of not leaching 100 percent.

T3A DR. GROSS: Okay. We've been talking for 20 minutes, and we have still avoided the question. So anybody have any other comments before we address the question before us?

[No response.]

DR. GROSS: Okay. At Michael's suggestion, if that's okay with everybody, starting at the top, any comments on embossing? Michael?

DR. COHEN: I have a few comments, but, again, we are talking about the respiratory use specifically? That's fine if we are.

DR. GROSS: Well, go ahead and distinguish what you want.

DR. COHEN: Well, I think for the respiratory use, at least now there's not a great variety of agents that are packaged in this type of plastic, which may have an impact on my comments with injectables, et cetera. I don't know what the future growth will be.

But with the embossment right now, I think it's pretty clear that we really can't leave things the way that they are and that there are some changes that we heard from--I believe it was from Cardinal Health that possibly could help here. One of them was the large type, and I thought that was a world of difference between that and the old type.

However, I should point out that we're talking about clear containers now, colorless containers. We're not talking about color containers, and there's a whole set of problems with that that I don't even know if we're going to get into. But I would certainly discourage the use of color differentiation.

But, at any rate--

DR. GROSS: Because?

DR. COHEN: Well, again, you know, the area of growth, confusion with other medications. Are you coloring them by class of drug or by individual drug? If it's by individual drug, are there enough colors? Et cetera, et cetera. But, at any rate, we can get into that a little bit later.

But I also want to point out that when you take these clear containers, what we saw was the container against a dark background. When you put them against the table here or a lighter, white background, the readability still leaves something to be desired. Plus, you know, the way that the photographer took the picture or something may have impacted, you know, how we viewed that as well. But I still think it really does have some possibility for us there with the large type.

The other concern with that, though, is that in using that large type, it forced them to place the strength of the medication on the opposite side. In reality, I still think there

will be some medication errors where people will leave these on a counter or in a bin, for example, see, you know, Ipatropium or whatever the medication is, and not pick it up and turn it over. So you'll have some confusion between strengths still.

So, with those caveats, I think that is one thing that should remain on the list, the embossment with larger characters.

DR. GROSS: Anyone else want to comment? Yes, Stephanie?

DR. CRAWFORD: I'd actually like to address my question to the agency. What would be the feasibility from a regulatory perspective of increasing the type, knowing that other content would have to be removed from the immediate container?

MS. HOLQUIST: Well, right now there is a regulation for what's allowable for the smallest size label, and it's pretty minimal. Basically it's the name of the product, either the proprietary name, the established name, the

manufacturer, the lot number, and expiration date. I don't know how much less of that that you can include because if there is a product problem with a specific lot number, you're going to need that information with each nebule. If it's on like one of these flanges and it's removed, that information is gone, so basically your stock is pretty much wasted because you'd probably have to throw it out because it's in doubt whether it's that affected lot.

It would be great if nobody put a proprietary name on there, but we know that's not going to happen. So, you know, it has to be the name of the drug and it has to be the strength because there are multiple products. So I really don't know how we could eliminate much more than what's required on there.

DR. GROSS: Robyn?

MS. SHAPIRO: This is probably a stupid question. Can you different-color the embossed figures so that you have embossments, or whatever the noun is, in a different color so there is

contrast?

DR. SADEGHI: [Inaudible, off microphone] like a stamp, you have an ink layer [inaudible].

MS. SHAPIRO: Right.

DR. GROSS: Brian?

DR. STROM: I want to come back to Michael's suggestion, which I think makes enormous sense. I think from the list of things you just gave us that are now required, there is a very big difference between the importance of the drug name and the strength versus the lot number, for example. And to say that they're equivalent, I think from a clinical point of view, you don't need the lot number. And if there's a problem, yeah, you'd like to know the lot number, but chances are it's going to have been thrown away by then. The container will have been thrown away regardless.

It would be nice to have the lot number on it, but I would not by any means consider it equivalent to the drug name. And so the idea of having the drug name in big print like we saw and the lot number on the flange on the bottom in small

print and the expiration date on the flange on the bottom in small print--again, I don't think it should be unavailable, but I think the two are dramatically different in their clinical importance. And to differentiate between them in the label personally I would think would make a lot of sense.

DR. SULLIVAN: Let me see if I can respond. I think we have to be a little bit careful because there is a specific regulation about minimum requirements in labeling, and we can presume that a lot of thought went into that. And the requirement is regarding drug products that are so small that you have to really minimize what you put on there. And through the process that regulations were developed, it was determined that this was the minimum set. And I think we ought to be careful that in solving this problem we don't perhaps brush aside what probably was considered very carefully.

And I would think that in a setting of particularly a drug recall that it would be

critical to be able to have the lot number there. And this is just an off-the-cuff remark, but I do want to respect the process that apparently was undertaken to make the regulation to think carefully about what's the minimum amount of data that should be there.

DR. STROM: If I can follow up, let me just clarify. I'm not saying--I'm not disagreeing with you. I'm not saying that the data shouldn't be there. What I'm saying is the weighting of the data and the importance of the data and the utility of the data are very different, that the lot number is important when you have a recall, which is hopefully uncommon. The drug name and dose is important every time you give it, and so the data--I'm not saying the data should be eliminated. I'm saying there should be a differentiation between the size and how they're provided. So if you have a fixed amount of space, use most of it for what is most important and you need every day; and if you can't normally read the lot number without a magnifying glass, who cares?

[Inaudible comment off microphone.]

DR. STROM: You can't anyway, yes. Yes.

DR. SHAH: I think currently we are doing in a sort of way that the lot number and expiration date is going to on the bottom flanges, which is always tiny, small. So I agree with him that the increase of the text size does make a dramatic difference. So I think there is an opportunity over there to make an improvement as far as the medication error is concerned.

DR. SULLIVAN: Yes, I thought the basis of that slide was that in order to increase this size, we'd have to eliminate some of what's currently required. And if we were to say we agree with that, we ought to think very carefully.

DR. GROSS: Leslie?

DR. HENDELES: A compromise might be to use the first and second bullet where you increase the print size, leave on the essential information, but put one unit in a foil pack. That would solve all of those problems.

DR. GROSS: Yes?

DR. STEMHAGEN: One of the things that's not on the list is changing the size and shape and differentiating by size and whether that's even a possibility, you know, different doses at different sizes and things. We saw a couple different shapes, but we didn't really talk about that kind of change in packaging.

DR. GROSS: Thank you, Annette.

Any other comments on embossing? Arthur?

MR. LEVIN: In terms of shape and size--I mean, it's a little off embossing, but are there any studies that look at the ability of people to recognize that in the field? It strikes me it's an accident waiting to happen. But I just don't know if there are studies out there that look at these issues of differentiation by side and shape in the clinical setting. If people are indeed carrying dozens of vials in their pocket, you're asking an awful lot if you expect that to make a difference or reducing the possibility they may pick the wrong dose or the wrong drug.

DR. GROSS: I guess part of that question

is: Does the FDA--can the FDA sponsor research studies to deal with some of these questions?

DR. SHAH: I'll just say one more thing regarding the shape--

DR. GROSS: No answer to that question?

DR. SHAH: No. I think we can take it to the agency, but I think it's a policy issue, and I think they will have to consider that.

DR. GROSS: Okay.

PARTICIPANT: [Inaudible comment off microphone]--once you do that, [inaudible] same product, and then you have to standardize it across the board. One manufacturer makes it this shape, another makes a different shape, [inaudible].

DR. SHAH: I was just making the same point, that, you know, if you are just going to rely on the shape, oh, this particular shape is associated with this drug product and somebody decides to make for some other drug product a similar shape, then we are still going to have a similar problem.

DR. GROSS: Brian?

DR. STROM: Just involved with the shape thing, I think it's probably--I'd be interested in Michael's answer, but my reaction is it's similar probably to the color issues, which I think is what Michael is suggesting. To the degree you give people an alternative cue, they'll use that cue instead of the name, and you're more likely to have errors, therefore, because people are using that cue instead of the name. I would rather people have to use the name but it be legible. They're less likely to make errors, I think. But, again, you know, I'd like to see data.

DR. STEMHAGEN: I was thinking that we're trying to squeeze a lot of information on a small thing. If it were bigger, you'd have a little bit more space to make the print larger. That's where the size issue was--

DR. GROSS: Let me see if I can summarize the sense of the group on the embossed issue: If embossing is to be continued, it should be done where the drug name and dose is much larger print, and yet we still have to consider what to do about

expiration date and lot number, although that could be smaller. Is that sort of the sense of the group?

PARTICIPANT: Yes.

DR. GROSS: Okay. Let's go to number two, unit package overwrap. Anyone want to comment on that? Yes, Jackie?

DR. GARDNER: As mentioned earlier, I favor this one in conjunction with the former so that the embossed product that's inside would also have the larger, more legible features that were mentioned in bullet number one, and this would give us the opportunity for a good deal more in the way of information, identification, and bar coding.

DR. GROSS: Henri?

DR. MANASSE: I would urge us or urge the agency and the manufacturing industry to explore a mechanism whereby that outer overwrap cannot be separated until actual use of the drug from the original vial. So when you rip off the outer wrap, that then opens the package for use.

DR. GROSS: So your comment addresses the

issue brought up by many of the respiratory therapists that they'll take it out of the wrap and put all of them in a jumble in their pocket, and then the wrap is sort of useless for identification.

DR. MANASSE: Exactly.

DR. GROSS: I don't know if that's--I guess anything's mechanically possible to attach the two.

Any other comments on the wrap? Michael?

DR. COHEN: Just I absolutely agree with what Henri was saying about, you know, having a foil wrap but being able to tear it at the same time as you open the container.

And just to point out that I have absolutely no doubt that people will remove--unless we do that, people will remove them from the overwrap. We've seen that with, you know, nurses administering drugs that are packaged in cartons, for example, and sent as unit doses or some other type of outer wrap.

DR. GROSS: Okay. So the sense of the

group is that the unit package overwrap is a reasonable idea, but we still have to deal with the issue of it being discarded well before the drug is administered. Is that fair enough? Well, the new data curmudgeon's comments, Jackie, about having more data, we all agree with.

[Laughter.]

DR. GROSS: Okay. The next is the printed, elongated bottom tabs. I know the one I saw that I liked with the refresh label. The black writing, although small, was pretty clear, even for these eyes. Any other comments? Can you see it, Arthur?

[Laughter.]

DR. GROSS: Okay. Any other comments?

DR. STROM: Is there a concern about leaching in that setting?

DR. GROSS: Dr. Shah, could you answer that? If you put a printed label on the tab attached to the main vial, I guess it's theoretically possible that some of that print could eventually leach in, but it's less likely.

DR. SHAH: Again, if that is in an overwrap pouch and then it is a closed environment and if there are volatile solvents into the glue which has been used, then, yes, that is a possibility. That will be exactly the same thing. Instead of the close contact, it is a little bit away, but it still will have that possibility.

DR. GROSS: Okay. Any other comments on the elongated tabs? Do people like them?

DR. STROM: Let me suggest, maybe this is a summary, I think, of the sense that they look attractive, but if they raise the same concern about leaching, they're no advantage. So what's needed before a decision is made is a similar study to the kind that you did with the marketed products to find out if, in fact, there's leaching, given what we're hearing is it's just theoretical.

DR. GROSS: Right. More data.

DR. CRAWFORD: Dr. Gross?

DR. GROSS: Yes, Stephanie?

DR. CRAWFORD: Could I just add that I think and the sentiment of the committee right now

is that we're not making a recommendation for this because we don't have evidence that it won't cause more problems than it solves for this particular one.

DR. GROSS: So we need some data before a sense can be formed, and that, you know, probably applies to almost everything that we're going to comment on.

Okay. Paper labels, not glued to the tab but glued to the actual vial where the medication is. Any comments on that?

DR. HENDELES: Isn't there a problem with that?

DR. GROSS: Oh, well, this is what we're supposed to say, yes. Right. So Leslie's vote is--

[Laughter.]

DR. GROSS: Leslie's vote is, hello, there's a problem.

[Laughter.]

DR. GROSS: Okay, Michael?

DR. COHEN: Obviously there's a concern

about the safety at this point. I should point out, though, that whether we put labels on it or not, I think in some cases with unit-dose drug distribution, the pharmacy is going to put labels on them of their own. So that's going to probably seep in if we don't do something to change it otherwise.

DR. GROSS: Okay. So the--yes, Henri?

DR. MANASSE: Michael raises a really important point which hasn't been part of the dialogue today. As manufacturers decrease the production of unit-dose packaged drugs, it forces hospitals into being in the packaging business. And most hospitals are not experts in packaging, and, consequently, this issue of the leaching and the paper label attachment is probably a warning that has to go out to hospitals who do engage in the packaging business, because we've now introduced a packaging phenomenon that's not well understood.

DR. GROSS: Leslie?

DR. HENDELES: By extension, then,

pharmacists in the community who compound nebulizer solutions need to have that same warning. It shouldn't be just in the hospital because that's a whole other problem that's outside the control of the FDA. But, still, if there's a potential problem with commercial products, it's equally a problem with compounded nebulizer solutions.

DR. GROSS: Yes, Arthur?

MR. LEVIN: I want to follow up because I always thought we were hardly using unit-of-use packaging from manufacturers as a source compared to everywhere--it's one of these things, America versus everywhere else in the world where unit-of-use packaging is the standard. And you're saying it's getting--actually, there's less unit-of-use packaging being delivered by--which is really troubling. You know, if that's the trend, then looking at solutions that are dependent on manufacturers to do the right thing is crazy, because then we need to really be looking at where they get--at the repackaging problem. So, I mean, I think that's another piece of data that we need

to have, that if we're looking to have manufacturers use unit-of-use packaging as part of the solution or most of the solution to the problems we're discussing, and indeed they're doing less and less of that and there's repackaging at the community pharmacy level, the mail-order pharmacy level, or at the hospital or other dispensing level, then all of this is besides the point. So we need to know more about that.

DR. GROSS: Michael, another comment?

DR. COHEN: The term unit of use is different than unit dose. We were speaking about unit dose, meaning the individual dose for that patient. Unit of use would be package that contains perhaps a supply of medications just for that patient.

DR. GROSS: Okay. So the sense of the group with paper labels seems to be it's less than ideal and it's probably something that should be avoided. But, once again, there is no data to show the human toxicity from the observed leaching of compounds, and that would just make, you know, life

easier if it was at all possible to get that, which it may not be.

Ink without label is probably even worse than paper labels, but, Curt, did you want to say something?

DR. FURBERG: I just want to say that for the paper labels, is it possible to have a warning box like we have for drugs, warn against using paper labels directed at the pharmacists.

DR. GROSS: Gene?

DR. SULLIVAN: You're saying that if manufacturers proceeded--or continued to use embossed or debossed and the pharmacist chose--they thought it was best to take their own label and stick it on?

