POST-MARKETING SAFETY REVIEW
Division of Medication Errors and Technical Support
Office of Drug Safety
(DMETS; HFD-420)

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TO:

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THROUGH:

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PRODUCT NAMES: See Table 1 (Page 2)	**SPONSORS**: See Table 1 (Page 2)

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BRIEF SUMMARY: The Division of Medication Errors and Technical Support (DMETS) conducted a post-marketing review of medication error reports submitted to the Agency through the MedWatch Adverse Event Reporting Program and Drug Quality Reporting System (DQRS) with regard to the labeling and packaging of various drug products packaged in low-density polyethylene (LDPE) plastic vials.

DMETS RECOMMENDATION: Due to the challenging nature of the issues explored and described in this consultation, DMETS recommends a collaborated effort from the Office of New Drugs, Office of New Drug Chemistry, Office of Generic Drugs, DMETS, CBER and the pharmaceutical industry to identify potential solutions to these problems. Most importantly, DMETS acknowledges that practitioner/caregiver input is vital to the identification of solutions that will not create new problems for those who administer these medications. It may be beneficial to discuss the issues surrounding safe use of drug products in LDPE plastic vial containers in a public forum.

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Table 1. NAMES OF PRODUCTS AND SPONSORS

NDA # ANDA#	Division	Project Manager	Established Name	Proprietary Name	Dosage Strengths	Sponsor
19-773 19-269 19-243 73-533 75-358 75-050 72-652 75-063 74-543 75-343 75-394 74-880 75-664 75-129	HFD-570 HFD-615	Craig Ostroff H. Greenberg	Albuterol	Ventolin Proventil	0.083%, 0.5%	GlaxoSmithKline Schering Alpharma Bausch and Lomb Hi Tech Pharma Ivax Pharms Morton Grove Nephron Roxane
20-949	HFD-570	Craig Ostroff	Albuterol Sulfate	AccuNeb	0.021% 0.042%	Dey
20-950	HFD-570	Craig Ostroff	Albuterol and Ipratropium	DuoNeb	0.083%-0.017%	Dey
18-761 71-786 70-804 75-586 771-855 71-726 75-403	HFD-570 HFD-615	Sandy Barnes H.Greenberg	Metaproterenol Sulfate	Alupent	0.4%, 0.6%	Boehringer Ingelheim Dey Morton Grove Nephron Novex
20-228 75-111 75-693 75-835 74-755 75-313 75-562 75-441 75-867 75-507	HFD-570 HFD-615	Ladan Jafari H.Greenberg	Ipratropium Bromide	Atrovent	0.02%	Boehringer Ingelheim Alpharma Aslung Pharm Bausch and Lomb Dey Ivax Pharms Nephron Novex Roxane Warrick Pharms
20-929	HFD-570	Colette Jackson	Budesonide	Pulmicort Respules	0.25 mg/2 mL 0.5 mg/2 mL	Astra Zeneca
18-596 75-067 75-585 74-209 75-271 75-346 75-333 75-175 75-437 20-479	HFD-570 HFD-615 HFD-570	Colette Jackson H.Greenberg Colette Jackson	Cromolyn Sodium	Intal Gastrocrom	10 mg/mL 100 mg/5 mL	Aventis Pharms Alpharma Dey Ivax Pharms Morton Grove Novex Roxane Warrick Pharms Celltech Pharms
87-389 86-711 88-226 87-324 86-899	HFD-615	Harvey Greenberg	Isoetharine	None None None Beta-2 None None	0.1% 0.08% and 0.143% 1% 0.167% 0.2% 1%	Dey Intl Medication Nephron Roxane Roxane Roxane
20-837	HFD-570	Craig Ostroff	Levalbuterol	Xopenex	0.021% base and 0.042% base	Sepracor
20-533	HFD-170	Kimberly Compton	Ropivacaine	Naropin	2 mg/mL, 5 mg/mL, 7.5 mg/mL, 10 mg/mL	AstraZeneca
Pre-1938	HFD-615	Harvey Greenberg	Sodium Chloride	NONE		Various
50-753	HFD-520	Raquel Peat	Tobramycin	Tobi	300 mg/5 mL	Chiron
06-488	HFD-170	Kimberly Compton	Lidocaine HCl Injection USP	Xylocaine	1%, 1.5 %, 2%	AstraZeneca
Pre-1938	HFD-560	David Hilfiker	Racepinephrine	Racepinephrine	2.25% (0.5 mL unit of use vial)	Nephron (over-the-counter)
17-651	HFD-180	Diane Moore	Heparin	NONE	10 units/mL	APP
CBER	HFM-570	NA	Dornase alfa	Pulmozyme	1 mg/mL in 2.5 mL	Genentech

POST- MARKETING SAFETY REVIEW

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

DATE OF REVIEW: August 13, 2002

NDA/ANDA NUMBER: See Table 1

NAMES OF DRUGS: See Table 1

NDA/ANDA HOLDER: See Table 1

I. EXECUTIVE SUMMARY

The Division of Medication Errors and Technical Support (DMETS) identified safety concerns involving several drug products, packaged in low-density polyethylene (LDPE) plastic vials following receipt of 87 cases of medication errors through the FDA Adverse Event Reporting System (AERS), as well as the Drug Quality Reporting System (DQRS). In some cases, the patient received the wrong medication or the wrong strength of the medication. The outcomes of these errors ranged from "no patient harm" to "difficulty breathing". Since many of these medications are used to treat pulmonary conditions, there is potential for an error to result in life threatening respiratory complications. See Table 1 on page 2 for a complete list of the drug products identified in the medication error reports submitted to the AERS and DQRS reporting programs.

After careful analysis of the reports received, DMETS identified nomenclature, packaging or labeling issues that may be contributing to medication errors involving these products. This post-marketing safety consultation summarizes the error-prone characteristics of the various drug products that are packaged in LDPE plastic vials. In addition to medication error reports, DMETS also considered information provided by Nephron Pharmaceuticals, a letter from Senator Harkin, a Draft guidance for Industry document from FDA, a letter from the USP Safe Medication Use Expert Committee, and the medication safety literature.

Due to the challenging and complex nature of the issues explored and described in the review, DMETS recommends a collaborative effort from the Office of New Drugs, Office of New Drug Chemistry, Office of Generic Drugs, DMETS, CBER and the pharmaceutical industry to identify potential solutions to these problems. Most importantly, DMETS acknowledges that practitioner and caregiver input is vital to the identification of solutions that will not create new problems for those who administer these medications. It may be beneficial to discuss the issues surrounding safe use of drug products in LDPE plastic vial containers in a public forum. DMETS recommends that members of the groups listed above meet to identify ways to ensure that the outer (secondary) labeling and the primary container label are readable for all products packaged in LDPE vials.

II. BACKGROUND

The Division of Medication Errors and Technical Support (DMETS) conducts monthly post-marketing meetings consisting of a panel of safety evaluators who review medication error reports submitted to MedWatch, the FDA Safety Information and Adverse Event Reporting Program. After review of these reports, DMETS conducted a search for additional reports in the Adverse Event Reporting System (AERS) database, as well as the Drug Quality Reporting System (DQRS) database. After careful analysis of the reports, DMETS identified safety concerns related to the labeling and packaging of various drug products in LDPE plastic vials. In addition to the analysis of the medication error reports, DMETS also considered information provided by Nephron Pharmaceuticals, a letter from Senator Harkin, a Draft guidance for Industry document from FDA, a letter from the USP Safe Medication Use Expert Committee, and the medication safety literature as outlined below.

A. Information from Nephron Pharmaceuticals

Between February 28, 2002 and October 2, 2002, Nephron Pharmaceuticals submitted data to the United States Pharmacopeia (USP) in response to safety concerns with the LDPE plastic vial containers. The submissions were sent in response to several customer complaints about the readability of the medication container label information. The products specifically addressed in the submissions were IPRATROPIUM BROMIDE Inhalation Solution 0.02% and ALBUTEROL SULFATE Inhalation Solution. In response to the customer complaints, Nephron decided to manufacture individual foil pouches for each plastic vial. In March 2002, Nephron indicated that the individually packaged ALBUTEROL SULFATE Inhalation Solution 0.083% (NDC 00487-9501-01) and IPRATROPIUM BROMIDE Inhalation Solution 0.02% (NDC 00487-9901-01) vials would be available later this year. Nephron states that the ALBUTEROL SULFATE Inhalation Solution 0.5% was recently approved in an individually foil pouched unit-of-use (0.5 mL) container. (See Figure 1) Nephron also states that they have expanded this concept to provide individually pouched vials for <u>all</u> of Nephron's sterile unit-dose or unit-of-use products.

Figure 1. Individual pouches proposed by Nephron

B. Congressional Inquiry

On May 22, 2002, Dr. Lester Crawford received a letter from Senator Tom Harkin. This letter was in regard to a concern over the FDA policy on medication labeling. Specifically, the products of concern were IPRATROPIUM BROMIDE 0.02% and ALBUTEROL SULFATE 0.083%. Both products are packaged by Automatic Liquid Packaging for Alpharma Inc. One of the Senator's constituents wrote a letter to him with several questions to determine why the "different colored labels" are no longer used on the plastic vials. In addition, the letter describes the "raised letters" as "hard to read". The author also notes that customers in an older age segment will likely have difficulty reading the plastic vials that have the raised letters instead of the colored labels. Finally, there is a request to "reconsider putting easily readable labels on these liquid packaging medicines again."

The materials from Senator Harkin also include a letter from Alpharma Inc. This letter describes the reasons for the design of this package. The letter includes statements regarding the need for sterile products, foil wrappers to protect the drug product from light and prevent medication errors, an embossed product name, lot number and expiration date to make this information "always present and legible". "The raised letters that are part of the vial can never become smeared or defaced through normal handling or wetting." In addition, Alpharma states that these letters serve as a textured surface to assist in gripping the vial when opening by twisting off the top.

