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EXHIBIT 12

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 Stenhagen, 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.

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P R O C E E D I N G S

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

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

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

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

20 MS. JAIN: Thank you.

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

DR. MANASSE: My name is Henri Manasse.

2 I'm chief executive officer and executive vice
3 president of the American Society of Health-System
4 Pharmacists, a membership organization that
5 represents about 32,000 pharmacists practicing in
6 hospitals and organized health systems.

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

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

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

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

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

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

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

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

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

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

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

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

Errors and Technical Support.

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

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

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

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

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

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

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

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

22 With respect to FDA's invited industry

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

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

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

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

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

11 Thank you.

12 x DR. SELIGMAN: Good morning. On behalf of

13 the Center for Drug Evaluation and Research, it is
14 my pleasure to welcome members of the Drug Safety
and Risk Management Advisory Committee and members
16 of the public to today's meeting. As always, we
17 greatly appreciate the time and efforts devoted by
18 the committee members and all participants in
19 providing advice to the FDA on important public
20 health issues.

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

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

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

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

the process reduce or eliminate medication errors.

2 Then later this afternoon, we will receive an
3 update on the Lotronex risk management program.

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

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

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

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

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

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

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

potential for medication errors.

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

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

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

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

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

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

containers. They include bronchodilators, such as
2 Albuterol, Ipratropium, Metaproterenol, and
3 Levalbuterol; also a mast cell stabilizer, cromolyn
4 sodium; an inhaled steroid, Budesonide; and an
5 antibiotic, Tobramycin.

6 These products are inhalation solutions,
7 or sometimes suspensions, that are intended for
8 oral inhalation using a nebulizer. One thing to
9 keep in mind is that the manufacturing processes
10 and materials for inhalation products are very
11 carefully controlled in order to maintain a very
12 high standard of product purity. That is, a
13 significant amount of attention is paid to the
14 manufacturing processes and the materials used so
15 that the content of contaminants is minimized.

16 This would include contaminants that arise during
17 the manufacturing processes, so-called process of
18 synthetic impurities; contaminants that arise due
19 to degradation of components of the formulation; or
20 the subject of today's concern, contaminants that
21 enter the formulation from the packaging materials,
22 so-called leachables.

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

7 These inhalation products are used by
8 patients with a variety of pulmonary disorders,
9 most commonly patients with asthma, COPD--which is
10 chronic obstructive pulmonary disease, a category
11 of lung disease comprised of chronic bronchitis and
12 emphysema--and cystic fibrosis. Although these
13 diseases are distinct, in general they are
14 characterized by fixed or variable obstruction to
15 airflow and a variety of patterns of histologic
16 abnormalities, including various patterns of airway
17 inflammation. In addition, asthma in particular is
18 associated with an underlying propensity for
19 allergic responses. And most of the diseases are
20 associated with a sensitivity to nonspecific
21 irritants which result in acute bronchospasm, a
22 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 bronchoconstriction and a delayed late-phase response characterized by airway inflammation and airflow

limitation.

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

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

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

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

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

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

the immediate packaging environment.

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

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

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

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

3 DR. GROSS: Thank you, Dr. Sullivan.

4 The next speaker will be Shah.

5 MS. JAIN: He is not here.

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

7 Dr. Marci Lee will now talk about

8 medication errors and low-density polyethylene
9 plastic vials.

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

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

22 Our error analysis included in your

background package was from 87 relevant reports.

2 These came from patients, caregivers, and
3 practitioners, such as respiratory therapists and
4 pharmacists, who reported to the programs listed.
5 These reports were received between January 1993
6 and August 2002. Many reports involved difficulty
7 reading embossed product containers. Some reports
8 were actual errors where the wrong medication or
9 the wrong dosage strengths were dispensed.
10 Although some of these were detected before the
11 medication was administered to the patient, some
12 were not. The outcomes of these reports ranged
13 from no harm to difficulty breathing, which can be
14 life-threatening. The remainder of the reports
15 described the potential for confusion and errors
16 with these products. Subsequently, as of April
17 2004, 51 additional relevant medication error
18 reports were identified for a total of 138 reports.

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

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

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

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

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

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

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

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

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

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

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

placement of this label.

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

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

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

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

8 One reason noted in our analysis for the
9 overwrap to be removed is an effort to fit the
10 products into a medication cart. The foil overwrap
11 and carton for many inhalation solutions use color
12 to differentiate the dosage strength. Most foil
13 overwraps contain multiple unit dose LDPE vials.
14 For example, the foil overwrap for Xopenex contains
15 12 vials.

Carol, if you'll pass the sample?

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

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

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

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

22 At this point we would like to stimulate

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

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

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

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

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

8 We have a sample of this also going
9 around.

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

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

the product.

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

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

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

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

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

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

still sources of volatile chemicals with the shrink
2 wrap approach.

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

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

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

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

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

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