DR. FURBERG: Yes, that's correct. I mean, have you ever addressed that, warnings directed at the middleman, the pharmacist, rather than at the health care provider and the patient, warn them against doing things to the vial?

DR. SULLIVAN: Right. I think--

DR. FURBERG: Any label, doing whatever,

removing the overwrap, et cetera.

DR. SULLIVAN: You're right. It seems unwise for people who are not expert to be using materials that are not well characterized and applying them directly to a permeable container closure system, and certainly that is something that--a practice that shouldn't be undertaken. I think that we're today trying to talk about what to ask the manufacturers to do in regards to what they can do to improve the legibility so that perhaps pharmacists won't feel compelled to do what maybe they are doing.

DR. SHAH: Can I add to that? Especially on the labeling, there is clearly a warning that says open just prior to use, so they are not supposed to remove it from the container.

DR. FURBERG: You can add to that.

DR. SHAH: Yes, we can add it, but this is just the practice and that's what happens, I guess. And I guess at that point I don't think the agency has a control over that, and I think that's another way to educate the people and then get the message

around, I would think.

DR. SULLIVAN: It's been our informal assumption that if they were individually wrapped, it would greatly decrease the likelihood of respiratory therapists, you know, going in the morning and unwrapping 20 and then putting them in their pocket to care for patients through the day. I think that's probably less likely, and we could get some input from the speaker from the Respiratory Care Association. Intuitively, it seems less likely that would occur. I think you can't, just as you can't--you know, patients at home may take out five pills from their bottle and they're divorced from the labeling, that could happen. It's been our assumption that it would be much less likely if there was just one vial per pouch.

DR. FURBERG: But you could still use the overwrap to have a warning.

DR. GROSS: Karen?

MS. STEWART: [Inaudible, off microphone.] I think if it--the problem comes when they package

multiple [inaudible].

DR. GROSS: This is another favorable push for a unit package overwrap.

Is there anyone who would like to speak in favor of ink without label directly on the LDPE vial? Michael?

DR. COHEN: I don't want to speak in favor of it, but one of the examples that was shown was an injectable with the ink embossed--or printed right on the label. That was the Naropin injection. And I'm wondering, you know, if there's a concern with patients with respiratory disorders, is there a concern with systemic use of a drug like that? Do we know anything about that, as a matter of fact?

DR. SULLIVAN: So the question is: Is there a difference in our concern regarding the level of contaminants? I think from a pulmonologist's perspective there is, that particularly because of the nature of the patients we treat, who can be very sensitive--you know, I touched on it my talk. We haven't spoken too much

more about it, but patients that actually develop specific immunity. So they're allergic to things, and atopic patients, asthmatics, are more likely to develop specific immunity, and probably physiologically, humans are more likely to develop specific immunity when drugs are administered by the inhalation route than by other routes, like oral or even IV. So I understand your point about separating these drugs. The issue of there being multiple routes of administration is important because you mix up between the routes.

The specific concern about the chemical impurities to me is particularly important for inhalation drugs.

DR. COHEN: I guess it leads me to ask the question then: Will you allow--I mean, we have already several injectable products in this type of plastic. There will be saline and heparin and, you know, various products like that. And I'm wondering, I guess, if you would allow then the use of ink on these containers, because that would solve our problem if there's no concern at FDA for

the ink and the volatiles from the ink. With systemic use.

DR. GROSS: Yes, Brian?

DR. STROM: Speaking not as a pulmonologist but a general internist, I worry about IV injection of contaminants more than pulmonary. I mean, yes, it may be less sensitizing perhaps than the lungs, but, still, IV injection of contaminants I would think would be at least as worse.

DR. SULLIVAN: Well, I mean, of course, all the products are carefully controlled, and I don't have the expertise--maybe Dr. Shah does--about the particular controls that are put on oral products or IV products. But we very closely control inhalation products because of the issues of irritants and because of the issues of sensitization. And which is a greater risk I guess I won't firmly state, so--

DR. GROSS: The sense of the group seems to be, in the absence of human data of actual risk, our recommendation would be to avoid the ink

without label directly on the vial containing the medication. Is that fair? Anybody disagree with that?

DR. COHEN: I have a--

DR. GROSS: Michael disagrees.

DR. COHEN: These types of packages are used widely in other countries for parenteral medications, and I don't know that there's been anything ever reported, you know, as an adverse effect specifically tied to the inks. I don't know. But, you know, I express the same concern that Dr. Strom has. If there's any evidence at all that there's leaching of the ink through the plastic, through the semipermeable membrane, that would be a concern systemically. I just didn't know.

DR. GROSS: Leslie?

DR. HENDELES: There's actually precedent with sulfites and tartrazine, other substances in medications that cause reactions in selected patients. So I think if there's any way of avoiding putting something in that you don't know

to be safe, you should avoid it because there are examples of other contaminants causing the reaction than the drug.

DR. GROSS: The question is for the specific ones, do we know them to be unsafe? Yes, Brian?

DR. STROM: I guess my sense in a data-free world that we're operating in here is to share the concern that you expressed, Peter, of a consensus of let's not use it here because of the risk of contaminants. But I would take that further in two ways. One is I would extend that for intravenous use; and, second, I would call for data. It would be nice to know if any of these things mattered, not just in terms of measuring contaminants but even in animal studies, if we can't identify it.

I would think in the respiratory situation would be one of the hardest places to get data on the clinical importance of them. But perhaps in an intravenous setting, it might be more possible to get some data in terms of different products of the

same drug, for example, that have ink on the label versus don't have ink on the label and is there a difference in subsequent allergic reactions to them.

DR. GROSS: Okay. The next one is tactile recognition, use of textures on the LDPE vials. Anyone want to comment on that? And maybe could someone from the FDA elaborate on what you mean by textures. Do you mean smooth versus rough? Or do you mean feeling the letters? What's meant by that?

MS. HOLQUIST: A combination of any of those things, by using the type of letters that you can feel, by the different shapes, or should we make the vial feel from for different products? We just threw it out there as another suggestion.

DR. GROSS: Jackie?

DR. GARDNER: It seems that the point that was brought up about standardization with various manufacturers applies here as well and should be considered.

DR. GROSS: Good point.

Michael?

DR. COHEN: Again, I'll join the data camp. I don't think we know much about the tactile cues. I mean, from a human factor standpoint it certainly makes sense, but using them on actual drug products, I don't know of any history with other products where that's been successful.

Perhaps the shape of the container as a tactile cue, the octagonal shape, the hexagonal shape, et cetera, square. We used to do that with insulin vials, for example. That might have been effective. But if that's the case, I don't think you have enough different shapes that could be used, and it also puts burdens on the manufacturers and elevates the cost when you have these different shapes.

DR. GROSS: Again, a suggestion to the FDA from a research point of view. When we had that conference--I guess it's almost a year ago now--on look-alike, sound-alike drugs and someone spoke on human factor engineering, it might be interesting to get some input from that kind of person and have

them test some of these issues.

Brian?

DR. STROM: I would also echo my comment before, like with color. Anything that takes people--there aren't enough options in textures in order to replace the use of names. And anything that removes people's attention from the drug name I think might be more likely to cause problems than less, though, again, that's supposition without data to prove that.

DR. GROSS: That brings up an issue that the Joint Commission has dealt with on using two patient identifiers. Should there--you're suggesting you'll confuse people, and, you know, does that rule apply at all to drug use that there be two kinds of identifiers, or at least not another identifier that might confuse them?

DR. STROM: I guess my--I think the difference versus the Joint Commission situation, the Joint Commission is asking for two unique identifiers for the patient. What we're talking about here would be one unique identifier, which is

the name, and another unique identifier, the texture or the color--which isn't unique. There aren't enough unique options in order to make it unique. If it really was possible to have--you know, how many products are we talking about here, 30, 40? There aren't that many textures. And if it were really possible to have enough unique colors or unique textures, you might think about that, though I would still think then training people to remember which texture corresponds to which name would be hard as well.

So it's different than the Joint Commission situation where you're talking about a patient's name, which is unique to that patient, and both identifiers have that same name. The equivalent here would be having the drug name both embossed and also on the overwrap. And we are suggesting that that makes sense here.

DR. GROSS: So the sense of the group seems to be that tactile recognition is not recommended and may confuse. Does anybody disagree with that?

[No response.]

DR. GROSS: Okay. The next item is shrink wrap labels as an example that was circulated around, and not attached to the LDPE vial itself but to a tab or an appendage attached to the vial. Is that what the FDA means by that? Anybody have any comments? Michael?

DR. COHEN: This would be my number one preference, as I mentioned before, because it gives you so much flexibility. You can easily see the black type on a white background. You can put bar codes on it, et cetera. But, you know, I have a concern if FDA has a concern about the volatility of those inks, except, you know, I'd love to see the studies that you were talking about because it just seems to me that this is not an ink that is in direct contact with the LDPE plastic. It's on the overwrap itself. I understand that it still might be volatile within that micro environment, et cetera, but it might be at a level that's not even close to, you know, causing a problem. I just don't know. But I'd love to see the studies.

MR. LEVIN: Just a point of information. I would guess that there are inks and there are inks. Are there vegetable dye inks? Are there different kinds of inks that may increase or lessen the potential toxicity?

DR. SHAH: Yes, as I mentioned in my presentation, there are water-based inks and there are organic solvent-based inks. So if you have carefully selected ink formulations in which you do not have volatile components, then there is pretty much not any likelihood of any volatile to be present in the ink formulation that may migrate to the vial. So that is a possibility. People can think about that.

MR. LEVIN: Is that something that the agency could stipulate, that inks used--I mean, for example, if this was the model and then further stipulate that inks used would have to not--you know, would not contain volatile substances to minimize risk? It's a question.

DR. SHAH: I don't know. I will have to ask our, you know, upper office and then find out

about that. I'm not sure about that.

DR. GROSS: Any other comments? Yes, Brian?

DR. STROM: I just want to echo the comment that in many ways this is attractive. It just would be nice to see before that the kind of studies of contaminants that we saw before deciding. So I guess my recommendation would be a conditional, this is preferable after those studies are done. Without those studies being done, we don't know that this is any better than the current approach in terms of leakage.

DR. GROSS: And that's part of one of the requests, that whatever we recommend doesn't create additional problems. So we do need that data.

Okay. So what Brian said I think sums up what the group thinks. Fair enough? Okay.

The last is glass ampules, and perhaps someone could comment from the FDA or Michael or anyone, why did we move away from glass ampules in the first place to plastic? Was it accident prone or what?

DR. COHEN: I'm sorry. I raised my hand too--I don't know why we moved away from it, but I'd hate to be a respiratory therapist if I had to crack open all those glass ampules.

DR. GROSS: Right. So it's an accident issue.

MS. HOLQUIST: Also, I think it lends to errors, as you saw by Marci's slide with the acetylcysteine where it comes in an IV route and a respiratory route, and so it was confused because it looked like an IV product.

DR. GROSS: Okay. Any other comments on glass? Brian?

DR. STROM: In follow-up to that comment, should we think about a recommendation that the plastic--especially if the plastic is being widely used now in respiratory and it's not being widely used elsewhere but beginning to, that, in fact, that distinction--we're talking about tactile and whatever--be kept clean, i.e., that the plastic be used for respiratory and for parenteral use it be glass?

MS. HOLQUIST: I think it's a good recommendation, but, again, it's something we have to bring back to the agency and provide to all the other review divisions that are involved. It's not just the pulmonary division.

DR. GROSS: Okay. I guess you're all getting hungry. I'm not sure if lunch is here, but we'll probably break pretty soon.

Annette, did you have a comment, or anybody?

[No response.]

DR. GROSS: Okay. So the sense then is the last comment that Brian made, if glass is used at all, there probably should be a distinction that plastic be used as pulmonary inhalation medication and glass be used for other uses, such as intravenous use. Is that fair?

[No response.]

DR. GROSS: Okay. Why don't we take a break and we'll address 1b, 2, and 3 afterwards. We have an hour for lunch.

[Luncheon recess.]

AFTERNOON SESSION

[12:50 p.m.]

DR. GROSS: Okay. We will begin where we left off, and that is Item 1b. The question was: Please identify creative solutions or alternative packaging designs that improve legibility and address the problem of ingress of chemical contaminants, and at the same time, do not create new problems.

Would anyone like to comment? Leslie?

DR. HENDELES: How about tying a ribbon around the end of the plastic vial, and on that ribbon you can imprint "Albuterol, 0.083 percent."

DR. GROSS: I don't know whether to say thank you or less levity.

[Laughter.]

DR. HENDELES: Yellow ribbon.

DR. GROSS: Okay. So you're tying a yellow ribbon around the medication.

DR. HENDELES: Yellow for Ipatropium, red for Albuterol.

DR. GROSS: All right. That's a creative-

DR. HENDELES: Red and yellow for the Duovent.

DR. GROSS: Okay. Are there any other creative suggestions? Jackie?

DR. GARDNER: You know, there are thousands, and I have information that the manufacturers are actually working on some of them. And so I think rather than trying to come up with good ideas, however good that was, Les, maybe what we should do is encourage the people who have the most to gain from this to bring forward creative solutions that put all these objectives into play and give us some things to choose from--maybe not today but when they're ready--because they will have tested them as well.

DR. GROSS: Like we saw this morning, okay.

Henri?

DR. MANASSE: I think as we consider new options and new directions in this area, I would hope that the industry and the FDA would very carefully consider symbologies that are

electronically readable for patient verification. I think the system is moving in that direction. There are available technologies for that verification, and particularly patient-level verification. Adding these technologies is going to be important. I know what the issues are in terms of the bar code and the size of the bar code, but there are other symbologies that can be applied, like dot matrix technologies, et cetera, that wouldn't take the kind of space. But as we get creative in this packaging, I think we should be real sensitive and help motivate and move the verification mechanisms along.

DR. GROSS: Any other comments? Yes, Art?

MR. LEVIN: Just to reiterate the importance of also looking at the community pharmacy, ambulatory population, including the elderly, that use these products where the solutions may have to be different, frankly, than they are in the inpatient clinical setting. And remember that that's probably an increasing population of use, and that we need probably to

look at the research that's going on now in health literacy and cultural competency, et cetera, et cetera--in other words, a very broad view of what we need to know and sort of think out of the box on how to make this happen.

DR. GROSS: I think that's a very good point. Just like they say children are not little adults, the elderly are not young adults, and we have different considerations for all those groups.

I'm amazed--oh, thank you, Brian, for coming up with something.

[Laughter.]

DR. STROM: I just wanted to return to Leslie's comments about the relative benefit and safety of these products as a class versus the MDIs and whether there should, in fact, be at least labeling comments or instructions that might provide some of the alternative data or in some way begin to push the field toward using the safer alternatives instead.

DR. GROSS: Okay. There being no more comments for Item 1b, we'll move to number 2.