C. Draft guidance document

On July 26, 2002, a *Federal Register* notice announced the availability of a draft guidance for industry entitled, "Inhalation Drug Products Packaged in Semipermeable Container Closure Systems." http://www.fda.gov/cder/guidance/4168dft.pdf This draft guidance provides recommendations on: (1) Appropriate protective secondary packaging, (2) embossing and/or debossing of the primary container in lieu of paper labels, and (3) general guidance on the number of unit-dose containers to be contained within each protective secondary package. The guidance identifies potential sources of chemical contamination for inhalation drug products in LDPE plastic vials. The FDA recommendation for labeling is to directly emboss the information on the plastic vial to prevent contamination by components found in paper labels (e.g., adhesives, varnish, ink). A secondary package is also recommended to protect the drug product from environmental contaminants. The guidance states that the ideal approach for the secondary package is to individually wrap each container.

D. USP Safe Medication Use Expert Committee (SMU EC)

On October 28, 2002, Yana Ruth Mille, Chief, FDA Compendial Operations Staff, received a letter from the USP Safe Medication Use Expert Committee (SMU EC). This letter was in regard to a continuing concern of the Committee and also healthcare practitioners regarding the inability to identify drug products in plastic ampuls that is secondary to inadequate labeling. The letter describes practitioner reports submitted to the USP Medication Errors Reporting Program that identify embossed imprinting as being difficult to read and sometimes illegible. The author states that the SMU EC unanimously voted to encourage FDA to establish an alternate method of labeling these plastic ampuls, so that these products are clearly identifiable. Since the use of plastic ampuls with difficult-to-read or illegible labeling continues to be the subject of numerous medication errors. The SMU EC recommends that the FDA cease approving these products in these containers, until a suitable resolution is identified.

E. Product Information for drug products that are packaged in LDPE vials (See Table 2.)

Table 2. PRODUCT INFORMATION TABLE

Product Name	**Established name** **Dosage form** **(ORAL, INHALATION OR INJECTION)** **Dosage strengths**	**Usual dose**
Ventolin Proventil	Albuterol Sulfate Inhalation Solution 0.083%, 0.5%	ADULT: 2.5 mg 3 to 4 times daily by nebulization PEDS 2 to 12 years: 2.5 mg 3 to 4 times daily by nebulization. Children less than 15 kg who require less than 2.5 mg/dose should use the 0.5% inhalation solution. Deliver over 5 to 15 minutes.
AccuNeb	Albuterol Sulfate Inhalation Solution 0.021%, 0.042%	PEDS 2 to 12 years: 1.25 mg or 0.63 mg administered 3 or 4 times daily as needed by nebulization. Deliver over 5 to 15 minutes.
DuoNeb	Albuterol Sulfate and Ipratropium Bromide Inhalation Solution 0.083% - 0.017%	One 3 mL vial administered four times daily via nebulization with up to two additional 3 mL doses allowed per day.
Alupent	Metaproterenol Sulfate Inhalation Solution 0.4%, 0.6%	Administer the unit-dose vial by oral inhalation using an intermittent positive pressure breathing (IPPB) device. ADULTS: 0.2 mL to 0.3 mL (or 5 to 15 inhalations via a hand bulb nebulizer) PEDS 6 to 12 years: 0.1 mL to 0.2 mL
Atrovent	Ipratropium Bromide Inhalation Solution 0.02%	500 mcg (1 unit dose vial) administered 3 to 4 times daily by oral nebulization, with doses 6 to 8 hours apart.
Pulmicort Respules	Budesonide Inhalation Suspension 0.25 mg/2 mL 0.5 mg /2 mL	PEDS 12 months to 8 years: 0.5 mg once or twice daily OR 1 mg once daily.
Intal ********** Gastrocrom	Cromolyn Sodium Inhalation Solution 10 mg/mL ********** **Oral Concentrate** 5 mL/100 mg	ADULTS AND PEDS over 2 years: 20 mg inhaled 4 times daily at regular intervals. Hand operated nebulizers are not suitable. [Gastrocrom Dosing]********** ADULTS: 200 mg by mouth 4 times daily; Do NOT mix with milk, juice or food. PEDS 0 to 2 years: 20 mg/kg/day PO divided QID PEDS 2 to 12 years: 100 mg PO QID; MAX DOSE is 40 mg/kg/day; PEDS over 12 years: 200 mg PO QID; Do NOT mix with milk, juice of food.
None	Isoetharine Inhalation Solution 0.1%, 0.08%, 0.143%, 1%, 0.167%, 0.2%	Hand bulb: 4 inhalations Oxygen aerosolization: 0.5 mL IPPB: 0.5 mL
Xopenex	Levalbuterol Inhalation Solution 0.021%, 0.042%	PEDS 6 to 11 years: 0.31 mg administered 3 times daily by nebulization; do not exceed 0.63 mg 3 times daily. ADULTS and PEDS 12 years or older: 0.63 mg administered 3 times daily by nebulization; Once foil pouch is opened, use the vials within 2 weeks; Once the vial is removed from the foil pouch and is not used immediately, protect from light and use within one week. Discard if solution is not colorless.
Xylocaine	Lidocaine Hydrochloride **Injection** 1%, 1.5%, 2%	Dose depends on the indication for use. The maximum recommended dose per 90 minute period of lidocaine for paracervical block in obstetrical and nonobstetrical patients is 200 mg total. One half of the dose is usually administered to each side. Inject slowly 5 minutes between sides.

Product Name	Established name Dosage form (ORAL, INHALATION OR INJECTION) Dosage strengths	Usual dose
Naropin	Ropivacaine **Solution for Injection** 2 mg/mL, 5 mg/mL, 7.5 mg/mL and 10 mg/mL	Dose depends on the indication for use. For surgical anesthesia, the dose ranges from 5 mg – 300 mg. For labor pain management, the dose ranges from 20 mg – 40 mg initially followed by 12-30 mg/h (continuous infusion or incremental injections). For postoperative pain management, the dose ranges from 12 – 28 mg/h as a continuous infusion.
Tobi	Tobramycin Inhalation Solution 300 mg/5 mL	ADULTS and PEDS 6 years and older: 300 mg twice daily in repeating cycles of 28 days ON and 28 days OFF. Doses should be 12 hours apart. Administer over 10 – 15 minutes
Pulmozyme	Dornase alfa Inhalation Solution 1 mg/mL in 2.5 mL	One 2.5 mg single-use ampule inhaled once daily using a recommended nebulizer. Some patients benefit from twice daily administration. Pulmozyme should not be mixed with other drugs in the nebulizer.
None	Heparin **Solution for Injection** 10 units/mL in 5 mL	IV flush to maintain patency of indwelling IV catheter in intermittent IV therapy or blood sampling; not intended for therapeutic use.

III. ROOT CAUSE ANALYSIS

This safety review focuses on the medication error reports submitted to FDA with regard to drug products packaged in LDPE plastic vials. DMETS will identify ways in which the manufacturers can minimize the risk potential and decrease the medication errors associated with these products.

Several issues have already been raised by the draft guidance, the letter from Senator Harkin and his constituent, the USP Safe Medication Use Expert Committee and the Nephron Pharmaceuticals Corporation. Some of these issues include the need for sterile drug containers, the risk for contamination of the drug product and the need for protective secondary packaging. In addition, some users of these products identified the readability of the embossed label on the LDPE plastic vial container as difficult and problematic.

A. Adverse Event Reporting System

DMETS searched the FDA Adverse Event Reporting System (AERS) database for all post-marketing safety reports of medication errors reported for "tobi", "albuterol", "naropin", "pulmicort", "duoneb", "ipratropium", "xopenex", "gastrocrom" "xylocaine", "heparin" "pulmozyme" "cromolyn", "atrovent", "intal", "levalbuterol" using the Meddra Preferred Term, MEDICATION ERROR. This search strategy retrieved 60 pertinent cases of medication error. The error cases are summarized in Appendix A.

Of the 60 medication errors reported on these drug products, a total of 13 (22%) **actual** errors were identified. The **actual** errors included those in which the wrong medication or wrong dosage strength was administered to the patient (46%) and those that were detected prior to medication administration to the patient (54%). A total of 47 (78%) **potential** medication errors were reported citing concerns for difficult-to-read label information and look-alike packaging for the drug products packaged in plastic vials.

B. DQRS

In addition, the Drug Quality Reporting System (DQRS) database was searched for similar reports with “albuterol”, "alupent ", "atrovent", “duoneb ", "ipratropium ", "proventil ", "pulmicort", "sodium chloride ", "ventolin", and “xopenex”. A total of twenty-seven pertinent medication error reports were retrieved with this search and are summarized in Appendix B.

Of the 27 medication error reports, all but one were **potential** medication error reports citing concerns regarding the labeling and packaging of the drug products.

C. Safety Evaluator Risk Assessment

DMETS has identified several additional concerns for inhalation and injectable solutions packaged in LDPE vials. These concerns are based upon careful analysis of the medication error reports summarized in APPENDIX A (AERS Reports) and APPENDIX B (DQRS Reports).

1. Difficult-to-Read Labels and Look-alike Packaging among Inhalation Solution Products

Although the use of embossed label information addresses the concern for drug product contamination by the volatile components of the paper label, it also creates an opportunity for medication errors. The fact that these vials are difficult to read is likely a contributing factor in almost every medication error reported to FDA. This is a concern that has been voiced by numerous practitioners, patients and caregivers.

See the excerpts below that describe the readability of the embossed label information from some of the medication error reports:

> “…raised lettering in clear plastic…very difficult to see clearly the name of the drug, the product ingredients, the lot numbers, and the expiration date. While the foil pouch is clearly marked, we have noted the practice of opening the pouch, taking the vials out and then discarding the pouch. The result is loose vials that are not clearly marked.”
>
> “The raised lettering on the clear plastic container…makes it difficult to read the name of the product and the ingredients.”
>
> “..both in clear containers with raised lettering making it difficult to read the name of the drug.”
>
> “…they have to be angled just right in the light to read it.”
>
> “Label on individual vials is almost impossible to read in most light. This is an embossed label…”
>
> “…the product identification can be very difficult due to the low visual contrast between the label and container.”
>
> “None of the information on the vial is legible, imprinted clear on clear.”

The letter from the USP SMU EC states, “This imprinting is perceived by healthcare practitioners reporting to the USP Medication Errors Reporting Program as being difficult to read and sometimes illegible.”

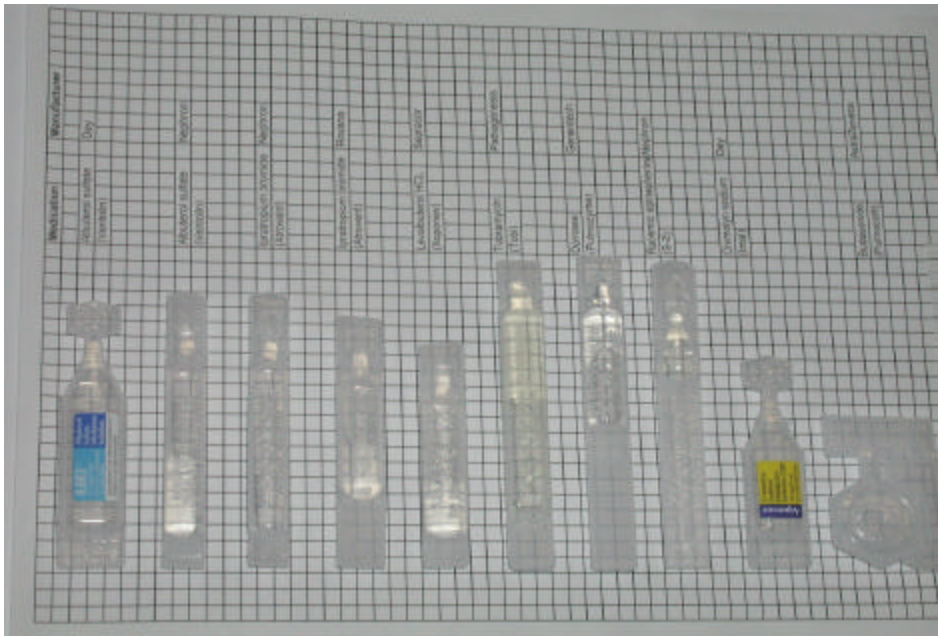


Photo submitted with ISR # 3895532-9

2. Difficult-to-Read Labels and Look-alike Packaging for Oral and Injectable Products and Potential for Confusion with Nebulizer Medications

   A. In addition to the multitude of inhalation solutions, there is an oral drug product that is packaged in LDPE plastic vials. Gastrocrom was identified as having packaging similar to Xopenex. In one medication error report of ACTUAL confusion, an error occurred when someone was returning unused medications from the patient care area to the pharmacy stock.

   B. A new concern identified is the potential for confusion between the inhalation drug product with several <u>injectable</u> solutions now available in plastic ampules. Multiple medication error reports warned of potential for confusion with injectable medications packaged in similar plastic vial containers. The main concerns expressed were the readability of the labels on the PolyAmp DuoFit containers and the potential for confusion with inhalation solution products. Although the label information is not embossed on the Naropin containers, it appears as black type on a clear label affixed to the plastic ampul. Additionally, the POLYAMP DUOFIT plastic ampules are made of <u>polypropylene</u>.

      See the excerpts below from a medication error reports that describe safety concerns for the PolyAmp packaging:

      > “Astra Zeneca is ceasing to manufacture their glass vials of **Naropin** (Ropivacaine) and some **Xylocaine** (mainly the MPF). They have created a POLYAMP, a plastic ampule to which a syringe can be directly luer locked...In addition, the smaller amps could possibly be mistaken for <u>nebulizer meds</u> that come in similar containers (they look like the ‘pillows’).” [See page 10 for product photos.]

"We have noted an issue with the new polyamp packaging by AstraZeneca for Xylocaine-MPF 2% and Naropin 10 mg/mL. Both containers are identical in size, shape, clear color, and black writing once removed from their overwrap packaging. Our LDRP noticed the potential medication error on their epidural cart when the medications were removed from their original packaging so that they would fit in the cart."

Figure 2. Naropin and Xylocaine POLYAMP DUOFIT

C. In addition to Naropin and Xylocaine, there is also a **Heparin** 10 units/mL (5 mL) product available from American Pharmaceutical Partners, Inc. (APP), which is packaged in a plastic vial container. See Figure 3.

See the excerpt below from a medication error report that describes a safety concern for a heparin product packaged in a plastic ampule:

"Are you aware that APP is marketing a **heparin** 10 units/mL (5 mL) plastic container? One of their reps showing it to me last week. I showed him all of the respiratory medications and the poor labeling. He was also surprised. The clincher is that their heparin product is almost identical to the tobramycin for inhalation product, **Tobi**."

Figure 3. Heparin 10 units/mL (5 mL)

3. Routine Handling of the Inhalation Solutions

Another issue to consider is the routine handling of the LDPE vials containing inhalation solutions. While Nephron addresses this issue in their materials by stating, "We note that in prior complaints the end user bypassed this important packaging step by allowing respiratory therapists to routinely carry loose vials in their lab coats. Under such conditions, the manufacturer is not responsible for product contamination or misuse if the product was not retained in its intended package."

DMETS sees this as an opportunity for the industry to respond to the needs of the users of their products. Perhaps a foil pouch containing 30 vials is not the packaging configuration that best meets the needs of the practitioners and caregivers that administer these medications. Nephron has also proposed the individual foil pouch for individual vials of their medications. The best way to determine if this is a viable solution to the problem is to involve the practitioners and caregivers and incorporate their input into the problem-solving process. Additionally, the medication error reports demonstrate that the labels on the foil pouches containing 30 vials are not enough to prevent errors. As this is the current package configuration for most products and errors are still occurring.

DMETS acknowledges that while the proposal for an individually foil wrap plastic ampule is likely a step in the right direction to improve the safe use of these drug products, this proposal does not address the problem of what happens when the plastic ampules are removed from the foil. Even if the plastic ampules are individually foil-wrapped, there is still going to be the problem of unused, loosely stored plastic ampules that are difficult to read and error-prone.

See the excerpts below from some of the medication error reports that describe safety concerns with the vials that are no longer in the foil pouch:

> "While the foil pouch is clearly marked, we have noted the practice of opening the pouch, taking the vials out and then discarding the pouch. The result is loose vials that are not clearly marked."

> "The fact that the vials are packaged in clearly marked foil packages does not compensate for the poorly marked vials because the usual practice is take the vials from the packaging and throw away the foil wrapper."

"There is also a problem with the product being light sensitive. It comes in a foil pouch and then any product not used after two weeks is to be discarded. Why is the product not in an opaque container to begin with to eliminate the light sensitivity? The warning to discard discolored is not on the individual container, and even if it were it couldn't be read. The reporter considers this product to be poorly designed, poorly labeled, and dangerous."

"It is easy to administer one strength for another when both strengths are kept in a respiratory therapists pocket."

"Our respiratory therapists often carry individual unit dose containers in their pockets without the outside packaging."

4. Expiration Date Issue

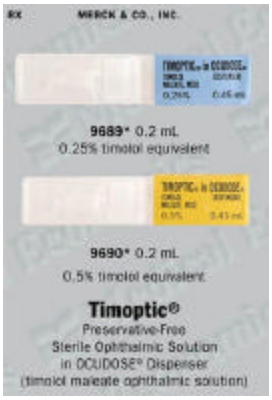
Another aspect of the problem with difficult to read container labels is that the expiration date is difficult to see. This places a burden on practitioners, who are trying to identify expired medications in their inventory.

See the excerpt below from medication error reports that describe the safety concerns with the readability of the label information, especially the expiration date:

"The plastic vials are impressed on one end with the lot number and expiration date on opposite sides. Due to the vial composition of clear plastic, it is difficult to distinguish what the expiration date and lot number are."

"The result is difficulty in confirming the name of the drug, the strength of the ingredients, and the expiration dating."

"…very difficult to see clearly the name of the drug, the product ingredients, the lot numbers, and the expiration date."



DMETS recommends that manufacturers consider alternative packaging configurations for the drug products that are currently available in LDPE plastic vials. One recommendation might be to consider something similar to the Timoptic OCUDOSE design below. (See Figure 4.) These container labels are similar to the paper labels used by some manufacturers. They are easier to see than the embossed labels and can use color to facilitate product differentiation.

Figure 4. Timoptic OCUDOSE

DMETS acknowledges that there are several factors that may contribute to the medication errors we see with the drug products packaged in LDPE plastic vial containers. Some of these factors include practitioners with poor eyesight, poor lighting conditions in the settings where these medications are administered, storage issues, and so on. However, there is room for improvement in the packaging of these products that would minimize the potential for error. By modifying the current practices of packaging and labeling the LDPE vials, the industry will relieve the practitioners and care-givers of the burden of relying only on their vigilance to prevent medication errors with these drug products.

Although we have identified many contributing factors to the errors described in the medication error reports sent to FDA, many of the errors go undetected and unreported. This is especially true for the inhalation solutions because it is common to administer more than one of these products to a single patient. For example, if a patient is to receive ipratropium and albuterol via nebulization, an error by which the patient receives albuterol two times in error and no ipratropium could go undetected because of the mechanism of action of these drugs. Even in this error scenario, the patient's breathing would improve and the treatment would be considered a success.

Several options for possible solutions to the problems facing our health care community have been proposed by different sources, such as the individual foil wrappers for each vial proposed by Nephron. DMETS believes we should consider changing the container material to something that is not permeable or use the texture and shape of the plastic vials to differentiate them. Another proposal submitted with a medication error report by a practitioner was to assign a universal color plastic for each inhalation solution to ensure that the vials do not look alike. Due to the complexity of this issue, these and other potential solutions to this problem need to be evaluated by OND, ONDC, OGD, CBER and the industry, while taking into consideration the input from the practitioners and caregivers that use these products.

IV. RECOMMENDATIONS

A. The recommendations should come from a collaborative effort of the Office of New Drugs, Office of New Drug Chemistry, Office of Generic Drugs, DMETS, CBER and the pharmaceutical industry.

B. Practitioner and caregiver input is vital to the identification of solutions that will not create new problems for those who administer these medications.

C. It may be beneficial to discuss the issues surrounding safe use of drug products in LDPE plastic vial containers in a public forum.