Please consider which stakeholder groups--we've discussed some of this already, but we should emphasize it now--be they manufacturers, practitioners, consumers, or others, can best advise the FDA about possible new packaging configurations that may resolve the issues we've discussed.

Jackie already suggested we should encourage the manufacturers themselves to do this. And consumers.

Yes, Henri?

DR. MANASSE: Peter, I again want to reiterate I think we ought to bring in the cosmetic industry packaging people. They have done some incredibly innovative things in packaging.

I think another sector that has a lot of experience in packaging has been the Department of Defense as we look at pouching food, for example, and sustaining it and everything else. So I think our colleagues in the military may be helpful here as well.

DR. GROSS: I heard someone say space,

involve NASA.

DR. MANASSE: NASA.

DR. GROSS: Okay. Leslie?

DR. HENDELES: In regards to the consumers, there are two lay organizations of people interested in asthma. One is Mothers of Asthmatics, and the other one slips my mind. But there are two organizations, and getting their input might be worthwhile. I can e-mail you the name of that second organization.

DR. GROSS: Fine. Michael?

DR. COHEN: I just want to say whatever anyone comes up with, I really think it will be a great idea to involve organized respiratory therapy, organized pharmacy, and probably--I don't know if FDA can do this, similar to what they do with the drug names, as we heard at the last DSaRM Committee meeting, the idea of failure mode and effects analysis for any of these packaging changes that are made to make sure that--or minimize the chance that there might be a medication-error-related problem with them.

DR. GROSS: Yes, a rigorous FMEA approach could be very helpful.

Yes, Curt?

DR. FURBERG: I just wonder whether this is a unique problem in the U.S. If it's not, let's check and see what other countries are doing, other regulatory agencies, other countries.

DR. GROSS: Okay. Good point.

Brian?

DR. STROM: One of the things we talked a lot about this morning is the need for additional data here. Some of it clearly needs to be generated by the manufacturer, but I wonder if there might be funding agencies--ARC, for example--more applied perhaps to CERTs. Perhaps there's people in the CERTs who might be interested in studying some of these issues.

DR. GROSS: Good idea.

Michael?

DR. COHEN: Just think a little bit more about that. It isn't even just these products. It's other medication-error-related problems with

labeling, packaging, you know, where is color appropriate, all that kind of stuff. It would just be so helpful beyond this if we could get the right research done. It just doesn't seem like things have been moving in that direction for whatever reason.

DR. GROSS: Curt?

DR. FURBERG: One way of getting research is to set up a meeting and invite people to come and present, and maybe it's time now to have a two-day workshop on these packaging issues and invite industry representatives, scientists, and others. It's one way of advancing knowledge.

DR. GROSS: Like was done for look-alike, sound-alike names a year ago.

Brian?

DR. STROM: Following up on Mike's idea of broadening the question, if the question were broad enough, you might be able to get the right group at NIH to be interested, focusing not so much on the specifics of the drug and the drug label because they're not going to care about that in the drug

labeling, but issues of patient perception and--well, safety is really an ARC issue. NIH isn't interested in patient safety. But it's--but NIH would be more interested in sort of understanding patient perceptions and, you know, what is it that--you know, issues of color and tactile and sort of, you know, more broader, definitive, and maybe the National Institute of Mental Health, maybe issues--maybe the NHLBI given the importance of this for respiratory, but NHLBI probably would care less about that kind of thing. But NIMH or the National Institute of Nursing Research might be another that might be interested. Another might be NIA, actually, the National Institute of Aging, which has a pharmacology program and the issues here in terms of the elderly being able to read labels correctly and perceive drugs correctly would be a big one. So in terms of looking at sort of who could potentially fund this, fund the necessary collection of data in a way that FDA can't, the NIA might be a logical one.

DR. GROSS: Any other comments?

[No response.]

DR. GROSS: Well, that was very creative. Thank you. That was very helpful.

The last question, number 3, is: Given what you have heard today, please describe an appropriate course of action to address the problems of ingress and medication errors due to legibility and similar packaging issues.

Henri?

DR. MANASSE: Peter, I'd like to focus on the ingress issue. I guess I'm impressed by how little we know about ingress in these kinds of plastics, the kind of chemicals that are creating the problem, the impacts that the ingress has on active ingredients. And it seems to me that FDA ought to be stimulating knowing more about this and then from that making a determination as to whether or not the appropriate statutory and regulatory things are in place to be able to pursue requests about these issues, particularly the toxicities, through the application processes and the master file, et cetera.

DR. GROSS: Leslie?

DR. HENDELES: I recommend that the agency just revise that draft guidance to take into account some of the issues that we discussed under 1a. I mean, I think that would be the appropriate direction.

DR. GROSS: Okay. Art?

MR. LEVIN: As we encourage manufacturers to be innovative in finding solutions, I'm worried about the issue of standardization because I think when everybody's looking at error prevention, standardization is certainly one of the big fix items. So I'm just raising the question of how do we balance the tension between innovative solutions and creating industry standards so that we don't have ten different ways that people are doing things, causing even more confusion than we have now. And I think it speaks to Henri's point about how the agency perceives its authority to require standards. Once finding the gold standard, then what does the agency do with that, and does it need additional authority, for example, to require that

that be the gold standard for all of these products which have basically been out there on the market? They're not going to be new drug applications. But could they go back and say, In the future over a period of time we expect you to convert to this gold standard of packaging?

DR. GROSS: Any other comments?

[No response.]

DR. GROSS: Okay. Well, I want to thank the presenters as well as the Advisory Committee members for this thoughtful exchange of information. And at this particular point, we are going to adjourn for a bit because the Lotronex part of the agenda was scheduled to begin about 3 o'clock. I think we'll be able to begin at 2:30. Is that it? 2:20. Okay.

If there's any change in that, we'll get the word around because everybody's staying pretty close. Okay. Thank you.

[Recess.]

x DR. GROSS: Good afternoon. I think we'll call the meeting to order. I'd like to begin by

reintroducing the people who are sitting around the table because we have a new group as part of the open public hearing. So if we can begin--oh, there he is. Next to Brian is?

DR. KRIST: My name is Alex Krist. I'm with Virginia Commonwealth University. I'm a member of the Gastrointestinal Drugs Advisory Committee, and I'm a family physician.

DR. GROSS: Brian?

DR. STROM: Brian Strom, University of Pennsylvania.

DR. MANASSE: I'm Henri Manasse. I'm the executive vice president and chief executive officer of the American Society of Health-System Pharmacists.

MS. SHAPIRO: Robyn Shapiro, Director, Center for the Study of Bioethics, Medical College of Wisconsin.

DR. STEMHAGEN: I'm Annette Stemhagen from Covance, a contract research organization, and I'm the industry representative to this committee.

DR. GARDNER: Jacqueline Gardner,

University of Washington, Department of Pharmacy.

MR. LEVIN: Art Levin, Center for Medical Consumers, and I am the consumer member of this committee.

DR. FURBERG: Curt Furberg, professor of public health sciences at Wake Forest University.

DR. GROSS: Peter Gross. I'm Chair of Medicine at Hackensack University Medical Center and New Jersey Medical School, and I'm Chair of this Advisory Committee.

MS. JAIN: Shalini Jain, Executive Secretary, Drug Safety and Risk Management Advisory Committee.

DR. CRAWFORD: Stephanie Crawford, University of Illinois at Chicago, College of Pharmacy.

DR. SELIGMAN: Paul Seligman, Director, Office of Pharmacoepidemiology and Statistical Science, Center for Drugs at the FDA.

DR. BEITZ: Julie Beitz, the Deputy Director in the Office of Drug Evaluation III in CDER.

DR. JUSTICE: Robert Justice, Director of Division of Gastrointestinal and Coagulation Drug Products at FDA.

DR. TRENTACOSTI: Ann Marie Trentacosti, Medical Officer, Division of Gastrointestinal and Coagulation Drug Products at the FDA.

DR. AVIGAN: Mark Avigan, Director of the Division of Drug Risk Evaluation in the Office of Drug Safety.

DR. GROSS: Okay. Shalini Jain will read the conflict of interest statement.

x MS. JAIN: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of conflict at this meeting with the following exceptions:

In accordance with 18 U.S.C. 208(b)(3), Dr. Brian Strom has been granted a waiver for consulting with two competitors on unrelated matters. He receives less than $10,001 per year from one firm and between $10,001 and $50,000 per year from the other.

Dr. Maria Sjogren has been granted a waiver under 208(b)(1) for consulting with the sponsor on unrelated matters. She receives less than $10,001 per year.

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

We would also like to note that Dr. Annette Stemhagen has been invited to participate as an industry representative, acting on behalf of regulated industry. Dr. Stemhagen is employed by Covance Periapproval Services, Incorporated.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial

interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

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

Thank you.

DR. GROSS: Dr. Paul Seligman will give an introduction to the Lotronex issue.

x DR. SELIGMAN: Good afternoon. It is my pleasure to introduce the second topic for today's meeting. This afternoon we'll be hearing an update on the Lotronex Risk Management Program. On April 23, 2002, the Gastrointestinal Drugs Advisory Committee and this committee met and recommended reintroduction of Lotronex tablets to the market with certain restrictions, such as having patient and physician registries and physician certification training for prescribing.

On June 7, 2002, FDA approved the

restricted marketing of Lotronex with a risk management program that was mutually agreed upon by the Lotronex manufacturer, GlaxoSmithKline, and the FDA. The details of this plan will be described in the subsequent presentations.

Today, GSK will be presenting an update report on how the drug is being prescribed within the parameters of the risk management program and what the impact of this program has been. The purpose of this discussion is primarily informational in nature to provide the committee an update. As a consequence, we have allocated a limited amount of time for presentations and discussion.

The risk management program that was implemented contained many but not all of the elements recommended by the Joint Advisory Committees in April of 2002. As we gain experience with risk management programs, we think that it is important that there be a public airing of how well these programs function and whether they meet the goals that were set out for them.

With that, I thank you for your attention and I thank the committee for being here today. We will have both the speakers at the open public hearing as well as the speakers who are on the agenda to have them use this podium in front of the committee.

So, with that, Mr. Chairman, I turn the proceedings over to you.

DR. GROSS: Thank you, Dr. Seligman.

x We will proceed with the open public hearing now. First I need to read this statement.

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

The first speaker is Dr. Sidney Wolfe.

DR. WOLFE: Right on time. In August 2000, almost four years ago, we petitioned the FDA to ban alosetron because, in our view, its serious, life-threatening adverse effects outweighed the marginally better-than-placebo effectiveness. At the time of our petition, FDA was aware of 26 cases of ischemic colitis in people using the drug. In the major randomized, placebo-controlled trials prior to approval, there had been three cases of ischemic colitis in 832 patients, or 1 per

277--again, with good ascertainment, in contrast to what we are having here--but none in 700 placebo patients. According to an FDA memo, in one large trial with adequate ascertainment--this is a different trial--adequate ascertainment of ischemic colitis, 10 out of 1,819 women being treated with alosetron for diarrhea-predominant irritable bowel syndrome developed ischemic colitis over the 24-week duration of the trial. There were no cases in the 899 patients in the trial treated with traditional therapy. By the time marketing was stopped in November 2000, there were 85 cases of ischemic colitis reported to the FDA among the estimated 275,000 patients who has used the drug.

Even though this is called the Drug Safety Committee, you know as well or better than I that this all has to be viewed in the context of drug benefit and, therefore, review of the evidence for benefit for at least one of the major trials for this drug is appropriate.

In an analysis we published in the Lancet of data from one of the clinical trials, which had

been misleadingly portrayed in a previous article in the Lancet by percent change as opposed to absolute scores, the figure of our look at the actual data can be seen on the second page of the testimony. And what you can see is there is barely a perceptible--it's statistically significant, but no one can possibly believe that this is clinically meaningful, the difference at 1, 2, 3, months between those given 2 milligrams of alosetron, twice the dose being used now, for starters, and those being given the placebo.

This excellent, hard-to-exceed placebo response rate--and that's certainly the challenge of treating this illness, is that the placebo response rate is extraordinarily high. This is consistent with findings from a published review of 27 randomized, placebo-controlled studies testing various treatments for irritable bowel syndrome in which the median placebo response rate was 47 percent, percentage improved, with rates as high as 84 percent, and 11 studies had placebo response rates of 60 percent or higher. Unlike alosetron,

placebos do not cause ischemic colitis.

Because IBS is a poorly defined disease, which, although capable of causing significant distress in some individuals, is neither progressive nor life-threatening, the occurrence of serious adverse reactions such as ischemic colitis and bowel obstruction without ischemic colitis, sometimes requiring surgery, tips the benefit-risk equation against the use of this drug.

The experience during the first one-plus years of this risk management program has hardly, as Glaxo claims in its statement, "been successful." Among the problems, somewhat predictable because of the lack of the kinds of controls that could realistically be taken only under an IND, were the following:

Twenty percent of the patients getting the drug not have all of the three criteria specified for getting the drug, which include frequent/severe abdominal pain, and frequent bowel urgency or fecal continence; and disability/restriction of daily activities. They may have one or two, but these

were the criteria, and 20 percent did meet these criteria.

Secondly, only 42 percent of patients with a Lotronex prescription has pre-enrolled in the survey program and only 36 percent completed the baseline questionnaire.

From the prescribing doctor's perspective, again, because this is not required, it happens, 20 percent of prescribing doctors were not enrolled in the prescribing program for Lotronex. That may or may not have something to do with the fact that so many of these average reactions were not reported by physicians.

These are all elements that certainly were thought of if it not specifically suggested by FDA staff and ourselves at the meeting a couple of years ago, and you can't do these things unless the drug is there under an IND. Marketing isn't compatible with those kinds of restrictions.

The most alarming finding during this period was the reporting of eight cases of ischemic colitis and, according to the manufacturer, eight

additional cases of "complications of constipation." I say according to the manufacturer because they list eight, and the FDA talks about five. The latter included a case of partial intestinal obstruction, one in which there was exploratory surgery for small intestinal obstruction, and a patient with diarrhea and intestinal obstruction.

Assuming the accuracy of the estimate of 9,365 patients getting alosetron during the risk management program, the rate of ischemic colitis--again, this is a low estimate--spontaneous reports was 8 per 10,000 or 8 per 9,365, or about 0.8 per thousand, and it's actually higher than the, again, spontaneous rate of reports during the earlier mktg phase, which was 85 per 27,000.

There are, of course, differences in the conditions for reporting that might explain some of this discrepancy, but I don't believe begin to explain all of it. Enrolled physicians agreed to report all serious adverse events as a condition of participation, but obviously 20 percent didn't

participate, and even those who did, so it appears, four of the eight cases of ischemic colitis were reported by patients, not physicians. Similarly, none of the eight cases of serious complications of constipation were reported by the prescribing physician. One was reported by a nurse. Either the patients did not tell the physicians who prescribed the drug that they had gotten ischemic colitis or physicians violated their agreement to report such cases.