D. Ensure that the outer (secondary) labeling and the primary container label are readable for all products packaged in LDPE vials.

DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

_____
Marci Lee, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support (DMETS)

Concur:

_____
Denise Toyer, PharmD Date
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

cc: ANDA See Table 1
HFD-615: Division Files/Harvey Greenberg, Project Manager
HFD-611: Peter Rickman, Division Director

cc: NDA See Table 1
HFD-170: Division Files/Kimberly Compton, Project Manager
HFD-570: Division Files/Craig Ostroff, Project Manager
HFD-570: Division Files/Parinda Jani, Project Manager
HFD-570: Division Files/Colette Jackson, Project Manager
HFD-570: Division Files/Ladan Jafari, Project Manager
HFD-570; Sandy Barnes, Chief Project Manager
HFM-224: Ann Gaines, Safety Evaluator

HFD-170: Bob Rappaport, Acting Division Director
HFD-570: Badrul Chowdry, Division Director
HFD-570: Guirag Poochikian
HFM-570: Karen Weiss, Division Director, DCTDA, CBER
HFD-330: Kathy Miracco, Office of Compliance
HFD-006: Anne Henig, OEP, CDER

HFD-420: Denise Toyer, Team Leader, DMETS
HFD-420: Sammie Beam, Project Manager, DMETS
HFD-420: Marci Lee, Safety Evaluator, DMETS
HFD-420: Carol Holquist, Deputy Director, DMETS

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APPENDIX A

Post-Marketing Reports involving low density polyethylene (LDPE) ampuls from the AERS database

ISR NUMBER EVENT DATE LOCATION ACTUAL OR POTENTIAL OUTCOME	Summary
3855426 FEB 2002 Unknown location Potential error	As you know, several of the respiratory medications available have similar, if not duplicative packaging. With the addition of **DuoNeb** to this group, we have yet another item to add to the category. I understand that the FDA has a lot to do with this by disallowing inks directly on the packaging and other stability requirements. We currently do not add any ancillary labeling – more steps in the process just adds more opportunities for error. Fortunately for us, most of these respiratory drugs (dispensed from Pharmacy) are given by the therapists, who can be alerted with relative ease.
3815572-5 SEPT 28, 2001 Potential error	The packaging for the inhalation product, DuoNeb, is difficult to read and there exists the risk of error in using the drug. **DuoNeb** consists of 3 mL inhalant solution (ipratropium and albuterol) packaged in a clear plastic vial, with several vials in a foil pouch. The pouch is clearly labeled DuoNeb with the ingredients, lot numbers, dating and other information. The problem occurs when the clear vials are removed from the packaging. The vials are clear plastic, containing clear solution. The lettering on the vials is not printed, but is raised lettering in clear plastic. This makes it very difficult to see clearly the name of the drug, the product ingredients, the lot numbers, and the expiration date. While the foil pouch is clearly marked, we have noted the practice of opening the pouch, taking the vials out and then discarding the pouch. The result is loose vials that are not clearly marked. In addition, the labeling on the foil package shows the albuterol sulfate content to be 3.0 mg. The small print makes the strength appear to be 30 mg. The practice of adding trailing zeroes to the strength of drugs is commonly implicated in medication errors. We feel that this type of packaging and labeling may lead to medication errors if the wrong vial is picked up.
3786947-8 Report date AUG 23, 2001 Unknown location Potential error	The raised lettering on the clear plastic container of **DuoNeb** makes it difficult to read the name of the product and the ingredients. If you do not look closely, you might not notice that DuoNeb contains Ipratropium Bromide and Albuterol Sulfate.

3794775-2 Report date SEPT 7, 2001 Potential error	Potential for error regarding the respiratory care unit dose medications Albuterol and **Cromolyn** (manufactured for Alpharma), **Pulmicort** Respules (Astra), and **Pulmozyme** (Genentech). These products are packaged in clear plastic single-use ampules whose labeling (on each ampule) is terrible. The letters are raised on the plastic container, but not in a different color. The letters are the same material as the plastic container. I have had many respiratory care therapists complain of this, concerned that a wrong dose or wrong medication will be administered to the patient. What were they thinking?
3786946-6 Report date AUG 29, 2001 Unknown location Potential error	The packaging of **Ipratropium** Bromide 0.02% 0.5 mg/2.5 mL (Alpharma) and Albuterol 0.083% 2.5 mg/3 mL (Alpharma) is similar. Also, both are in clear containers with raised lettering making it difficult to read the name of the drug. Suggestion: Attach a label to the container or add some color. The pharmacy is considering purchasing a different product at an additional cost because of packaging concern.
3869036-3 Report date FEB 12, 2002 Potential error	The packaging of some nebulizer solutions are very difficult to read. **Xopenex** and generic **Albuterol** (Alpharma) are in clear plastic ampules. The companies label the products by using raised lettering in the plastic. Besides the fact that one product looks like another, they have to be angled just right in the light to read it.
3469147 Report date MAR 5, 2000 Potential error	Similar packaging of Roxane's **ipratropium** premix unit dose amps and Alpharma's **albuterol** premix unit dose amps
3613218-2 and 3565542-X and DQRS M-129611 Report date SEPT 7, 2000 Actual error Patient survived	My mom has emphysema and has had severe difficulty breathing for 3-4 days. She hasn't been able to sleep or eat as her breathing was so difficult. I had been in constant contact with her doctor and my mother had said she needed to go to the hospital that her Nebulizer wasn't even helping. The problem turned out to be a severe mix-up with her nebulizer medications. Medicare has supplied Albuterol and ipratropium solution by mail to my mother for over a year. Recently Medicare has changed the drug supplier from Dey to Zenith Goldline and has changed the packaging of the vials. What she has always used was a clearly marked vial of **ipratropium** with green and purple label and a clear vial of **Albuterol**. With the new packaging – the ipratropium also comes in a clear vial. What has been happening is she has been getting the clearly marked old ipratropium and another clear vial but this vial was also ipratropium. If I hadn't caught this mistake I doubt my mother would be alive!!!!! This is a very SERIOUS PROBLEM!! We are talking about elderly people and also caregivers mixing these two meds and they should be advised of this change. Also, the clear vials are VERY difficult to read!! These two meds come premixed but we didn't know that until I called the company that provides the meds. Please help before someone dies from this change in packaging. Please help to see that these clear vials are better marked so they are easily identified. Thank you.

3778267-2 Report date AUG 14, 2001 Potential error	The product is **DuoNeb**, an inhalation solution of ipratropium and albuterol sulfate. The inhalation solution is packaged in "Sterile Unit Dose Vials" that are plastic. The problem is that the vials are clear plastic, the solution is clear, and the printing on the vials is not printing, but raised lettering in clear plastic. The clear plastic makes the lettering difficult to read. The result is difficulty in confirming the name of the drug, the strength of the ingredients, and the expiration dating. The fact that the vials are packaged in clearly marked foil packages does not compensate for the poorly marked vials because the usual practice is take the vials from the packaging and throw away the foil wrapper.
3771756-6 Report date AUG 1, 2001 Potential error	I would like to report that the labeling of **Xopenex** (levalbuterol) inhalation solution unit dose vials made by Sepracor Inc, Marlborough, MA 01752 USA provide an opportunity for medication errors due to their appearance. Both strengths 1.25 mg in 3 mL and 0.63 mg in 3 mL are manufactured in the same color and size container. Additionally, the medication and dose information is very difficult to read since it is embossed on a clear plastic. This is provided for your review. Please consider requiring a labeling change. Thanks.
3456491-6 Report date JAN 27, 2000 Potential error	A respiratory therapist brought this concern to the attention of the pharmacy. The inhalation solutions, **Ipratropium** Bromide 0.02% (Roxane), **Cromolyn** Sodium 20mg/2 mL (Arcola Labs), and **Xopenex** 0.63 mg/3 mL (Sepracor) unit-dose vials look almost identical to each other and the labels on the vials are difficult to read.
3569194-4 JUN 29, 2000 Unknown location Actual error Patient survived.	Healthcare provider entered prescription for **Intal** nebulization solution. It was filled with **Atrovent** nebulization solution and dispensed to the patient. Filling pharmacist realized error later in day and called patient at home. Prescription returned for correction. Patient was 5 years old.
3836346-5 Report date NOV 28, 2001 Unknown location Potential error	Three different medications are supplied in very similar unit dose vials. This greatly increases the chance of delivering the wrong medication to the patient, which could adversely effect clinical course. They look almost identical. **Cromolyn**, **Ipratropium**, and **Levalbuterol**. (Alpharma, Roxane, and Sepracor)
3838040-3 Report date DEC 10, 2001 Potential error	Alpharma **Ipratropium** Bromide inhalation solution 0.02% unit dose vial is identical in shape and size to Sepracor **Xopenex** (levalbuterol HCl) inhalation solution 1.25 mg/3 mL and 0.63 mg/3 mL. There is no color difference and no paper label on the unit dose vials potentially leading to drug administration errors.
3825538-7 JAN 29, 2001 Unknown location Actual error Patient survived	Doctor called in a prescription to the pharmacy and the intern tried to take it over the phone, but did not understand the doctor. I took over and received the prescription. The intern was confused. The prescription was typed into the computer as ipratropium instead of Intal (cromolyn), then the prescription was filled, but was not properly checked before dispensing to the patient's parent. Both the **ipratropium** 0.02% (Alpharma) and **cromolyn** 20 mg/2 mL (Alpharma) nebulizer solution boxes looked similar. Thus, it is hypothesized that the medication was picked before the prescription was typed in and it could have been typed based on the wrong medication selected. Patient was 2 years old. The doctor discovered the error after calling the parent's to follow up the day after the office visit.

3825509-0 Report date OCT 31, 2001 Potential error	The reporter may have not had an incident but they see a potential for errors with the product **Xopenex** (levalbuterol HCl) by Sepracor. They produce two strengths of the medication in unit dose packages. The unit packs look the same, the difference in dose is stamped on the vial, but it is the same color as the rest of the package. You have to look very hard in good light to note the difference.
3786966-1 Report date AUG 24, 2001 Potential error	This potential error was reported to me by the respiratory staff. We recently switched companies that supply respiratory product due to a contract change. The **ipratropium** bromide inhalation solution 0.02% 2.5 mL unit dose vials distributed by Alpharma (00472-0751-23) look identical to **Xopenex** inhalation solution unit dose vials (63402-0513-34). Both vials are opaque with raised lettered no color writing. They are very hard to read even when there was not a similar product. The respiratory staff is afraid that they will accidentally be substituted.
3803901-8 and 3692545-7 Report date MAR 30, 2001 Potential error	**Xopenex** 1.25 mg/3 mL and 0.63 mg/3 mL. Difficult to read imprint on unit dose packages – possibility of giving incorrect dosage. Suggest color coding or change labeling in both individual unit dose vials.
3805475-4 Report date SEPT 27, 2001 Potential error	I would like to report another two look alike respiratory drugs to the ISMP. **Ipratropium** Br 0.02% 2.5 mL inh soln and Levalbuterol HCl (**Xopenex**) 1.25 mg/3 mL inh soln. Both drugs are packaged in similar clear, plastic containers.
3728008-X Report date MAY 22, 2001 Potential error	**Xopenex** is packed in clear plastic tubes. The strength is on one end but difficult to read. It is easy to administer one strength for another when both strengths are kept in a respiratory therapists pocket.
3698827-7 MAR 12, 2001 Actual error Did not reach patient	Prior to administration of a dose of **Xopenex**, a physician noticed that the respiratory therapist had mistakenly opened the wrong strength of medication. By inspecting the unit dose package, the physician prevented the error. The error almost occurred because the two product strengths are virtually identical in appearance, the only significant difference being “0.63” embossed on one vial and “1.25” embossed on the other. Both packages are already difficult to read, being clear plastic with raised lettering. The potential exists to give 50% or 200% of the prescribed dose. Suggestion to prevent similar errors: The medication require different packaging and/or labeling. Printing the name and strength of the medication in color would be most useful. A consideration to prevent potential errors in the future is to remove the medication from the hospital formulary, since safe and effective alternatives exist.
3689503-5 Report date MAR 13, 2001 Potential error	The respiratory therapist at our hospital sees a potential error caused by packaging of the drug **Xopenex** (lebalbuterol, Sepracor) in the 1.25 mg and 0.63 mg unit dose vial. While outer wrappers (box and inner foil wrapper) of two strengths of the drug differ in appearance, the vials themselves are distinguishable only upon very careful examination of the labels. We feel the manufacturer should create vials of different strengths that are more readily seen as different. Any help you could give us to this end would be appreciated.
3683478 Report date	The product is packaged in a clear plastic container. There is no label on the container; the product information is imprinted on the plastic

MAR 5, 2001 Potential error	on the container; the product information is imprinted on the plastic, which is difficult to read. Fortunately this has not been either a potential or actual occurrence. However, I receive a number of phone messages from respiratory therapists and pulmonologists on staff regarding the labeling of the **Xopenex** (levalbuterol) jets. Any efforts you can utilize to encourage the manufacturer to change its labeling habits would be most appreciated.
3603388-4 MAY 11, 2000 Unknown location Actual error Patient did not use.	Patient received 1.25 mg/3 mL instead of 0.63 mg/3 mL **Xopenex**. The error was detected by the patient's mother, who returned the medication before administering a dose to her child. This product is very new to market. There is an error that when the labeling process, the NDC come out on label without name of product. The pharmacist who fills this RX did (not) know this medicine come out in two strengths, that she didn't check the NDC number is why the error occurs.
3641106-4 Report date JAN 3, 2001 Potential error	Possible confusion with (**Xopenex**) levalbuterol 1.25 mg/3 mL and 0.63 mg/ 3 mL once they are removed from outside packaging. The vials (plastic) are difficult to read and are the same size. Recommend vials of different colors.
3613219-4 and DQRS M-128797 Report date MAR 21, 2000 Potential error	**Xopenex** 0.63 mg/3 mL. All 3 package in same container with no differing marks. Potential error. Ingredients embossed on container, but look very similar and difficult to read.
3416728-6 Report date DEC 8, 1999 Potential error	Packaging for **Xopenex** is identical for 0.63 mg and 1.25 mg. The reporter is concerned that the look alike packaging for the different strengths could lead to a medication error. Both strengths are in same size containers. The plastic covering the product is embossed and difficult to read.
3668821 Report date FEB 14, 2001 Actual error No patient harm	Poor labeling on ipratropium bromide inhalation solution 0.02% unit dose vials 2.5 mL almost caused a med error in our ER. Once the outer foil packaging is removed it is very difficult to read the clear, raised letter on each unit. The manufacturer is Roxane. We will try to order another brand that has each unit more clearly marked.
3459383-1 JAN 28, 2000 Potential error	Packaging of **Ipratropium** Bromide inhalation solutions 0.02% (Roxane) does not have label affixed to it but is marked by raised lettering on plastic. As a result, it is difficult to read and may be mistaken for other inhalation solutions. Other manufacturers of inhalation solutions have colored labels that differentiate between different solutions so as to prevent such errors.
3869207-6 Report date JAN 28, 2002 Potential error	We are concerned about the new packaging for the unit dose inhalation solutions. The specific brand we are now stocking is Nephron Pharmaceuticals Corporation. The **albuterol** 0.083% solution and the **ipratropium** 0.02% solution both come in clear, unit dose vials. The vials are the same shape, with the ipratropium a little taller. The ipratropium has an embossed "I" on the top and the albuterol an embossed "A".
3837302-3 Report date	Respiratory therapist brought to our attention that the plastic ampules for Novaplus' **ipratropium** and Alpharma's **albuterol** look identical

NOV 27, 2001 Potential error	and have extremely difficult to read labeling – leading to a large error potential.
3782023-9 Report date AUG 13, 2001 Potential error	The packaging and labeling for **Ipratropium** bromide (Alpharma) and **albuterol** sulfate (Zenith Goldline) inhalation solutions are practically identical and hard to read. The drug names and dosing information are extremely hard to read due to their almost transparent font. There is a high potential for confusion among these two products.
3667775 Report date FEB 6, 2001 Potential error	It was brought to my attention by the respiratory department at some hospitals that the following inhalation products are packaged similarly and could contribute to a medication error. **Albuterol** sulfate (Zenith), **Ipratropium** (Roxane). They are in ready to use vials and the boxes are different but since most respiratory techs break open the foil packs and carry the vials, there needs to be some distinguishing features to the individual packaging (colored plastic in the vial or a label on the outside of the vial similar to Dey's albuterol inhalation solution.)
3863171-1 Report date JAN 22, 2002 Potential error	**Xopenex** Solution Inhalation 0.63 mg/3 mL (Sepracor)- Label unreadable – Absolutely hard to read ingredients. Cannot distinguish which is which. Serious patient safety risk. Resp Therapist complaining to us.
3863170 Report date JAN 22, 2002 Potential error	**Ipratropium** Bromide Inhalation Solution 0.02% (2.5 mL) (Nephron)- Label unreadable – Absolutely hard to read ingredients. Cannot distinguish which is which. Serious patient safety risk. Resp Therapist complaining to us.
3497904-3 Report date MAY 8, 2000 Potential error	**Ipratropium** Bromide 0.02% (Roxane) 2.5 mL inhalation solution and **Xopenex** (levalbuterol HCl) 0.63 mg/3 mL inhalation solution. Both drugs are in a clear plastic twist-off top unit-dose design with raised letters very difficult to read. Respiratory uses both drug and have already come close to a mixup. Both drugs need an adhesive label on the unit of use containers to prevent mixup.
3468841-5 Report date FEB 22, 2000 Unknown location Potential error	Pharmacist called to report possible mixup between **Atrovent** (Boehringer Ingelheim) and **Xopenex** (Sepracor) clear plastic ampules.
3456502-8 Report date Feb 10, 2000 Potential error	I am a registered respiratory therapist at a large hospital in New Jersey. We recently began using **Xopenex** (levalbuterol) in addition to our regular regime of **Albuterol** and **ipratropium** bromide (Atrovent). The potential problem lies with the packaging of Xopenex, which is almost identical to Atrovent.*******Both are packaged in unit dose vials that are clear with printing stamped on them, making them particularly difficult to differentiate. Until we started using Xopenex this was not a problem. However, it will be very easy to mix them up and give patients the wrong medication.**********The company representative from Sepracor acknowledged this problem and stated that it is very difficult to change the packaging because it was already approved by the FDA. Thank you for addressing this issue promptly before any serious medication errors occur.
3316590-6 Report date JUL 11, 1999	**Xopenex** (levalbuterol) 0.63 mg/3 mL and **Ipratropium** Bromide 0.5 mg/2.5 mL (Roxane). Look-alike products with hard-to-read labels.