The fact that 11 of 16 cases of ischemic colitis or complications of constipation were reported by patients as part of the Lotronex patient follow-up survey program may compensate for some, but we don't believe all or even most of the serious reporting deficiencies by participating physicians. There is little question that just as the 85 cases of ischemic colitis reported during 2000 were but a fraction of the actual cases, so, too, are these recent RMP, risk management program, ischemic colitis cases.

For effective, life-saving drugs, such as

some cancer therapies or the anti-psychotic drug clozapine, risk management is a critical part of their use, and we strongly support, as the FDA knows, risk management in those kinds of circumstances. But alosetron joins an increasing number of other drugs, none with unique, clinically significant benefits, that have been the subject of ultimately failed FDA-approved risk management programs--the diabetes drug Rezulin, the painkiller Duract, the GI drug cisapride, the blood pressure drug Posicor--and were taken off the market.

When I testified before this committee in 2002, I stated, "The reintroduction of Lotronex into the market, even with the restrictions proposed by Glaxo, would be a serious public health mistake, likely, if not certain, to result in the need to ban the drug again." It is time to end this failed effort to resuscitate markets and to take alosetron off the market. As we suggested in 2002, there is no reason why, under a carefully controlled IND, the drug could not be made available to, I would estimate, the several

thousand, at most, people who might still choose to use it. This has previously been done for the diabetes drug phenformin and the GI drug cisapride after they were taken off the market.

I'd just like to emphasize that of the reported 9,000-10,000 people using the drug, in the FDA's Executive Summary it says only 10 to 20 percent of these people were refilling it. So we may, in fact, be talking about a group of people that is one, two, three thousand people, not the 100,000 that the company claimed would be using the drug and which they used to help fend off an IND approach back a couple years ago.

Given the marginal evidence of effectiveness and the continuing serious risks of the drug, Glaxo's suggestion to relax the restrictions on availability of alosetron to increase its use is nothing but ghoulish. A quote from the end of their statement: "The primary concern at present relates to the low rate of product prescribing given our understanding of the target population...This may reflect unintended

barriers to prescription..." and they elucidate some of the unintended barriers, which is the time the physician has to spend explaining to the patient the benefits and risks of the drug and so forth. I find that this attitude, certainly it's consistent with trying to sell more drug, but it's inconsistent with the public health. And just in closing, I would just repeat it's time for this to be taken off the market. It gives risk management a bad name to keep doing things like this.

I'd be glad to try and answer any questions. That's just about ten minutes.

DR. GROSS: If there are no questions, thank you very much, Dr. Wolfe.

The next speaker, Dr. Lawrence Wilderlite.

DR. WILDERLITE: Good afternoon. My name is Lawrence Wilderlite. I am a practicing gastro-enterologist in Chevy Chase, Maryland. We're part of a private practice group of 13 gastroenterologists with three offices in the metropolitan area, downtown Washington, in Chevy Chase, and on Executive Boulevard here in

Rockville.

In the past, I was a speaker for GlaxoSmithKline upon the introduction of Lotronex in 2000 and presently am a consultant for GlaxoSmithKline.

I have been asked to talk today about the prescribing habits of this drug and the inability of patients to actually have access to the drug because of the restrictions that have been placed on this.

I have had extensive experience with the use of alosetron when it was first introduced, and our group has used it, given the patient clientele we have, many times. And we have had a favorable response with the drug and felt the drug to be quite helpful in our patient population.

Inasmuch as there has been no new medication or no recent introduction of any drug of this type over the last 20 years for the treatment of irritable bowel syndrome, we felt that this was going to be a very important agent and something that we would be able to use to help patients that

suffer from irritable bowel, in which we have no effective treatment today. Initially upon the introduction of this drug, it was embraced by the GI community and was embraced by gastroenterologists that I can talk to in the Washington area.

When Lotronex was recalled in 2000, it left a void, and that void is still vacant today. I feel our patients have no alternative to treat an illness that at times can be very devastating. Although not life-threatening, it is basically destructive to patients' lives and destructive to their ability to function in an environment in which they live.

The present registration system for this drug is extremely tedious. It takes a lot of time to register a patient for this. The patient needs to fill out papers. The GI doctor has to fill out the papers. The patient has to be advised about the side effects of the drug. The doctor has to register to be an appropriate agent to distribute the drug.

At the end of all this, we in our office do refer patients to a website where they can get more information about Lotronex, where they can understand what the complications and the possible side effects of the drug are before they enter into the program or begin taking the medication. We find--and I am not a member of that prescribing group. There are only two people in our group of 13 that elected to be registered for distribution of the drug, and of those two people, it came because they were quite friendly with one of the Glaxo representatives who asked them if they would register for this.

We find that patients become stigmatized after they read the side effects of the drug. As appropriate to Dr. Wolfe's comment, that many patients will not fill the prescription when they're given it. Many patients will not take the medication appropriately. Many patients will stop taking the medication. Patients will forget to take it or take it on an alternate-day basis rather than appropriately because they're afraid of having

some side effect and feel less is better than more. And eventually some of them will not come back or will not fill the prescription or, like many irritable bowel patients, these patients fail to come back again or don't show up in an office and go home and continue to suffer the symptoms they have.

Physicians, because they won't register for this program, go back to treat these patients with conventional methods, of which we have no conventional methods. Increasing fiber, anti-diarrheal type of agents that have been on the market and have been shown to be of little help to patients who suffer from this disease.

The physicians fear--and when talking to other doctors--that because of all the publicity given to the side effects of the drug, should a patient encounter a side effect or an adverse reaction to this medication, the physician is now liable for some litigation or malpractice suit, and, therefore, they're not pushing to use the drugs. They're not rushing in to join this type of

prescribing program.

The amount of time that this prescribing program takes is enormous. It takes a lot of time. There are many physician phone calls. There's a lot of interaction with the patient. Unfortunately, in today's environment where there is little compensation for the amount of time paid because of the insurance environment that we have, this type of interaction is difficult, and physicians shy away from spending the amount of time that is necessary to educate the patients for this.

The process is extremely cumbersome, and I find that in a group of physicians that we're friendly with in the Washington area, very few will enter into this registration process. What I do is refer patients to other people in our group. It changes the physician-doctor relationship, or I refer them to other doctors that I can find who are outside of our group to take care of these patients, or we continue to use the remedies that we have in place.

I feel that whether it be alosetron or not, the GI community desperately needs a medication to treat diarrhea-dependent irritable bowel syndrome; that the mechanism that is in place today needs to be streamlined to allow access to a medication that I feel can help irritable bowel sufferers.

The use of this drug is extremely limited and extremely confined to approximately--given Dr. Drossman's (ph) classification, less than 5 percent of people are available to receive this drug. I feel personally that this is too confining and that the drug or the use of this drug should be opened up. As different from the previous speaker, I think the drug is helpful and the drug needs to be freed up a little bit more in a more streamlined process to allow access to patients.

I thank you and I am open to any comments that you have.

T4A DR. GROSS: There being none, thank you very much, Dr Wilderlite.

We will proceed now with the sponsor

presentation. Dr. Craig Metz, the Vice President for U.S. Regulatory Affairs at GlaxoSmithKline, will present their risk management program for Lotronex.

MS. JAIN: Dr. Metz, before you do your presentation, we just wanted to introduce another committee member that joined us in the interim. Dr. Maria Sjogren joined our group. She is a representative for the GI community and also is a member of the GI Advisory Committee. Thanks for participating.

x DR. METZ: Good afternoon. My name is Craig Metz, and I am going to be providing the sponsor's update on our experience with the implementation of the risk management program for Lotronex today.

Joining us today are a number of external consultants who are involved with various aspects of the risk management plan for Lotronex and would be happy to answer any questions that you might have regarding their specific areas of responsibility for the RMP or any general questions that

you might have for them. I'm going to take just a quick moment to introduce our consultants.

We have Dr. Robert Sandler with us from the University of North Carolina. Dr. Sandler is involved with our Risk Management Plan Advisory Board.

We have Dr. Lin Chang from the University of California at Los Angeles, who has been involved with our educational program as well as a general consultant to us for some time on Lotronex.

We have Dr. Andrews from Research Triangle Institute. She's involved with our epidemiology program, specifically the patient follow-up survey for Lotronex, and she serves as the data coordinating center for the follow-up claims-based research.

We have Dr. Jerry Gurwitz with us from Meyers Primary Care Institute, University of Massachusetts. Dr. Gurwitz is also involved with the epidemiology program.

And, finally, we have Dr. James Lewis here from Georgetown University who chairs our Safety

and Review Committee.

Three underlying themes will form the basis of my presentation today. Those themes are the successful implementation of the risk management plan for Lotronex from the standpoint of the appropriateness of the prescribers, the patients, and the behaviors that have been produced through this program; the impact of the RMP itself on the safety profile and on the prescriber and patient, as well as on individual components of the risk management program itself; and the cycle of continual RMP evaluation and revision that is a normal part of the stewardship involved with conducting a risk management program.

During the course of my presentation, I'm going to share information with the committee that we didn't have when we last met to consider a risk management program for Lotronex, and that specifically is data on the impact of the interventions that we've attempted to put into place here. It's our hope that this data will guide our discussions with the agency and the

proposed modifications that we might make to this RMP as we move forward. But as importantly, the RMP for Lotronex has been a very rich learning laboratory for us with regard to general issues regarding conducting a risk management program and the impact of these different interventions in real-term use. So we hope that this information will tend to serve to inform discussions regarding the applications of these interventions elsewhere.

In my presentation, I'm going to provide a very brief background summary. I'm going to identify the goals of the RMP and describe the key elements of the RMP with results to date where appropriate. I will finish with some conclusions regarding the implementation of the RMP and a discussion of what we've identified as emerging issues.

Many of you will be familiar with the chronology of key regulatory events. Dr. Seligman has already covered some of these. Again, the product was voluntarily withdrawn in November of 2000. The agency and GlaxoSmithKline were

inundated with calls from patients demanding that the drug be made available to them again.

Subsequently, we submitted an sNDA in December of 2001 and met with some members of this committee and the GI Drugs Committee in April of 2002 to discuss the information included in that sNDA as well as the general framework that was being proposed for the RMP for Lotronex. In June 2002, that supplemental NDA was approved and the product was actually reintroduced in November of 2002 with a revised indication statement and a risk management program in place.

What we were striving to achieve when we developed the risk management program for Lotronex was a framework that would mitigate the risks associated with complications of constipation and ischemic colitis, but would do so in a way that would not create extraordinary barriers to patient access. And I think as we consider the information being presented today, success should be measured against this intent.

We intended to achieve this through a

focus on the following four goals: making Lotronex available to those patients for whom the benefit-risk is most favorable; prescribing Lotronex to appropriate patients by qualified physicians; educating physicians, pharmacists, and patients about the risks and benefits of Lotronex and how to manage those risks; and providing a framework for ongoing RMP evaluation.

A key element of making Lotronex available to a patient population for whom the benefit would clearly outweigh the risk was revising the indications statement to establish women with severe diarrhea-predominant IBS as the target population for treatment. On that basis, Lotronex is currently available for women with severe diarrhea-predominant IBS who have chronicity of symptomatology, generally lasting six months or longer; have had anatomic of biochemical abnormalities of the GI tract excluded; and have failed to respond to conventional therapy.

Additionally, diarrhea-predominant IBS is defined as severe if it includes diarrhea and just

one or more of the following: frequent and severe abdominal pain or discomfort, frequent bowel urgency or fecal incontinence, disability or restriction of daily activities due to IBS. And, again, I would stress that only one of these criteria are required for the patient to qualify for treatment--not two, and certainly not all three. Only one. Later in my talk, I'm going to come back to this description of a 5-percent estimate for the severe diarrhea-predominant IBS population.

And, finally, the indications statement states that in men, the safety and effectiveness of Lotronex has not been established.

So the four key components of the RMP that we've developed for Lotronex are: enrollment of qualified physicians in a physician prescribing program; a program to educate physicians, pharmacists, and patients about IBS and about the benefits and risks of Lotronex; a reporting and collection system for serious adverse events associated with the use of Lotronex; and, finally,

a plan to evaluate the effectiveness of the RMP for Lotronex. In the rest of my presentation, I'm going to go through each of these components in order.

To begin with, we have the prescribing program for Lotronex, and this was developed to address the goal of prescribing Lotronex to appropriate patients by qualified physicians. This is a picture of the key steps card that helps the prescribers navigate their way through the prescribing program for Lotronex. It's going to be difficult for me to use the pointer here in a very effective way, but you have the slide in front of you, and I'm going to walk you briefly through some of the steps.

So the physician, in the upper-left-hand portion of this chart, decides to enroll in the prescribing program for Lotronex. They receive a prescribing kit that I'm going to describe to you in a minute. The physician identifies an appropriate patient for treatment, goes through a counseling activity with that patient, gets the

patient to sign the patient-physician agreement with the physician. That agreement is then placed into the patient's chart, and a copy of that is given to the patient. The physician at that point affixes a Lotronex sticker to an original prescription, and at that point the physician also encourages the patient to enroll in the patient follow-up survey for Lotronex.

At that point the patient has a prescription with a blue sticker on it that they take to the pharmacist so that the pharmacist can fill that prescription. And, again, even the pharmacist has the opportunity to encourage the patient to enroll in that patient follow-up survey.

As you can see, this is a fairly complex, multi-step process. The act of physician enrollment actually involves the physician signing an attestation form that attests to his ability to diagnose and treat IBS, to diagnose and manage ischemic colitis, to diagnose and manage constipation and complications of constipation, as well as acceptance of responsibilities that include

education, completing the patient-physician agreement that I've just described, reporting serious adverse events, and affixing stickers to prescriptions. In a while I'll share feedback that we've received from physicians relative to the impact of this process on their practice.

The prescribing kit for Lotronex that the enrolled prescriber gets contains the key steps card that we've just discussed, prescribing information, medication guides, patient-physician agreement forms, the prescribing program stickers, and the patient follow-up survey pre-enrollment cards.

These are some of the steps that I've already described on the key steps card, but, again, there are a couple of things I'd like you to note. First of all, this is what's in the retail pack that the patient receives. It's a box that contains 30 tablets, a package insert, a medication guide, and the patient survey card. I have to remind you that no refills are allowed currently for Lotronex. All prescriptions have to be

original, and all prescriptions have to have an affixed sticker. There is no faxing, no electronic transmission of prescriptions for Lotronex. Those are not allowed.

In the event that a physician uses up the supplies in their initial kit, they can call the coordinating center for the PPL, and that coordinating center will check their name against the list of enrolled prescribers, and if they're on that list, they'll be sent a refill kit.

In the next portion of my presentation, I'm going to address the educational program that was developed to support the introduction of Lotronex.