Potential error	
3668823-4 Report date FEB 14, 2001 Potential error	**Xopenex** (levalbuterol) 0.63 mg 3 mL and **Ipratropium** Bromide 0.02% 2.5 mL (Roxane). A reporter wrote to suggest that labeling of respiratory inhalation treatment vials be considered as an issue by ISMP. Specifically, labeling of respiratory medication pre-mix vials by imprinting the labeling info during the molding process for the vial. Many people find this very difficult to read, including myself. Many inhalation solutions come in pre-mixed vials which are labeled only by the imprinting of product information on the exterior of the vial. The attached photo file demonstrates the anonymity of these vials. The addition of a paper label or a color identifier would greatly aid in the discrimination of one vial from another. On the left is levalbuterol, on the right is ipratropium. See Appendix C photo 1 for image
3698831-9 Report date MAR 29, 2001 Potential error	**Xopenex** (levalbuterol) 0.63 mg/3 mL and **Ipratropium** Bromide 0.02% (Roxane). Xopenex SVN package is very hard to read clear plastic with raised lettering for the drug name and strength. This product comes in two strengths. Identical packaging to Roxane product: Ipratropium SVN (Clear plastic with raised lettering). What a set up for a med error!
3710666-7 Report date APR 17, 2001 Potential error	The packaging for Dornase Alfa (**Pulmozyme**) 2.5 mg/2.5 mL container by Genentech NDC 50242-0100-39 is very similar to **Xopenex** and **Ipratropium** (Roxane). All are in clear plastic ampuls for nebulization. It is difficult to read the writing on the ampuls because it is the same color as the plastic ampul. Recommendations: Could the manufacturer add colored ink or a label to the products? We have made the following changes in order to prevent an error from occurring. 1 Two info-grams sent to all pharmacy location via the order entry computer pharmacy staff of the similar appearance of these products (Xopenex, Ipratropium and Pulmozyme). 2 The hospital has ordered a new brand of Ipratropium (DEY) 3 Central pharmacy will dispense all Xopenex in a zip lock bag with a label indicating that it contains levalbuterol.
3710664-3 APR 9, 2001 Actual error No patient harm	**Xopenex** (levalbuterol) 1.25 mg/3 mL and **Ipratropium** Bromide 0.5 mg/2.5 mL (Roxane). Xopenex was administered to a patient by the respiratory therapist instead of Ipratropium. No harm reported. Containers are very similar. Both are clear plastic amps for nebulization. It is difficult to read the writing on the amps because it is the same color as the plastic amp.
3762579-2 Report date JUN 13, 2001 Potential error	**Xopenex** (levalbuterol) 0.63 mg/3 mL, 1.25 mg/3 mL, and **Ipratropium** Bromide 0.5 mg/2.5 mL (Roxane). Levalbuterol (Xopenex) med nebs look almost exactly like the ipratropium med nebs from Roxane. There is a serious potential for error here!
3779866-4 Report date AUG 3, 2001 Potential error	Alpharma's **Albuterol** Sulfate and **Ipratropium**, and Sepracor's Xopenex are packaged in identical plastic vials with raised letters. Only the product name is different. The Alpharma products have an "A" or "I" on the appropriate tab on the vials but it is only on one side of the tab. Add some sort of coloring to the vials or use an actual label on the vials instead of the raised lettering.
3484929-7 MAR 20, 2000 Unknown location Actual error Did not reach patient	Gastrocrom (**cromolyn**) 5 mL (Medeva) and **Xopenex** (levalbuterol) 3 mL (Sepracor) have similar packaging and can easily be mixed up. There was an error after someone was putting away "returned" medications. However the error was discovered before the patient

	received the incorrect drug.
3935798 APR 19, 2002 Potential error	Our respiratory staff asked us to initiate a medication alert for some inhalation products. The unit dose packaging for the two strengths of **Pulmicort** Respules (0.25 mg/2 mL and 0.5 mg /2 mL) unit dose packaging are very similar. All are made of clear plastic and have raised lettering. None have any coloration for easy identification. Our respiratory therapists often carry individual unit dose containers in their pockets without the outside packaging.
3631747-2 NOV 4, 2000 Unknown location Actual error Did not reach patient	**Pulmicort** respules 0.25 mg/2 mL and 0.5 mg/2 mL are very similar in packaging size and were mixed up in pharmacy storage bins. The incorrect strength was placed in a patient's medication drawer. Respiratory therapist caught the mistake and the error did not reach the patient. Suggestions: If the company can't mark the plastic respule with a color or identifying mark, then the different strengths should be separated when shipped in, placed in well-marked bins and have some sort of identifying sticker placed on them when dispensed. Care should be taken when crediting and returning the respule to storage bins.
3650346 JAN 1, 2001 Actual error Unknown outcome	**Pulmicort** (Budesonide) 0.5 mg respules dispensed and administered instead of the 0.25 mg respules because of poor labeling; strength is a clear imprint on clear plastic and is very small, making it very difficult to read.
3698700-4 MAR 30, 2001 Potential error	**Pulmicort** Respules are manufactured in two strengths. Because the two product strengths are virtually identical in appearance, the only significant difference being "0.25" embossed on one vial and "0.5" embossed on the other. Both packages are already difficult to read, being clear plastic with small raised lettering. The potential exists to give 50% or 200% of the prescribed dose. Suggestions: The medications require different packaging and/or labeling. Printing the name and strength of the medication in color would be most useful. A consideration to prevent potential errors in the future is to remove the medication form the hospital formulary.
3745136-3 JAN 17, 2001 Unknown location Actual error Patient experience CNS and GI adverse effects	A three-year-old boy received **Pulmicort** 0.25 mg twice daily. After two months, he received Pulmicort 0.5 mg twice a day for a period of three weeks, in error.
3824265 OCT 12, 2001 Actual error Did not reach patient	Regular pharmacy staffing chose wrong medication. The prescription needed to be filled with **Pulmicort** 0.5 mg nebulizer solution (120 mL). In error, Pulmicort 0.25 mg (60 mL) was prepared. The pharmacist detected the error while counseling the patient.
3978167-9 AUG 15, 2002 Unknown location Potential error	Differentiation between **Pulmicort** Respules 0.25 mg/2 mL and 0.5 mg/2 mL is difficult to identify (hard to read strength imprinted on top). Dosing indicated on each individual ampule is only on top piece with no color contrast.

1944216 Report date APR 4, 1997 Actual error Patient had trouble breathing	NDA Field Alert report from DEY for **Ipratropium** Bromide Inhalation Solution, 0.02%. An elderly patient who mis-dosed herself due to a confusion with the packaging of the product. ******The patient reported she mistakenly treated herself with two doses of Ipratropium Bromide Inhalation solution, 0.02%, instead of her prescribed dosage of one unit-dose vial of ipratropium bromide combined in a nebulizer with one unit-dose vial of **Albuterol** Sulfate Inhalation Solution 0.083%, also manufactured by Dey Laboratories. As a result of these treatments, she did not receive the needed relief from the products, she had trouble breathing, and she could not walk. The patient reported that the graphics of the labeling are similar and the shelf cartons are similar in size and color as well.
3487461 APR 5, 2000 Unknown location Potential/?Actual Unknown if patient received wrong medication in error	Respiratory therapist (RT) was requesting missing dose of Tobi. When he came to get it he was unaware that **Tobi** and **Pulmozyme** looked so similar. When he went back to the unit, he found 3 amps (2 labeled and 1 unlabeled) There had been no extra requests for Tobi so it is questionable if the patient got the medication. Medications are too similar in appearance.
3973282-8 AUG 7, 2002 Unknown location Potential error	Are you aware that APP is marketing a **heparin** 10 units/mL (5 mL) plastic container? One of their reps showing it to me last week. I showed him all of the respiratory meds and the poor labeling. He was also surprised. The clincher is that their heparin product is almost identical to the tobramycin for inhalation product, **Tobi**.
3720124-1 Report date APR 30, 2001 Potential error	Astra Zeneca is ceasing to manufacture their glass vials of **Naropin** (ropivacaine) and some **Xylocaines** (mainly the MPF). They have created a polyamp, a plastic ampule to which a syringe can be directly luer locked. Unfortunately, the amps look almost exactly alike, plastic with black writing. Practitioner who have become accustomed to the color coding of the different strengths of the lidocaines will now have to read very carefully to make sure they not only have the right drug but also the right strength. In addition, the smaller amps could possibly be mistaken for nebulizer meds that come in similar containers (i.e. they look like the "pillows"). I have contacted Astra Zeneca and asked them to consider packaging modifications that would be more helpful in distinguishing the two products. I also asked them to consider larger print for the warning "Not for inhalation" printed on the amp. My requests are being forwarded to their product quality division.
3586159-7 Report date AUG 8, 2000 Potential error	Label on Astra Zeneca's PolyAmp DuoFit package (for **Naropin** and **Xylocaine**) is almost impossible to see. This may also be prelude to similar injectable labeling by other manufacturers. FDA should immediately examine this situation to prevent additional drug packaging that is similar. This will cause serious errors.
3254863-6 Report date APR 14, 1999 Potential error	The PolyAmp DuoFit packaging of **Naropin** (ropivacaine HCl) and **Xylocaine** MPF (lidocaine HCl injection USP) is very similar to that of **Ipratropium** bromide inhalation solution and could potentially be confused. Suggestions: Change the package, label well, distribute notices of potential for error.
3951163-3 Report date MAY 6, 2002 Potential error	We have noted an issue with the new polyamp packaging by AstraZeneca for Xylocaine-MPF 2% and Naropin 10 mg/mL. Both containers are identical in size, shape, clear color, and black writing once removed from their overwrap packaging. Our LDRP noticed the potential medication error on their epidural cart when the medications were removed from their original packaging so that they would fit in the cart.

APPENDIX B

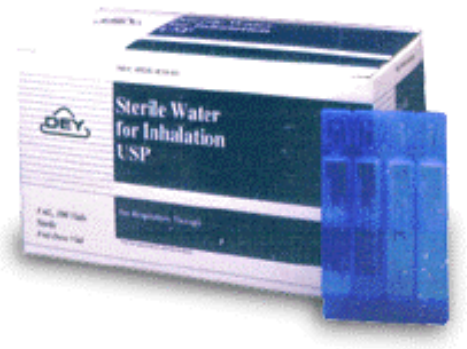
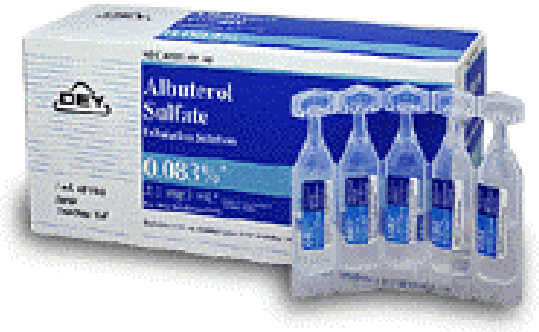
DQRS reports through 2002

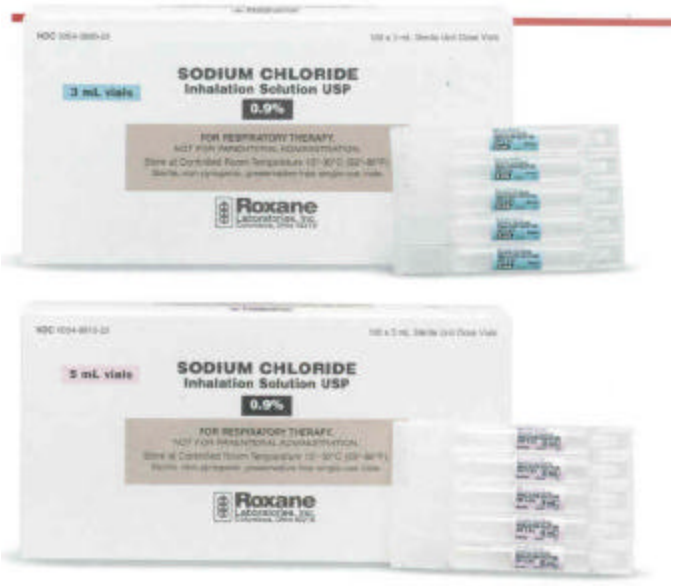
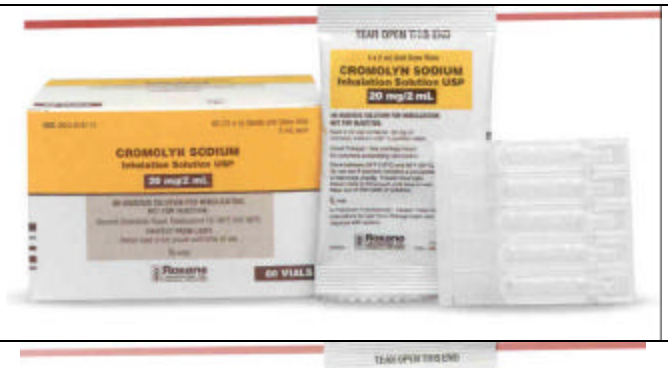
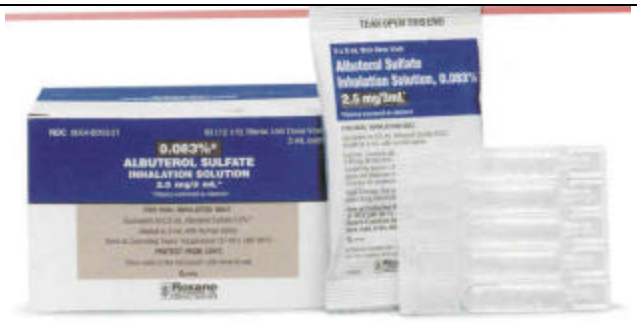
Albuterol inhalation	M 133173	The packaging of some nebulizer solution are very difficult to read. **Xopenex** and generic **albuterol** (Alpharma) are in clear plastic ampules. The companies label the product by using raised lettering in the plastic. Beside the fact that one product looks like another, they have to be angled just right in the light to read it.
	M 128924	The packaging on the above mentioned medications almost identical. The problem is compounded by the fact that the labeling is embossed making it extremely difficult to read. If there was a way to color code the containers or if the labels were printed so they could be easily read, it would correct the problem.
Alupent inhalation solution	D 100206	The plastic vials are impressed on one end with the lot number and expiration date on opposite sides. Due to the vial composition of clear plastic, it is difficult to distinguish what the expiration date and lot number are.
	U 017643	The expiration date is embossed on one side of a plastic tab that extends from the vials and the lot number is embossed on the other side, making both illegible. The reporter feels that the manufacturer should extend the tab so that the lot and expiration date are one above the other on the same side of the tab
Atrovent Inhalation solution	D 115046	Embossed label is difficult to read. Recommend affixing label with darker lettering.
	116620	Label on individual vials is almost impossible to read in most light. This is an embossed label on opaque plastic with clear liquid inside. A paper label attached to the vials would be much easier to read.
	M 116222	The reporter states the product information is printed on a clear plastic container and it is very difficult to read. Also, this product looks very similar to another product (**Ventolin** nebules) with the exception of the "V" shaped twist top.
	U 022262	Clear ampule for inhalation labeled in clear raised lettering. Concerned may cause administration errors. Should be labeled in black or possibly colored lettering. Very, very difficult to read.
Duoneb inhalation solution	M 131971	The product is **DuoNeb**, an inhalation solution of **ipratropium** bromide and **albuterol** sulfate. The inhalation solution is packaged in "Sterile unit dose vials" that are plastic. The problem is that the vials are clear, the solution is clear, and the printing on the vials is not printing, but raised lettering in clear plastic. The clear plastic makes the lettering difficult to read. The result is difficulty in confirming the name of the drug, the strength of the ingredients, and the expiration dating. The fact that the vials are packaged in clearly marked foil packages does not compensate for the poorly marked vials because the usual practice is to take the vials from the packaging and throw away the foil wrapper.
Ipratropium bromide inhalation solution	U 132897	Absolutely hard to read ingredients. Cannot distinguish which is which. Serious Patient Safety Risk. Respiratory therapist complaining to us.

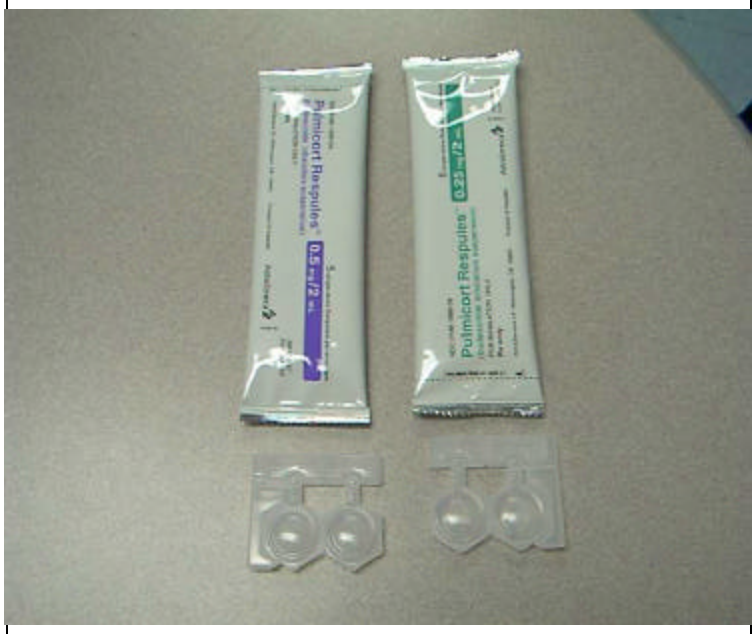
Ipratropium bromide inhalation solution	M 128923	The packaging on the above mentioned medications almost identical. The problem is compounded by the fact that the labeling is embossed making it extremely difficult to read. If there was a way to color code the containers or if the labels were printed so they could be easily read, it would correct the problem.
	U 023801	The labeling is imprinted into the clear plastic container making it very difficult to read. The reporter suggests that a painted label be applied.
Proventil Solution for inhalation	U 008130	Label is very difficult to read. It looks like 25 mg/3 mL rather than 2.5 mg/3 mL
Pulmicort Respules Inhalation suspension	M130437	Budesonide 0.5 mg respules dispensed and administered instead of 0.25 mg respules because of poor labeling; strength is a clear imprint on clear plastic and is very small, making it difficult to read.
Roxanol UD Oral solution	D 109832	Container too similar in design to saline containers by Wyeth and **Alupent** containers made by Boehringer Ingelheim. Expiration date on container impossible to read easily. Reporter's nurses are having to draw up solutions in syringes over concern of accuracy of actual volume in container.
Sodium Chloride	D 111575	Individual unit dose NaCl containers contain unreadable end crimp expiration due to color of plastic.
Ventolin Inhalation Solution	U 016233	The problem occurred on 1-7-1993. The product "label" consists of imprint of text into plastic unit-dose container. It is extremely difficult to read.
	018240	The respiratory therapy department has complained about "how hard it is to squeeze the dropper" (their complaint is how well the elderly could use the dropper while at home). Additional information per call to reporter 11-30-1993. Therapists have also complained that because the label goes completely around the container, it is difficult to tell how much solution is in the container.
Ventolin Nebules Solution Inhalation	M 112337	The product information is printed on a clear plastic container and it is very difficult to read. Potential error with other medications with similar packaging.
	U 017687	The problem occurred on 8-3-1993. Poor labeling of the product. Name of the product is hard to read as it consists of only raised lettering on the plastic vials. Very easy to mix up with Normal Saline for respiratory use. Interestingly, Roxane Laboratories also manufacturers the normal saline the reporter uses and this product is labeled in such a way that the product is easily identifiable. The product brochure for the **Ventolin** solution shows a clearly labeled vial. However, the product does not possess the clear labeling as in the brochure. See file for the photocopy of the product's label.
	019041	The problem occurred in 3-1994. Current nebules are prepackaged in opaque plastic. The label consists of raised lettering in the same material. Therefore, the product identification can be very difficult due to low visual contrast between the label and container.
Xopenex Solution Inhalation	M 128921	Label on **Xopenex** (levalbuterol) unit dose is impossible to read – raised plastic lettering. Need clearer identification.