The educational program for physicians is anchored by these two modules: Lotronex Tablets: Understanding the Risks and Benefits, and Current Thinking about IBS: An Educational Review on Irritable Bowel Syndrome.

In addition to that, 345,000 "Dear Doctor" letters were mailed at the time of product reintroduction, and we've put a reminder program in

place that I'll discuss with you in a moment that provides additional access to key educational messages for physicians.

For the patient, education consists of the medication guide, which, again, they can get from two sources. They can get that from the physician, and it's also included in product packaging.

Physician counseling and the requirement to sign the patient-physician agreement further reinforces the key product messages contained in the medication guide.

On the pharmacist level, at the time of product reintroduction 113,000 "Dear Pharmacist" letters were mailed. Through an initiative that's well outside the scope of normal product launch activities, we also had 25,000 outbound telephone calls to pharmacists. Those calls resulted in over 12,000 requests for additional information on Lotronex. We were impressed with this, and we think that this clearly indicates the potential power of these types of outreach activities focused at the pharmacist level.

In addition, we sent an informational piece on Lotronex to the National Board of State Pharmacists to be cascaded into the newsletters of its individual member states. And, finally, as with the physician, reminder letters to pharmacists also provide important information regarding Lotronex.

There are a large number of additional educational activities that GSK has implemented to provide further support for the appropriate use of Lotronex. These include a telephone conference series with physicians, speaker programs, informational booths at professional society symposia. There's a website, and we have call centers that can answer questions and provide information on the PPL itself. It can provide medical information, and they provide the sources of information to the practitioner and health care community.

And, finally, we're also providing independent grants for IBS education that's delivered at professional society symposia and

through other communication media. Again, while components of this educational program are obviously targeted towards a prescriber audience, the materials are available to the general health care practitioner community as well.

The next element of the RMP that I'd like to discuss is the reporting and collection of serious adverse events and adverse events of special interest associated with the use of Lotronex. This essentially comprises a safety overview.

Again, it's important to remember that there are some differences in the conditions under which AEs are reported currently versus the conditions that existed when the product was initially marketed. We currently have a different target population for Lotronex: females with severe diarrhea-predominant IBS, with the qualifiers that I've already discussed. Through our educational program, we believe that we have better-informed patients and physicians. We have an agreement from physicians to report serious

adverse events, and we have the patient survey, which is proving to be a non-traditional source of AE information, and the way we're handling that information will be discussed in just a moment.

So what are our sources for adverse events? They consist of the typical spontaneous reports and reports arising from a clinical trials program, but they also include the patient follow-up survey program.

The focus of our adverse event reporting is on these diagnoses and outcomes of special interest that were highlight as an area of concern during the initial marketing period, and those include ischemic colitis, mesenteric ischemia, occlusion or infarction, serious constipation, complications of constipation, as well as outcomes of special interest like intestinal or anorectal surgery and death.

Adverse events are reported in a typical fashion stipulated by the regulations. We have expedited reporting for serious, unexpected, spontaneous reports, and we also have expedited

reports for serious, unexpected, and attributable survey and clinical trial reports. But, in addition, we have a special agreement to expedite reports for all adverse events of special interest, regardless of their seriousness or expectedness.

The patient survey that we've been discussing a little bit is intended to measure patient knowledge, behavior, and certain RMP process elements. But through the process of either completing these forms in writing or over the phone, patients occasionally report adverse events. As part of the continual process of RMP evaluation and revision, we have developed a system for processing this adverse event information arising from the survey. To maintain patient confidentiality within the survey, Research Triangle Institute de-identifies the information on the adverse event report and forwards it to GSK. The GSK pharmacovigilance staff assess these reports for seriousness as well as special interest diagnoses.

For those cases assessed as serious or

possibly including diagnoses of special interest, RTI requests patient consent for GSK follow-up with the prescriber. When that consent is granted, GSK's Pharmacovigilance Department follows up with the patient's prescriber in a fashion similar to that that would be used during a spontaneous reporting context. And, again, adverse events arising from the survey are reported to the FDA as the data warrant.

So what is our experience to date? From November 20, 2002, until February 6, 2004, we have approximately 10,000 patients treated with Lotronex, or about 34,000 prescriptions. This has generated 127 post-marketing AEs, which include all spontaneous reports plus all patient survey reports that are deemed to be serious or reports of special interest as I just described on the previous slide.

Of the 127 post-marketing reports that we've received, 37 have been considered serious. Seventy-five percent of these 37 reports were GI in origin. What we're going to focus on are the 19 patients or cases that had diagnoses and outcomes

of special interest.

Of the eight reported ischemic colitis cases, six were medically confirmed. Those same six patients had colonoscopic or biopsy findings consistent with ischemic colitis. Three of the eight cases resulted in hospitalization. All of the cases of ischemic colitis resolved without sequelae. We have no reports of mesenteric ischemia. We have no reports of serious constipation. We do, however, have eight reports of complications of constipation. Three of those eight reports have been medically confirmed. Three involved fecal impaction. Three were associated with intestinal obstruction; there was one ileus, one ulcerated colon. Three of these eight patients were hospitalized, and three patients were managed in the ER only.

Four outcomes of special interest have been reported. There is one report of surgery which could not be confirmed by the patient's physician. This same patient also had a diagnosis of special interest involving a complication of

constipation. No deaths attributable to Lotronex have been reported. Of the three deaths that have occurred in patients taking Lotronex, two of those deaths came through the survey process and were reported by family members. One of those was in a patient with cancer, multiple myeloma. The other was in an AIDS patient. The other report that we have is a physician report of a suspected pulmonary embolism in an obese patient with a very complex medical history.

So, in summary, with regard to the safety of Lotronex, we have not seen any new safety issues. Recognizing that we have a very low rate of prescribing, we feel that the ischemic colitis and complications of constipation cases that we've seen are similar to those seen during the original marketing period, and we believe that the outcomes associated with those cases are generally less severe. We're also pleased by our review of the individual cases that suggest that prompt and appropriate action is being taken by the patient and the physician. What we're hoping to achieve

here is to change patient and physician behavior. We believe, in fact, that is what's going on.

But the final component of the risk management plan involves the implementation of a plan to evaluate the effectiveness of the Lotronex risk management program. This plan consists of three components: a retrospective study to compare the roster of physicians identified in a general prescription database as prescribers of Lotronex with a roster of physicians enrolled in the PPL, the prescribing program for Lotronex; the patient follow-up survey program that we've mentioned; as well as a longitudinal, claims-based observational study program.

First, the physician roster comparison. This is a study to compare physicians prescribing Lotronex within and outside of the prescribing program for Lotronex. The way that's accomplished is when the M.D. sends the enrollment form to the database vendor, the vendor sends that enrollment data to GSK. In parallel with that, GSK purchases a prescription data set from MDC Health. Those two

data sets are compared against each other, and through that process we determine who is prescribing within and outside of the program, and that information is reported to the FDA on a quarterly basis.

So what have we learned? These are the data that we have generated to date. As you can see, the number of prescribing program for Lotronex enrolled prescribers has generally remained at or above 80 percent since the program was initiated. We're actually quite pleased with this aspect of the RMP. This is the pattern of prescribing by physician specialty for the quarter beginning October 2003, which is representative of our overall experience. Prescribing, as you can see, is being driven primarily by the gastroenterologists. I think what is even more important is, of the prescriptions that have actually been written, 87 percent of those prescriptions had been written within the prescribing program for Lotronex, and we believe that that's a very good result.

In the initial marketing period, 50,000 physicians were prescribing Lotronex. Currently, only 5,053 have even enrolled to prescribe Lotronex through the prescribing program for Lotronex. What is particularly disconcerting is the fact that approximately half of the few prescribers who have enrolled have not written a single prescription. This may be a reflection of some of the RMP barriers that I'm going to discuss in a few moments.

And, again, part of the evaluation and revision of an RMP program, we've developed a follow-up system for non-prescribing-program prescribers. When these prescribers are first identified, an enrollment kit is forwarded to the prescriber. In addition, we forward a reminder letter to the prescriber's local pharmacy. If there is a second occurrence of prescribing by a particular non-enrolled prescriber, we forward them a reminder letter. If they transgress a third time, we forward a firmer reminder letter to them.

Now, the response to this process to date

is hard to determine, but overall what we're seeing is 75 percent of these non-enrolled prescribers comply in some way; 25 percent of them actually enroll and 50 percent of them stop prescribing Lotronex. And, again, this is a very dynamic situation. It can wax and wane over quarters, but, in general, this has been the response to this follow-up process.

Let's talk about the patient follow-up survey program, which is the next element of the RMP that we'd like to discuss.

The objectives of this program are to assess patient knowledge of the risks and benefit of Lotronex to assess patient behavior in relation to the recommendations in the risk management program and assess the extent to which the patient satisfies the product labeling requirements for treatment with Lotronex.

This is a flow diagram of how this survey process works. We receive the pre-enrollment card, and upon receipt of that, an enrollment package is forwarded to the patient, and that starts the

survey cascade, as you'll see on the left-hand side. If we don't receive survey forms back from the patient in prescribed time frames, there's actually a contact from RTI to the patient to encourage them to complete and return those forms to us.

So, to date, we have a 42-percent pre-enrollment rate for all patients who have received a prescription for Lotronex; 55 percent of those were issued by the prescribing physician. And, again, we didn't expect that. That's a little bit atypical. It's much higher than we expected.

Most of the patients that we see in the survey are middle-aged patients that are typical of the population that you would expect to be receiving drug and having diarrhea-predominant IBS. Eighteen percent of the patients are over the age of 65 years, and 7 percent of the patients are indeed male. Thirty-six percent of the patients that receive a prescription have actually completed the baseline survey form and entered the survey proper.

So, again, I think you can see from this table that what we've enrolled in this patient follow-up survey program is a very motivated cohort of patients. Recognizing the grace period for receipt of follow-up questionnaires from patients for whom that follow-up period has expired and questionnaire responses were due, I think you can see that almost all of those responses have been received across time. So, again, it seems like a very motivated cohort of patients, and they're doing their homework and sending it in.

What have we learned about these patients? Well, this table indicates that there's a very high rate of compliance with the key elements of the RMP process and also demonstrates that the discussions and activities that we wanted to have occur are indeed occurring. I think you can see 97 percent of the patients discuss with the doctor how Lotronex can help them; 95 percent discuss the reasons with the doctor why you would discontinue Lotronex; 91 percent have received the medication guide; 87 percent recall that a blue sticker was,

in fact, put on their prescription. So, again, from a compliance perspective, we're pleased at what we see coming through the patient follow-up survey.

Importantly, as far as patient appropriateness for treatment is concerned, this table shows that this survey cohort comprises an appropriate patient population for treatment with Lotronex. Ninety percent of these patients met the treatment and severity criteria. And, again, if you look at the individual criteria for treatment, 95 percent have diarrhea; 98 percent had IBS for more than six months, the chronicity that we were looking for; 96 percent had previous treatments for IBS; and 97 percent have said they had inadequate relief of symptoms. And, again, we believe that these are clear indicators of patient appropriateness.

If you look at the severity conditions that are required--and, again, I'll remind you that only one of these is required to qualify the patient for treatment, not all three. You have

cramps or bloating present in 87 percent, ranging up to a somewhat or very hard life in almost all of these survey patients. And if you look at the presence of all three severity conditions within an individual patient, you see that 80 percent of these patients have what you would describe as very, very severe DIBS. They have all of the severity conditions. And, again, I'll remind you that only one was required to qualify a patient for treatment. So I think this is a potential RMP impact issue that we're going to come back to at the end of the discussion.

The final component of the RMP evaluation is a program of longitudinal claims-based observational studies. The objectives of this program are to describe or characterize patients receiving Lotronex, to describe or characterize compliance with the prescribing program for Lotronex, and to evaluate the incidence of events in patients treated with Lotronex versus an appropriate comparison group.

These are three database sources that

comprise the longitudinal studies. In the aggregate we have approximately 8.5 million covered lives in this program. Again, recognizing that there's a lag period of about six months from the prescription to potential data extraction, 121 users of Lotronex have been identified through September of last year, the majority of which have come from the Engenics(ph) database. These 121 users received 277 dispensings of Lotronex and seemed to fit a pattern consistent with data that's been collected from other portions of the RMP; 89 percent of the patients are female; 69 of the first dispensings are coming from gastroenterologists. Importantly, this is an RMP process check: 70 percent of the patients' records did contain a signed patient-physician agreement. And, obviously, it probably goes without saying that program viability is being impacted by low product uptake.

At this point, I'd like to take a moment to give you our overall evaluation of the implementation of the risk management program for

Lotronex.

We certainly believe that we have successfully implemented all of the elements of this complex, integrated risk management program. We are pleased by the number of physicians prescribing within the PPL context, but we're even more reassured by the fact that the overall number of prescriptions coming out of the PPL is so high at 87 percent. Data from the patient follow-up survey program indicates that the key product use that we wanted to have delivered to the patient by the physician is, in fact, being delivered and that the patients being selected for treatment are appropriate.

We believe that patient and physician behavior is consistent with the goals of the RMP. Recognizing once again that we have a very low prescribing rate, we still feel that qualitatively the adverse events and special interests that we have observed are few and the outcomes being observed are generally less severe.

We have entered into this process of

continual RMP evaluation and revision, and through that process we've devised a program for follow-up for non-prescribers. We've revised the patient survey questionnaires to include new questions. And we've developed a reporting paradigm for adverse event information arising from the patient follow-up survey.

While we certainly believe that the RMP has been successfully implemented, we also feel that there is still much work to be done to optimize product availability to appropriate patients. For the remainder of the presentation, I'm going to focus on the key issues that have arisen regarding the impact of the risk management program on product use relative to Lotronex. These issues are certainly instructive in a general sense when one considers the use of these risk management interventions for other products.

So the issues that I'm going to focus on really are impact of the RMP on the practitioner and patient, which can be collectively viewed as potential product access issues, and the impact of

the RMP on some of its individual components.

These are sources of feedback and data that we've been collecting on the RMP. We've done some fairly unique physician- and patient-focused field research. We have information coming out of our clinical trials programs. We have interactions between our sales force members and practitioners. We have information coming into our customer response center. And we have interactions with our key opinion leaders.

What are we learning? At the prescriber level, we've received considerable feedback on this attestation process. Physicians are unaccustomed to signing a document like this and feel that somehow there's been a unique transfer of liability from GSK to the prescriber. One might wonder if that isn't being somehow reflected in the fact that treatment seems to be being reserved right now for patients that only have the most severe presentation of severe diarrhea-predominant IBS. In addition, physicians feel that having to sign an attestation form is an affront to their

professional training and somehow constitutes an unnecessary duplication of the licensure process. So one of the questions that we're dealing with right now is: Is there a less intrusive way to ensure prescribing by appropriate physicians with a focus more on education rather than attestation?