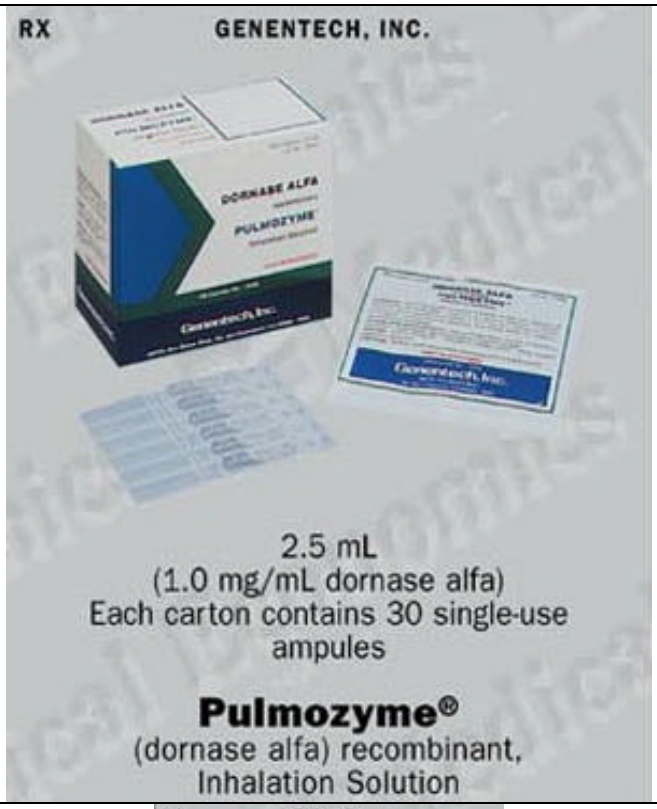
Xopenex Solution Inhalation	131036	1.25 mg/ 3 mL and 0.63 mg/3 mL – difficult to read imprint on unit dose packages. Possibility of giving incorrect dosage; suggest color coding or change labeling in both individual unit dose vials.
	132242	1.25 mg/ 3 mL and 0.63 mg/3 mL - difficult to read imprint on unit dose packages. Possibility of giving incorrect dosage; suggest color coding or change labeling in both individual unit dose vials.
	133174	The packaging of some nebulizer solutions are very difficult to read. **Xopenex** and generic Albuterol (Alpharma) are in clear plastic ampules. The companies label the product by using raised lettering in the plastic. Beside the fact that one product looks like another, they have to be angled just right in the light to read it.
	U 026514	The problem was observed on all dates. The product is manufactured in clear plastic vials with the imprint into the plastic vials. None of the information on the vial is legible, imprinted clear on clear. The very real possibility exists that the wrong medication or dose can be given because none of the information is able to read. Why would the FDA allow anyone to label a product in this manner? There is also a problem with the product being light sensitive. It comes in a foil pouch and then any product not used after two weeks is to be discarded. Why is the product not in an opaque container to begin with to eliminate the light sensitivity? The warning to discard discolored is not on the individual container, and even if it were it couldn't be read. The reporter considers this product to be poorly designed, poorly labeled, and dangerous.
	132898	Absolutely hard to read ingredients. Cannot distinguish which is which. Serious patient safety risk. Respiratory therapist complaining to us.

APPENDIX C - Images of Products

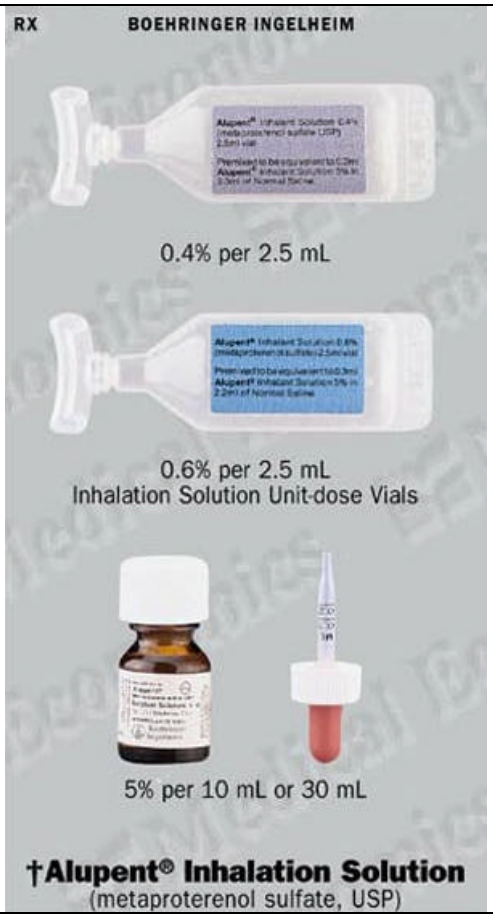
DEY Sterile Water for Inhalation USP Embossed label	
DEY Sodium Chloride Inhalation Solution USP Embossed label	
DEY Albuterol Sulfate Paper label	
DEY Ipratropium Bromide Inhalation Solution Paper label	

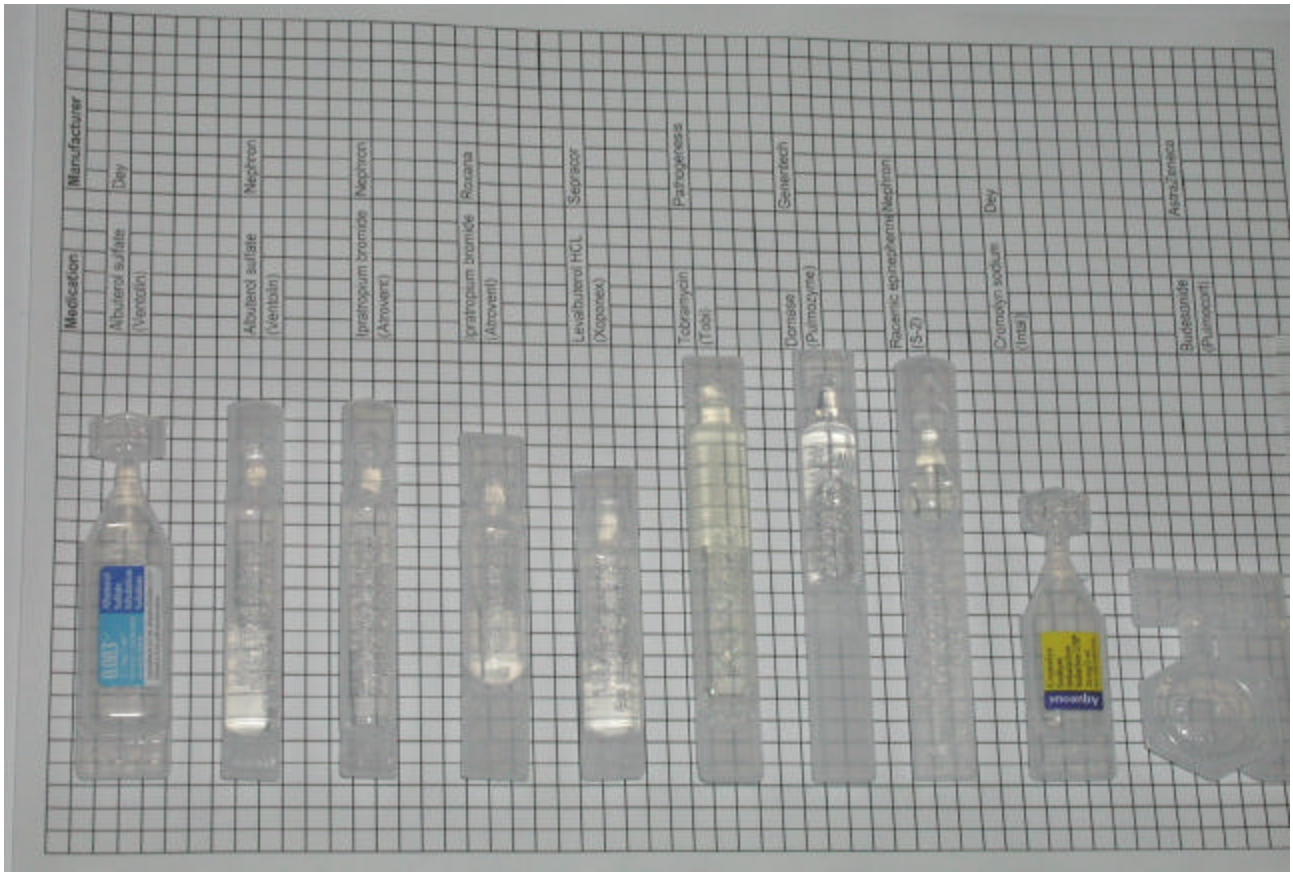
Roxane Ipratropium Bromide Embossed label	
Roxane Sodium Chloride Paper label	
Roxane Cromolyn Sodium Embossed label	
Roxane Albuterol Sulfate Embossed label	

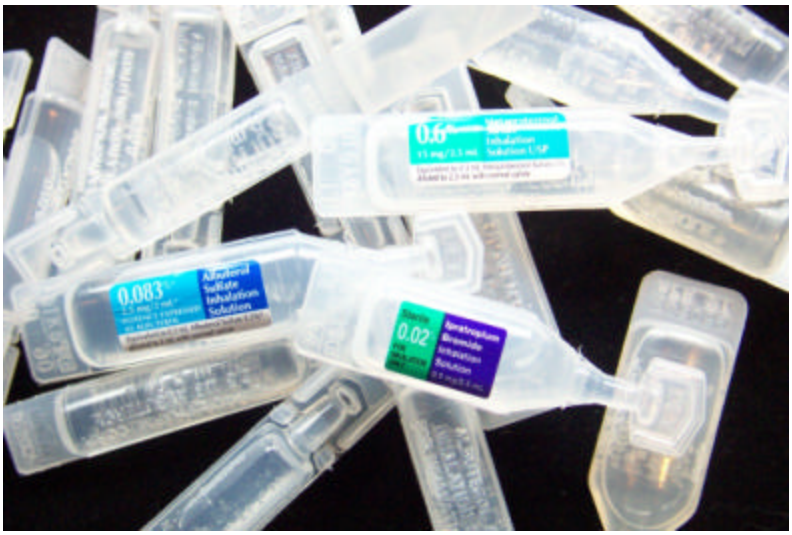
AstraZeneca Pulmicort Respules Embossed label	 
DEY DuoNeb Embossed label	

Genentech Pulmozyme Embossed label	
Sepracor Xopenex Embossed label	

Boehringer Ingelheim
Alupent
Paper label






0.083
Albuterol Sulfate Inhalation Solution
0.02
Ipratropium Bromide Inhalation Solution
0.6
Inhalation Solution USP

REFERENCES

1 ISMP *Medication Safety Alert!* Atrocious labeling of plastic ampuls needs action now by FDA and manufacturers. Volume 7 Issue 10 May 15, 2002.

2 ISMP *Medication Safety Alert!* Safety Brief: Xopenex and Ipratropium have look-alike packaging. Volume 5 Issue 7 April 5, 2000.

3 Some product images in Appendix C are from the electronic Physicians Desk Reference (PDR) © 2002 Thomson MICROMEDEX http://www.thomsonhc.com/pdrel/librarian/PFParentUsageId/1077303

4 Some product images in Appendix C are from ISMP. www.ismp.org