As you've already heard this afternoon, we've learned that fulfilling the RMP requirements is time-consuming and falls well outside of the normal clinical practice patterns. There's also some uncertainty regarding the origin and purpose of the RMP. Some people believe it's an IND study. People genuinely misunderstand the current marketing context for Lotronex. To us, this represents a communication or education challenge that needs to be addressed for Lotronex. But, again, it needs to be proactively considered in the implementation of other RMPs. We need to address that confusion before it occurs.

As previously mentioned, physicians have also expressed some confusion about the importance or utility of certain labeling statements like the

statement that the severe diarrhea-predominant IBS population comprises about 5 percent of the total IBS population. They really don't know how to use that information when considering whether or not the patient that they're looking at should be treated with Lotronex. So it's information that confuses rather than enlightens.

From the patient perspective, we've learned that the language in the product labeling tends to frighten the patients rather than inform them. We are getting this message clearly from our field research, but even more importantly, this is a clear message coming out of our clinical trials program, and that's a context where we believe that patients typically feel safer receiving medication because of the oversight that they get.

In our current clinical trial program, 28 percent of the patients who were screened for study inclusion who the physicians believe would otherwise be appropriate for Lotronex therapy refused to participate because, after reading study information that's similar to product labeling,

they stated that they were afraid to take Lotronex. And, again, this is a phenomenon that we don't have any precedent for within our GSK clinical research programs.

And, finally, there is this requirement to sign a special document, this patient-physician agreement, that is somewhat disconcerting to some potential patients. Again, it's something unusual, they don't typically have to do it, and it gives them pause.

As far as the claims-based observational studies are concerned, again, it's obvious that the low physician-patient uptake has had a serious effect on this program. Currently we have 10,000 patients and have extracted data from 121. At the current rate of prescribing, where we need 2,000 patients to support meaningful analyses, we would need 155,000 patients treated with the drug, and that could take 15 years at the current rate. So, again, this is a problem that we're going to have to address as we move forward.

Again, you know, we certainly believe that

we've successfully implemented the RMP for Lotronex and are effectively managing risk. However, we have identified a number of RMP-related issues that may be posing a barrier to access by appropriate patients. And our ultimate goal is to modify the RMP to improve product access for appropriate physicians and patients while continuing to effectively manage the risk.

Ten thousand patients have received Lotronex since the product was reintroduced. Current estimates from the literature suggest that the severe DIBS population ranges in size from 111,000 to perhaps as high as 2.9 million. It is not 10,000. We will continue to work with the FDA to close this apparent gap between patients who need Lotronex and those who are receiving it.

And with that, in the interest of time and out of respect for the mental health of the Advisory Committee, I will stop talking and yield to the podium to Dr. Justice.

DR. GROSS: Thank you very much, Dr. Metz.

The next speaker is Dr. Robert Justice,

Director, Division of Gastrointestinal and Coagulation Drug Products, who will give the FDA update on Lotronex.

x DR. JUSTICE: Good afternoon. I would like to take a few minutes to discuss our view of the Lotronex update that you've been provided.

I will cover six topics: background on the adverse event and marketing situation around the time of withdrawal and on discussions about how to provide access; risk management goals and how they are being met; patient access issues; physician enrollment process issues; labeling and the tension between informing and frightening; and, finally, our conclusions.

This slide is taken from a presentation at the April 2002 Joint Advisory Committee meeting and presents data on the number of cases of ischemic colitis, small bowel ischemia, and serious complications associated with--complications of constipation associated with Lotronex during the period of initial marketing in 2000.

For ischemic colitis, there were 18 cases

in the clinical trials, 84 cases in post-marketing, for a total of 102 cases, with 11 surgeries and two deaths. For serious complications of constipation, there were 11 cases in the clinical trials, 113 post-marketing, for a total of 124 cases, with 35 surgeries and two deaths.

In 2000, there were approximately 534,000 prescriptions and 275,000 patients. Off-label uses included diarrhea, inflammatory bowel disease, custodial care, managing nursing home patients, and constipation-phenomenon irritable bowel syndrome.

The prescribers at that time were predominantly primary care physicians: 32 percent were general practitioners or family practitioners, 24 percent were internists, and 31 percent were gastroenterologists.

Given the adverse events of ischemic colitis, small bowel ischemia, and serious complications of constipation, four options were considered: restricted distribution to gastroenterologists only; IND access; suspension of marketing until a hearing before an advisory

committee; and withdrawal.

As you've heard GlaxoSmithKline chose to withdraw the drug from the market in November of 2000. In 2001, access became an issue, and approximately 5,000 e-mails from patients were received by the FDA.

In 2002, GlaxoSmithKline and the FDA agreed upon a restricted distribution and risk management program, and Lotronex was reintroduced into the market.

The Lotronex risk management program includes four goals. The first is enrollment of qualified physicians in a physician prescribing program. A decision was made to allow enrollment of physicians possessing certain qualifications for diagnosing and managing IBS and drug adverse events as opposed to certifying physicians by developing a whole new program of education and certification. Physician attestation of qualifications is allowed, and this is not a precedent for FDA or for physician maintenance of privileges or licensure. Participating physicians must attest that they are

knowledgeable of the benefits and risks of Lotronex and about the management of IBS and drug adverse events. The attestation and the patient-physician agreement include features of informed consent so that patients and physicians are fully able to decide about the appropriateness of Lotronex treatment.

The second goal is the implementation of a program to educate physicians, pharmacists, and patients about the risks and benefits of Lotronex.

The third goal is the implementation of a reporting and collection system for serious adverse events.

The fourth goal is the implementation of a plan to evaluate the effectiveness of the Lotronex risk management program. We believe that these goals are being achieved.

Regarding the issue of patient access, GlaxoSmithKline estimates that there are 185,000 women with severe IBS in the U.S.; however, as you've heard, only about 10,000 have tried the drug. Whether additional women will seek treatment

is unclear. Some will decide not to start Lotronex after discussion of the risks and benefits. Others who start the drug may not continue. In the clinical trials that excluded severe diarrhea patients, those on Lotronex had a 13- to 16-percent increase over placebo in the median percentage of days with urgency control. In the subset of patients with urgency at baseline on five or more days per week, there were 13 to 21 percent more patients on Lotronex compared to placebo, with urgency no more than one day in the last week of the trial.

The goal of GlaxoSmithKline and FDA is to ensure access to patients whose diarrhea-predominant IBS is so severe that they will reap the benefits of the drug over its risks and be under the care of qualified physicians. We are working together to try to identify unintended barriers to patient access.

Regarding the physician enrollment process, physician responsibilities in the prescribing program must be clear, and the program

still needs to ensure that only qualified physicians are enrolled. These doctors must attest to their abilities and knowledge and take on responsibilities such as patient counseling, reporting of adverse events, and applying Lotronex blue stickers on prescriptions so pharmacists will know that they're enrolled in GSK's prescribing plan.

Not all physicians may wish to accept these responsibilities or are able to manage the disease and drug adverse events. However, GlaxoSmithKline and FDA are looking at ways to improve the physician enrollment process and are evaluating other possible means of attestation to ensure qualifications. For example, phone-in attestations may be an option as well as the current fax-in forms.

As was mentioned, there is a perception of liability transfer to the physician. Perhaps the fact that liability is not being transferred can be made clearer.

Regarding the issue of labeling, there's a

tension between describing risks that may be frightening and providing adequate information to allow patients and physicians to make informed decisions. FDA will consider labeling changes that enhance clarity and education. However, any changes in the labeling such as the indications must be supported by clinical trials data on effectiveness and safety. In addition, the labeling must include accurate information on the magnitude and severity of adverse events.

In conclusion, we recognize that there is a tension between managing risk, providing access to the drug, ensuring appropriate use, and business considerations. How drugs are used is influenced by many parties in the health care system. We think there may be room for improvements in the risk communication and processes and are working with GlaxoSmithKline on them. Overall, at the present time the risk management program appears to be managing risk and assuring appropriate use.

At this point I would like to open it up to committee questions of GlaxoSmithKline, FDA, and

for further discussion. Thank you.

DR. GROSS: Thank you, Dr. Justice.

Are there any questions from the committee members for any of the speakers? Jackie?

DR. GARDNER: Two points of clarification, if Dr. Metz could help me. The first is whether there is any restriction on the quantity of drug that can be prescribed. I appreciate that your packages come in 30s, but a prescription for 90 is allowable, for example. Is the quantity restricted?

DR. METZ: Right now, what we're requiring is a prescription--what we're providing to the patient is a package of 30. It is possible that a physician could prescribe multiples of that. But I don't think we have any direct data on whether that is, in fact, happening and on what scale it's happening.

DR. GARDNER: But it's not prescribed by the program.

DR. METZ: No.

DR. GARDNER: And the second question I

have relates also to access but to the post-marketing surveillance. Regarding your population-based surveillance, do you know whether this drug is on the formularies of those HMOs?

DR. METZ: You're going to have to speak to a microphone, Bob.

DR. SANDLER: Right now our estimate is that 87 percent of prescriptions are reimbursed in some fashion when covered through managed care. So it may not necessarily be on a formulary, but it will be covered.

DR. GROSS: Stephanie?

DR. GARDNER: Dr. Metz, I'm sorry. That doesn't answer our question, because if it's not on those formularies, you're not going to find scrips, and there's no point in doing the post-marketing surveillance

DR. METZ: Dr. Gurwitz?

DR. GURWITZ: My name is Jerry Gurwitz. I represent the HMO research network CERT, the Center for Education and Research on Therapeutics, that is conducting one of the studies, and nine health

plans are involved in our study, our component of the epidemiology program. In all of the health plans involved in our study, the drug is available. The access to prescribing the drug varies according to the plan. Many of the plans require prior approval for a prescription. But none of the plans forbid prescribing, and all of the plans, if approval is given, will allow it to be prescribed.

DR. GROSS: Okay. Stephanie?

DR. CRAWFORD: Thank you.

Dr. Metz, in slide 46 on patient appropriateness--this is the one where you have the categories for men and women and overall met treatment and severity criteria for women, 90 percent, men, 84. I have actually two questions.

My first one is: Why is the men not zero based on the label indications?

DR. METZ: Well, there's a difference here. It's not indicated for use in men, but men that are using it can still meet the criteria for treatment. So there's a difference here. You know, the question is: If we had a box in there

that said women for whom it was--or patients for whom it was indicated, then you'd have a number for females, but for men you would have zero because it's not indicated for use in men. But now the real question is: Of the men that receive Lotronex, did they have the disease that would have qualified them for treatment for Lotronex? And the answer to that is 84 percent of them did have the disease. Is that--

DR. CRAWFORD: I understood how it was meant. I guess I'm asking are you--the second question, which is not so quick, is: You were rather general in some of the things you were alluding to, saying perhaps things from the sponsor's perspective could be handled through education, et cetera. Can you be more specific? And as part of that, are you also saying that perhaps the indications should include men or not?

DR. METZ: No, again, right now we're not considering any change in the indications statement because, as Dr. Justice has suggested, those types of changes are going to require data from

additional clinical research.

I think what we're looking at and, again, what we're working with the FDA on is looking at the product information, the product labeling, and trying to provide a little more balance, trying to present the information in such a way that it's not naturally intimidating or frightening to the patients. So, you know, we're looking at making modifications that provide balance and clarity, and I think that's the approach that we're trying to take as far as the risk management program is concerned.

And as far as the attestation process, as Dr. Justice mentioned, we're taking a look at that and seeing where the points of tension are between the physician attestation process and see if there's another way to address it to take some of the venom out of that, if you will, and make it more acceptable to the practitioner.

Again, that's an area that we just have to focus on because the feedback that we've gotten from the field indicates that that's an issue for

some of the practitioners.

DR. GROSS: You mentioned that 80 percent of the prescribers were in PPL.

DR. METZ: Right.

DR. GROSS: How did the other 20 percent write for the drug? And why was it honored?

DR. METZ: Okay. Well, they can write a prescription for the drug. There is no mechanism that we have to keep them from doing that. But it would be akin to a physician writing an off-label prescription for a product, which they have the right to do.

Now, at the pharmacy level, obviously, there is a little bit of tension created because for the pharmacists that are aware of the program, they're faced with filling a prescription that doesn't have a sticker on it and what they're going to do about that.

So, again, we've addressed that with some of our follow-up information. We have that follow-up letter that goes to the pharmacist when we've identified non-enrolled prescribers, just

reminding them that this is the program that's in place for Lotronex and, you know, encouraging them to hopefully contact the prescriber and say, you know: Are you enrolled? I got a letter from GSK or from the prescribing program for Lotronex that says there ought to be a sticker on these prescriptions.

But, again, we can't force that conversation to occur, and what we're finding is 13 percent of the prescriptions that are written are coming outside of the program.

But, again, you know, we have no benchmark against which to judge that, but 87 percent is pretty encouraging to us, frankly. We're very relieved because we had no idea what would happen.

DR. GROSS: And from the patient's point of view, I guess it's not possible in the current program, but would it be possible once the patient and the physician work out their agreement to have the patient obtain prescription renewals, let's say, for the next two monthly ones, attain them without a visit and maybe just see the physician

four times a year instead of monthly for prescription renewal?

DR. METZ: That's an excellent point, and oddly enough, we're in some discussion around how to address that issue. Because, again, I think with these risk management programs, you start out in one place, and after you've had some experience with the product being marketed under those types of programs, you use the data to decide where to go next. And I think we feel that maybe the time is right to take a look at this refill procedure and, as you've suggested, make sure that the important conversations occur first early on. But then after that, once the patient is in a "stable situation," perhaps you could provide for refills and, again, reduce the need for those recurrent visits. I think that's a very good point.

DR. GROSS: Henri?

DR. MANASSE: Dr. Metz, I have two questions. One relates to the intense time that it takes both physicians and pharmacists to participate in this program and do the required

safety net activities. What kind of dialogue has gone on within GSK to deal with the time, cost, financing component of the management of the program? Question number one.

Question number two: Have you explored all of the different places and mechanisms by which prescriptions get filled by patients and the fact that all of these different ways probably require different ways of managing the program? I refer specifically to where the patient has a choice in terms of going to pharmacies, both in hospitals and in communities, versus forced mail-order, for example, in some health plans--my point being, again, and my question relating then to how have you thought about these issues, and are there ways that these can be tinkered with, if you will, to enhance the participation of providers?

DR. METZ: Let me try to answer the first question first, as best I can remember it, and that was with regard, if I understand it, to the internal burden with GSK of running this very complex program--

DR. MANASSE: It's placed on the providers and the time and energy that it takes and the problems of remuneration we heard from one of the speakers today.

DR. METZ: Well, you know, again, if I understand the question, we are looking into that issue, and we're trying to decide which of these points should be addressed--you know, what points could be addressed to relieve as much of that burden or tension as possible, while maintaining the integrity of the RMP framework itself. And, you know, it's a balancing act, and we're into those discussions with the agency, and we're going to look for ways to make this less onerous without undermining the integrity of the system that we believe has worked fairly well up to this point.

DR. GROSS: Brian--

DR. METZ: Now, there was a second question, and that second question was really have we looked into the other mechanisms or avenues for patients filling prescriptions and whether, in fact, there are any barriers there that we didn't

envision that we should perhaps address moving forward. And, honestly, we have not looked into that right now. We'd be interested in hearing some views on that because I think that's a very important point. And, again, we've been, you know, dealing with this, but I think as we move forward and if we consider some other ways to address the refill phenomenon, that's got to come into play.

So, again, we'd be interested in hearing some advice about that.

DR. STROM: I have two questions. One is: When we met about this two years ago, one of the ideas of the attestation and the debate about attestation and certification and gastroenterologists, primary care doc, was the goal to have this drug prescribed by a subset of physicians who really knew how to use the drug. And given the numbers you just described about 10,000 patients and 5,000 docs, or even 2,500 docs prescribing it, that's an average of four patients per physician, which isn't very impressive.

What proportion of patients are getting

their prescriptions from physicians who are prescribing it to more than one patient?

DR. METZ: I think we have a slide on that. Yes, we've got a bar graph with the numbers of prescriptions. Just a second. We'll see if we can find that.

But you're right, again, if you--recognizing that no refills are allowed, some of those numbers that you see are original prescriptions for the same patients, so you're absolutely right, the number of patients per physicians who do choose to treat is pretty low.

DR. STROM: But, if anything, that argues there should be fewer certified physicians rather than more.

DR. METZ: Okay. Here we go. Here's the prescribing activity, and what we see here, this is total numbers of prescriptions. And, again, it gets hard to put a denominator with that because we don't have any refills that are allowed. But, anyway, I think what you can see is in the one to five range, very negligible. There are a few, a

few more actually, roughly twice as many dedicated prescribers, if you will, that are driving prescriptions beyond six to ten, out to greater than 15 prescriptions. But it's a very small cohort.

DR. STROM: The second question: As you were talking about, one of the key issues here is mitigate risk, and when dealt with this two years ago, one of the concerning questions, obviously through no fault of anybody, is that there was no way to predict--let me back up. It appeared that a relatively small subset of patients actually benefited from it. We saw two sets of data indicating only about 10 percent of patients continued the drug long term for a symptomatic drug, and it looks like that's what happening again now that the drug is on the market. So there's only a small subset of people who get the drug who will benefit. And there were no risk factors that were identified in the data then that could predict who was likely to benefit and who was not.

In the same way, the risk of suffering a

serious event is obviously much less than 10 percent, but even in your new experience here with incomplete reporting, it's still one in 300 patients suffering serious events. And part of the problem is, at least as of two years ago, we couldn't predict who would benefit. We also couldn't predict who would be hurt. So that the only way to mitigate the risk was to restrict its access and to, in fact, limit it to as few people as possible, because 100 percent of the people who got the drug would be at risk of getting the adverse events, where only roughly 10 percent of the people who got the drug would benefit from the drug.

In the interim, where you've got other clinical trials underway and additional experience, are there any more data you could share with us that would give information about predictors of either who is likely to be that 10 percent who benefit or who is likely to be in that one in 300 who will suffer serious adverse events?

DR. METZ: No, we don't have any new

information. Our clinical trials program is ongoing, and, again, we just simply don't have that information available as we sit here today. And, again, you're absolutely right, the ischemic colitis we believe is idiosyncratic; therefore, we can't predict.

However, what we do think that we're seeing here is some improvements in the outcomes, and, again, our goal for this risk management program was not based on a target number but was based on changing behavior, prompt recognition and action on behalf of the patient and physician. So that's where we are right now.

DR. STROM: But just as a follow-up comment, the logic of two years ago, which you're describing to me still holds, is if you can't predict who's going to benefit and you can't predict who's going to be hurt from it, the only answer is--we didn't want it unavailable because we thought there were people who clearly needed it, but the only alternative was to greatly limit its access as much as possible.

DR. METZ: Well, again, you know, we feel that with this specified target population, we've got a target population for whom we believe the benefits will outweigh the risk. And we believe it's an appropriate target population for treatment, and we believe within this framework that we have developed here, risk can be effectively managed and people can have the opportunity to benefit from Lotronex. And I think that's what we're trying to provide here is that opportunity. So, you know, we'll finish our clinical trials program and hopefully be generating some data that we can share in the future. But we are where we are.

DR. GROSS: Robyn has the next question.

MS. SHAPIRO: I think this may pick up some of that. As I understand it, then, part of the qualification requirements for the doctor is so that he or she could properly manage in the event of something bad happening. But it's not clear to me from your presentation about what you want to do about what you've already put in place to try to

make that happen. In other words, the perception of the liability transfer I think is ridiculous, and they will always be afraid about that and upset about that. You're not going to answer that.

Anytime when you want to require qualified people, that's an affront, I guess, to licensure and training. But if you believe that that's important to be able to pick up--I don't think that any of these issues are significant enough or even credible to go back on the required training thing.

DR. METZ: Let me just address that question in two ways. First of all, we're not talking about completely walking away from something. What we're talking about is trying to modify what seemed to be perhaps the most offensive elements of it. They don't like the signature process. So, you know, as Dr. Justice has suggested, is there another process to ensure that they're qualified yet somehow or another doesn't serve as an affront to them and recognizes some of those sensitivities. But, actually, I'd like to let Dr. Sandler address just some comments from his

perspective on this process and some of these intangibles, if you will.

DR. SANDLER: I think that as a physician the program has incredible barriers and I think it's hard to convey. And to sit down with a patient and ask them to sign this form I think is insulting for physicians and somewhat demeaning.

I think to be able to give the patient an information sheet and to sit down with them and say if you get constipation, stop the drug and call me, if you get bad abdominal pain, stop the drug and call me, that permits me to educate that patient, just the way I do with every other patient. This program becomes special, and by doing that we set up barriers. And we're denying access to a drug that helps a lot of people. Dr. Stronk (ph), whom I admire a lot, said that everybody has a risk but nobody has a benefit. Well, going into it, the probability is everybody has a chance to benefit and everybody has a chance to risk. We can't predict.

MS. SHAPIRO: But you're talking about

what was going to be my second point. My first point is: Do we do away with the required qualifications attestation? And that's different than the agreement and the time that it takes to do that. But let me just talk about that, too, and then you can come in on both.

One of the points in here is that it must scare patients away because after they go through this process, whether it's the signing of the form or hopefully, more importantly, the discussion, some of them don't want to take the drug. Well, that's informed consent.

DR. SANDLER: That's fine.

MS. SHAPIRO: I mean, that is what the plan is. When they hear things--

DR. SANDLER: What about the patients that are denied the chance to even get the drug because Dr. Wilderlite, he's a competent gastroenterologist, and he's afraid to use the drug. He's afraid of litigation, he's afraid of--and the process is so time-consuming that we've set up barriers so he doesn't want to use the drug.

MS. SHAPIRO: The time-consuming thing just gnaws at me because while I'm very cognizant of the fact that, particularly today, doctors don't want to talk to patients because they don't get paid for it, they have to talk to patients, and particularly when they're dealing with a risky drug, they have to talk to patients. And our reimbursement system should figure out a way to make it worthwhile. But even before it does, they have to talk to patients.

DR. SANDLER: I couldn't agree more. So let me answer your question about the attestation and then answer your question about talking to the patients. There's probably a way to do this short of a doctor saying, "I attest that I know how to take care of IBS patients. I know how to take care of ischemic colitis," signing a form. I think there are ways that the agency and the sponsor could work to figure that out.

MS. SHAPIRO: Without assuring that they do? Without kind of assuring that they really do know how to pick up on the signs and symptoms that

would suggest that a patient's in trouble?

DR. SANDLER: Well, the system now doesn't assure it either. They just sign the form and say they can do it.

MS. SHAPIRO: Okay. Well--

DR. SANDLER: There's no way to guarantee it. They're licensed--

DR. GROSS: I think we're going to have to go on to the next question. Alex, do you have a question?

DR. KRIST: The question that I was wondering leads a little bit on what Brian was saying. Back in 2002, there were discussions about whether the lower dose, which is now the starting dose, would have less risks of adverse events and whether the risk of adverse event would go down over time or whether most of the risk was when a patient initially started the medication. And I heard you say earlier that we don't necessarily have information about who's going to be at risk. But part of my question that I'm wondering is I'm just interested in the systems in place for

watching this to see if the lower dose will result in less adverse events and if the risk of adverse events will change over time that a patient is on the medicine.

DR. METZ: Well, you know, again, we have a survey that gives us information about the starting dose that patients are taking, and we're reassured by looking at that patient survey data that they are indeed starting with that initial dose that we wanted them to use. But I think in a longitudinal way, I'm sure that we have the ability to monitor across time in the fashion that you've suggested.

Elizabeth?

And, again, that's some information hopefully that we'll get out of that ongoing clinical program that was part of our series of Phase IV commitments. You know, that's the richest context for that type of information, but I'll let Elizabeth--

DR. ANDREWS: We do at every follow-up in the survey, we ask what their current dose is, and

I don't have the exact percentage. I can get it. But a substantial number of people are still on the lower dose. I think your question was something else, which was what is the efficacy at the lower dose.

DR. KRIST: The risk across time.

DR. METZ: Risk of adverse event on the lower dose and the risk of adverse event over time. And, again, within the survey context, we don't have the ability to do that, but we have a very large clinical trials program underway, and those doses are included there, and that is going to be the richest source of that information. But those studies are not completed yet. They are enrolling.

DR. GROSS: Curt?

DR. FURBERG: We heard quite a bit about the good news, and I want to commend GSK and the agency. We didn't hear much about the troubling news, at least two aspects of it. One is the very low participation rate and the patient follow-up survey program, 36 percent responded. I find that very, very troubling. And the other one is the low

physician reporting rate those serious adverse events. Most of the serious events came from patients.

So my question then is to you and your company: What are you doing about it? One thing is to take care of the issues and increase the use, but you also have to get better information, better data for us that we can assess the impact of the program.

DR. METZ: Well, as far as, you know, the general perspective on survey participation in this type of context, I think I'll let, again, Dr. Andrews address that. But I would tend to disagree with you. You know, given the experience with these types of instruments, we're not disheartened by 36 percent.

Now, you know, are there other things that we should look at or could look at to change participation rates in future surveys and what are the dynamics around the patient's willingness to participate in these surveys? I think these are interesting research questions that I think we need

to look into as this field evolves. But I'll let Dr. Andrews talk--

DR. FURBERG: I think you're saying you're going to overcome barriers for the other areas. This is an area that also has barriers, as you said, and you need to overcome them. And 36 percent is unacceptable, in my view.

DR. METZ: I'll let Dr. Andrews address that.

DR. ANDREWS: Well, 36 percent is--the issue is whether the patients are representative. Are there biases because of the low participation rate? A 36-percent participation rate doesn't necessarily mean that it's biased, just as a 90-percent participation rate might not mean that it is completely unbiased.

What we have looked at in terms of representativeness is we've looked at the age and gender of the patients, geographic region of the prescriptions, and specialty of the physicians, and compared with sales, and we see the patterns are almost identical. So that is--

DR. FURBERG: It doesn't carry the day at all. I mean, those are fairly insignificant, nonspecific factors. The reason why someone doesn't respond could be that they had a bad experience and just said, "I'm just out of it." And we never find out about it. I think we have an obligation to get as complete information as we can from that part of the program.

DR. METZ: Again, that's a point well taken. Would we be happier if it was 50 percent or 60 percent? We would both be happier.

DR. FURBERG: I'm just suggesting devote some effort to that as well.

DR. METZ: Yes, I agree. And the second point that you made, I'm sorry, Dr. Furberg, was?

DR. FURBERG: The physicians, the lower reporting of adverse events. Most of the events are coming from patients, which is unusual. And here are they objecting to it, or is it just--

DR. METZ: Again, I'm not a physician. I don't even play one on TV. But I'm going to pretend for just a moment.

You know, when we talk about seriousness, seriousness means different things to different people. To a practitioner, they have a practical definition of seriousness based on the practice of medicine. We have a regulatory definition of seriousness based on the regulations, and perhaps what we haven't done a good job of doing is communicating to the practitioner community what it is we want them to report here. We've said you should report, but I'm not sure that we educated them as far as what to report.

DR. GROSS: Our next question is from Maria.

DR. ANDREWS: I was going to make the comment, I just wanted to make sure that you are aware that the participation in the survey is voluntary.

DR. FURBERG: I understand that.

DR. ANDREWS: And so for a voluntary program, the participation rate is actually quite high.

DR. FURBERG: I'd disagree with that,

DR. SJOGREN: Actually, I'll take up that point because where I work, we have several programs in which we do follow-up, and it is across the board 30-percent response. When I looked in the literature, it is 30 percent no matter what. And so we put a follow-up program in place thinking that we were going to do better, and it came out right at 30 percent. So their 36 percent I think falls within the literature, at least from what I recall in my research. It's unfortunate, but that's us, that's human beings. We don't like to answer questionnaires; we don't like to be followed up. And I think that's part of the problem that you're facing, and I don't think you're going to be able to solve it. Just look in the literature and you'll see everybody's 30 percent. Actually, you are 6 percent above.

But the question I wanted to--or the analysis that I did looking at the data and looking at what the FDA gave me to review is that indeed, although there were patients that has ischemic colitis, all of them resolved. And I think, you

know, talking as a clinician--I mean, I wear several hats, but one of them is as a clinician. If things resolve, you don't think that they are serious. So that's possibly the cause why my colleagues are not reporting to you.

Now, if we are in the midst of a clinical trial and you have an ischemic colitis or you have a hospitalization, then you absolutely report as a serious adverse event, but not in the practice of medicine. And these observations are part of the program that you and the FDA put together.

The fact that, when I did some rough calculations, you had less than 4 percent adverse events in this program and then, as was pointed out before, the serious adverse events--by seriousness considering ischemic colitis or some other diagnosis--was 0.3 percent. So the program is a success in regards to if you apply this medication to the appropriate patient. Then you have a small rate of adverse events in general and not dismissible but a small rate of serious adverse events especially when those serious adverse events

resolve, because you remove the drug and the patients just can go back to their normal life.

So I think, you know, the program that you put together is very good because it proved the point that the appropriate patient that takes the drug, then the risks are minimized.

So talking now on the subject of being a clinician and having ten gastroenterologists that work with me and many friends in the community, I've asked in the past if they use Lotronex, and they've all told me no because when they enroll or attempted to enroll, they got boxes and boxes and boxes of paperwork to fill out, that it is horrendous. They're very upset, the community of gastroenterologists in general, because there are patients in which, although the disease may not be life-threatening in the sense that they die, it is life-threatening in the sense that the guys cannot get out of the house or have to have an office right next to a bathroom. There are things in gastroenterology that should not escape us, and I think the appropriate patient with this drug should

have access to it.

And I think that the reason for meeting today is to find a way to make it more accessible. Obviously, there were very serious side effects before. There was misunderstanding. There were physicians that perhaps were not following the letter of the intent of the FDA. But those things I think we can work with and make the program more feasible for our patients and for our physicians.

DR. METZ: Okay. That's our intent. It's a continual cycle of evaluation and revision. The advantage that we have right now is at least for a change we have some data that we can deal with as far as the potential impact of these things. And, yes, there are things both good and bad that we need to address as we move forward. But we think it's important to continue to make this available to these patients because this disease really insulates them from their activities of daily living.

DR. GROSS: Mark, did you have a comment you wanted to make?

DR. AVIGAN: Right. I just wanted to speak to the observation of the adverse events, the eight cases of ischemic colitis that were basically predicted and pretty much on track with the usage that currently exists. And then the question came up of the distribution of severity of outcomes out of those eight cases.

Just to point out that the severe outcomes, the bad clinical actors that were observed in the previous experience, and just to sort of go back to the April 2002 tabulation, so in the post-marketing sort of ratios, out of 84 cases of ischemic colitis, 10 developed surgical outcomes and two were associated with death. So it's a subset of the denominator of ischemic colitis. So there may--there are two possibilities. One is the early observation of ischemic colitis by the clinician, the patient really mitigates the risk for a bad outcome. But the other is that because there were less patients exposed, you don't have the full distribution of severity of outcomes because of purely the number that actually got the

adverse event.

I just wanted to point that out, and I was going to ask you if you--and we already spoke about this a bit, whether you could distinguish between these two because that's an important point about your evaluation of the success of the risk management.

The second question--and I just raise it as a question raised before--you mentioned that of the patients who are currently treated, 80 percent have all three severity criteria. So my question--and you may not have the answer, but one that should be raised--is: Of those patients who have frequent and severe pain, which is the first criteria, what percentage of those have frequency urgency or incontinence and/or the third criteria, which is the restriction in lifestyle? In other words, what is actually the--if you already have one, what is the percentage of all three in order to understand whether you're being overly stringent because 80 percent have all three?

DR. METZ: Let's take the second question

first. And, Dr. Chang, maybe from your clinical perspective, it's the issue that we've discussed around what's the likelihood that a patient would have one or two of these things versus having all three. Again, so the issue is, you know, is it fair to hypothesize that this all-three phenomenon does really represent a severe end of the spectrum? Or is there something else going on here?

DR. CHANG: There have actually been studies that have shown that if you have pain, that's a predictor of impact of quality of life. So I would imagine that the patients with severe irritable bowel syndrome who have severe pain or frequent pain are really going to have number three, which is disability or disturbance of quality of life.

There hasn't been data on the urgency or fecal incontinence, but you can imagine that you if you have fecal incontinence, you're going to have an impact on your quality of life every time you step out the door. But if you're going to assess urgency and that with pain, I don't think they're

really tied together. I think it's tied with discomfort. But with quality of life, you have to only look at a subgroup of IBS patients, which are the diarrhea predominant group. And my guess would be, my impression is that urgency is probably a strong predictor of impact on quality of life in that group of patients.

DR. METZ: So it sounds like one and three and two and three go together, but one, two, and three seem to define, you know, a severe end of the spectrum. And I guess as far as--you know, we've been talking about these diagnoses of special interests and these outcomes, and if I could just have Dr. Lewis make a comment from his perspective, having reviewed this and chairing that Safety Review Committee.

DR. LEWIS: Thank you. I chair a Safety Review Committee which we look at all the events of special interest regarding what is reported to be ischemic colitis or constipation complications. And in doing that, it's revealing that certainly not all the cases that are filed as that diagnosis

turn out to be that diagnosis. We spent weeks developing criteria, methodology to put together a true way to diagnose these conditions, which can be done for any adverse event. I mean, we do it for liver disease and other things.

And with the cases that we've seen in this program, while many of them were ischemic colitis, several of them were not by the criteria that we use. The first and foremost is somebody has got to look in the colon and see if it even looks like ischemic colitis. People can have rectal bleeding from lots of different reasons, and pain. It could be diverticulitis, for example. So we have criteria that we use.

We also then--what's not shown here is we made a causal relationship jump to whether Lotronex might have been responsible for the constipation or the ischemic colitis, and there we have similar criteria and methodology we put together, and only a minority of those cases could we actually say Lotronex seems to be responsible in a probable or a definite manner.

We still don't know why ischemic colitis occurs. The latest epidemiologic studies suggest that it might even be the very far spectrum of what we call irritable bowel syndrome. Remember, we still are learning about this syndrome. We now know it's not just with Lotronex. Tegasorade (ph)--I just got my letter yesterday, the "Dear Doctor" letter telling me Tegasorade, which works on a different serotonin receptor, is also associated with the condition. I haven't reviewed those cases so I don't know how accurate it is. But it is a learning process. I think we're learning more about ischemic colitis in the last couple of years and into the future than we ever expected to, and it's important that we do that.

But just in terms of what we continue to do is try to identify in the future what patients might be at risk, and that will be very important to know so that we might not give certain patients Lotronex or the other drugs as well, because right now we don't know. And some form of monitoring is certainly important. An educational program that

we're doing and telling patients what to expect and stopping the drug if they get those symptoms is crucial.

DR. GROSS: We have three more questioners before we close for the afternoon: Art, Annette, and Jackie.

MR. LEVIN: I've been struggling with how to put this as a question rather than a rant, but first of all, just a few comments and then my question.

I assume you're aware that in the context of risk management programs, this is risk management lite compared to some others. There are other programs out there that manage the prescribing and dispensing of medications about which we serious questions as to the trade-offs between risks and benefits and a lot of unknowns that manage it much more rigidly than this does. And the notion that we're scaring patients away, I mean, I would call your attention to the Med Guide, which I think is mild and doesn't even follow the guidelines in having the black box warning at the

top of the Med Guide. It gets into the risks, I think, in a very general way.

That said, it strikes me in listening to your presentation that you're looking to the wrong entity to fix the problem, if there is indeed a problem with access, because I think having barriers is what risk management is about. I mean, it sort of defines it.

I think we have to recognize that this was an extraordinary case, the first time in history where a drug which had been withdrawn came back on the market and about which there was little known about how to predict risk, and that everybody, including all of the patients that testified that day, seemed willing to ensure this special program in order to have access to the drug.

I think the problem is in the prescribing community. I mean, I would ask you to think about where is the problem. And I am somewhat--I'll use the word--angry that the prescribing community describes a conversation with a patient about benefit and risk and signing their name to a

page-and-a-quarter attestation as so burdensome that they opt out of this program. And it strikes me that if a physician believes that this is a drug for the patient sitting in front of them, it borders on either misconduct or malpractice not to prescribe that drug because they have to sign an attestation or they have to go into a program which is designed to protect them and to protect the patient from harm.

I would argue that your education--it's not a matter of relaxing the risk management program. It's a question of educating the prescribing community that the things they're afraid of they should not be afraid of, that this program is in place to benefit everybody, and they've got to give it a chance. And maybe if we do learn how to identify patients that are at risk and can be more scientific in selecting who gets this drug and not, we can change the program.

To date, there's no more data than we've ever had, and I would argue to look to altering the risk management program at this stage is simply

unacceptable in terms of protecting the public health. And I think really what we should be thinking about is how do we educate the prescriber community to get over their fear and to prescribe this drug when they believe it's appropriate for a patient. You guys are very good at educating doctors about your products. You detail very well. And I don't know why you can't be doing educational detailing to that effect.

DR. METZ: On that?

MR. LEVIN: Yes.

DR. METZ: I didn't hear the question so--

[Laughter.]

VOICE: It qualifies as a rant.

DR. METZ: You said you weren't going to do that, but I feel--so do you feel comfortable with my answer then? Thank you. I mean--

DR. GROSS: You can advise physicians there are billing codes for time they spend with a patient, which goes along with Art's comment.

Annette?

DR. STEMHAGEN: I just wanted to confirm,

in terms of the evaluation criteria, we're talking--I think you have Slides 45 and 46--about compliance and appropriateness. And very high percentages, everybody looks great. But my understanding is this is only based on that 36 percent. So we could be getting the best compliers because they're the people feeling motivated, I'm doing what I should and I'm going to tell you about it. So understanding all the limitations of survey research, I do it all the time, trying to urge that there be some other mechanisms put in place to evaluate it, to get a higher percent so we can really feel comforted by the percentages.

DR. METZ: You know, we put that program in place. That's the claims-based epidemiological research which was to look at that at the back end, if you will. But, unfortunately, that aspect of the program is dependent on patient uptake, and right now it's not providing any value.

DR. STEMHAGEN: Well, I'm not sure exactly--in terms of the claims database, there are patients' self-reported criteria for whether you

are the right candidate, and that's not going to be captured in the claims database. You'll have to go back to the records, and that may still not be captured unless the physician specifically asks those questions.

So while I agree it's another evaluation tool and I think it's an important one, I'm not sure it's going to get to all of these questions, either.

DR. METZ: You know, again, you're right. We have to make some qualitative assumptions about the generalizability of that cohort, you know, to all patients that are receiving Lotronex. And you heard Dr. Andrews speak to the kinds of things that we're looking at. But, you know, you can't say definitely, you know, these people are representative. We hope that they are, obviously.

DR. GROSS: Jackie?

DR. GARDNER: In 2002, when we met, one of the discussions was around whether to restrict prescribing to gastroenterologists, and I recall that the Chairman of the Gastroenterology Advisory

Committee, I think--I may be ascribing it incorrectly to him--said that won't work because some of us have taken our practice in some other directions--and I wanted to say liver disease or something that he said. And so that's why it wasn't restricted to gastroenterologists; therefore, an attestation program was set up with their concurrence because not every gastroenterologist knows guts and so on--

DR. METZ: Is going to look at IBS, right.

DR. GARDNER: Right, exactly. And some family practitioners really do.

I'm struck by the difference in this meeting and one we had a couple of months ago around Accutane, in which those prescribers also are severely restricted. They have the same kind of sit-down and sign things. They've got to do pregnancy tests. And we heard a lot about a lot of things at that time, but I didn't hear this kind of resistance to getting involved in these programs.

So my point is that FDA, with a risk management program that is at least as onerous as

this one, nonetheless, has somehow managed to find a way to make it more acceptable to the constituency such that, as you know, not only is Accutane tremendously prescribed, more even than we probably would want it to be, perhaps, but it also has four generics and yada, yada. I mean, it's not running into this prescribing limitation issue. And so I would suggest that you all look to models within FDA for ways to handle this attestation to make it--to eliminate this accessibility burden.

DR. METZ: And, again, we take the point on perhaps an additional educational focus. We do have a large educational program ongoing, and, again, that's another area where one could make modifications and see if you can get some incremental gain out of that. But that's a multifactorial problem. Let's face it. There are lot of things intersecting here that need to be addressed in a careful, prudent way. And I think that's what we're about here.

DR. GROSS: A special request from Stephanie for the last word.

DR. CRAWFORD: Thank you, Mr. Chairman. Actually, I was just asking for a word, not necessarily the last.

I would like to actually give you a kudo because I've read some of the press that appear today--that made it appear that the risk management program is negative before we had this meeting. I want to congratulate you on your risk management program for alosetron because many aspects of the program seem to be working.

From the information presented, one of the major concerns that this committee expressed two years ago was what appeared to be a very large, inappropriate prescribing. Without a question, that has gone down. I am not convinced that the low numbers of prescriptions of patients is due mainly to unreasonable barriers. It could be that it's being prescribed more appropriately and patients are making good, informed decisions. We don't know. I know all the discussion we've had from that.

That said, however, I am in favor of any

improvements to the existing programs. Specifically for me, I would be in favor of revising any language that would ensure that the patient agreement forms are clear and informative, and I will just leave it at that, and also possibly extending the supply, dispense. I don't want to discuss in terms of what you say, the refill phenomenon as much as I prefer that any changes be in terms of the day supply, because it's a huge difference if the physician prescribes a 30-day supply and you can refill it three times versus if he or she prescribes a 90-day supply that you're refilling three times. So think in terms of day supply, not refill, if there is any change to that.

Thank you, Mr. Chairman.

DR. GROSS: A pleasure, Ms. Vice Chairman.

[Laughter.]

DR. GROSS: We began the meeting and we'll end the meeting with a thank you to Brian Strom for his invaluable service to the committee. We really appreciate having you as a colleague over the last few years. Would you like to make any comments?

DR. STROM: Sure. Thank you. I guess I began with a comment, and it's only fitting I end with a comment.

I just wanted to follow up on a few loose ends and some comments that were made. One is I think compared to Accutane, and in response to Art's comment also, there's a big difference here in efficacy. And I think to blame it on the physicians and to say the physicians don't want to prescribe it--well, there may be a reason they don't want to prescribe it. That's something to keep in mind.

Second, I think the use of the claims databases make sense. I think it is striking that the proportion of users in the claims databases, given the population numbers we saw, is much lower than the proportion of the general population we're seeing. So what it's saying is our managed care organizations are saying don't use this, even more than the rest of the general public is.

Third, Curt talked about 36 percent and the concerns of 36 percent, and there was a lot of

argument about 36 percent. Personally, as an epidemiologist, I would consider that a shockingly low number. On the other hand, I think it's important to realize certainly no NIH grant would get funded with anything less than 80 or 90 percent. From a marketing study, it's high, but it's--I think we heard in the Accutane situation about numbers that were comparable. So I don't fault the survey, necessarily. I think in part it's the situation. But I think it's important that what that means is we're missing two-thirds of the people and we're missing, as Annette was saying, the two-thirds that are probably most likely to be the problem people. So we can't rely on those data because they're giving us biased information.

The same thing in underreporting. Clearly, there's vast underreporting, as you indicated. I don't blame the system because docs don't report, you know, exactly as you're saying. But what it does mean is the rates we're looking at here are much lower than the real rates that are

out there.

I want to emphasize again that part of the goal here is to create a barrier, and the barrier is working. And so the goal isn't to eliminate the barrier.

And I'll conclude with just a comment. I was one of those who was skeptical of the program two years ago. I think it's working. I mean, I am very encouraged in many ways by what we're seeing. I wouldn't want it changed in major ways. Until we have data on predictors of efficacy or predictors of adverse events, then I think it should be refocused accordingly.

DR. GROSS: I'd like to thank Glaxo and the FDA people for their presentations and input, and once again thank the Advisory Committee members and advisers for their comments. Thank you all. Have a good trip home.

[Whereupon, at 4:29 p.m., the meeting was adjourned.]

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