

Poor labeling on inhaled medications should concern community practitioners

Practitioners have been reporting concerns with the labeling of unit-dose respiratory therapy medications packaged in plastic (low density polyethylene – LDPE) containers for almost a decade. Poor legibility of these products has been a frequent concern reported to the USP-ISMP Medication Errors Reporting Program (MERP). In fact, FDA has received more than 100 error reports through the MERP and the FDA MedWatch programs combined. This problem with legibility is evident to some practitioners (nurses, respiratory therapists) as well as caregivers and patients who administer these medications. Unfortunately, ambulatory care pharmacists and physicians may not realize the extent of the problem because they often do not see the individual unit-dose containers.

Many inhalation products intended for use by nebulization (e.g., albuterol [**PROVENTIL**], ipratropium [**ATROVENT**], albuterol-ipratropium combinations [**DUONEB**], levalbuterol [**XOPENEX**], cromolyn [**INTAL**], budesonide [**PULMICORT RESPULES**]) are packaged in plastic LDPE containers. These medications are generally dispensed in boxes that contain foil pouches, each holding multiple unit-dose containers. However, many of these containers have little difference in shape or color. Even worse, the containers have the drug name, concentration, lot number, and expiration date embossed into the plastic using transparent, raised letters,



Top: Albuterol Sulfate
Middle: Xopenex (levalbuterol HCl)
Bottom: Ipratropium Bromide

making it virtually impossible to read (see photo). Some of these products are also available in multiple dosage strengths, but poorly visible labels make it hard to differentiate them. This embossing method of labeling is used because FDA no longer permits paper labels or ink printing on these containers.

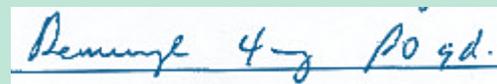
LDPE is permeable to volatile chemicals (such as those that are used in label adhesives, paper, and ink) and contamination of inhalation solutions could occur resulting in the potential for patient harm. In fact, FDA studies have shown that 29 of 37 samples tested positive for volatile chemicals. The *cont'd on page 2*

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■ **Indication: Alzheimer's disease.** If pharmacists were provided with or inquired about the indication, several dispensing errors could have been prevented when the antidiabetic agent **AMARYL** (glimepiride) was dispensed instead of the Alzheimer's medication **REMINYL** (galantamine). In one case, a gentleman took his wife's prescription for a new medication to the pharmacy. The physician wrote for "Ramiryl 2 mg." The pharmacist on duty interpreted and dispensed the prescription as Amaryl 2 mg. After one week, the patient's husband returned to the pharmacy with the medication and informed a different pharmacist that the physician told him that it was the wrong medication. After reviewing the original prescription, the pharmacist was unsure of what other medication the physician intended to prescribe, so he asked the man if he knew what condition the medication was supposed to treat. Only after being informed that it was for Alzheimer's disease did the pharmacist realize that the intended medication was Reminyl. The patient's husband then stated that his wife was just released from a 3-day hospitalization due to hypoglycemia.

In another case, a 78-year-old woman with a history of Alzheimer's disease was admitted to the hospital with severe hypoglycemia (blood glucose on admission 27 mg/dL). A review of the medications she was taking at home revealed that she had been taking Amaryl 4 mg BID instead of Reminyl 4 mg BID. We have received several reports of other similar errors.

Similarities in the written (see image) and spoken drug



names, as well as overlapping

dosage strength (4 mg) and frequency of dosing likely contributed to these errors. In addition, if prescriptions for Amaryl are more commonly encountered than those for Reminyl, confirmation bias (seeing that which is most familiar, while overlooking any disconfirming evidence) may lead pharmacists into "automatically" believing a prescription is for Amaryl.

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LDPE labeling (cont'd from previous page)

presumed source of the volatile chemicals was the packaging and labeling materials used, such as adhesives, varnishes, inks, and solvents.

A recent report from a pharmacist working in a pharmacy that specializes in providing respiratory medications indicated a high level of awareness at her practice site. She explained that typically their patients receive both albuterol sulfate and ipratropium bromide and mix them together in a nebulizer just prior to administration. The most common complaint received from patients is that they cannot differentiate one container of medicine from the other. Patient calls of this nature occur daily, and on several occasions she has received calls from panicked patients who inadvertently used two containers of the same medication instead of mixing one of each. She went on to say how difficult it is for someone with normal vision to read the embossed labels, let alone an elderly patient with declining vision.

We have heard from both practitioners and patients who have or were considering using marking pens on individual containers to color code or mark a letter indicating the drug name or affixing labels to them as a means to easily identify these medications. However, because other substances have been shown to permeate through the plastic containers, it seems reasonable that the ink from a marker and volatiles from the label adhesives could do the same. Therefore, we would not recommend these practices.

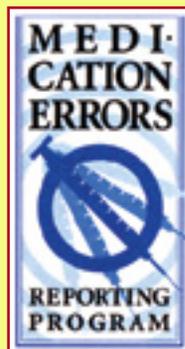
On May 5, 2004, the FDA Drug Safety and Risk Management Advisory Committee met to discuss how to prevent errors with drug products marketed in unit-dose plastic containers composed of LDPE. While a solution to the labeling problem was not determined, a number of alternative recommendations were considered, including: (1) embossment using large, easy-to-read fonts, (2) aluminum over-wrap for each individual unit-dose, semipermeable container as protective secondary packaging and labeling, and (3) plastic shrink-wrap over each package to provide background for lettering and bar codes. However, the Committee noted that, even though inks and glues used for the latter two methods are not in direct contact with the LDPE packaging, migration of chemicals in the microenvironment of the packaging might still occur. Thus, additional FDA studies to determine if such packaging is acceptable were also suggested, which means that additional time is necessary to satisfactorily resolve this problem.

Until the FDA clears up this labeling problem, consider the following measures to prevent errors with these products:

- Avoid adding labels to or writing on individual containers.
- When storing these medications (in physician offices, pharmacies, patient homes, etc.), ensure that plastic containers are stored in their original boxes, whenever possible. Avoid storing individual plastic containers together in a single location since many products look alike and could be inadvertently mixed together.
- Keep in mind that many of these medications are packaged in foil pouches due to light sensitivity. Manufacturers of such products recommend storing unopened containers in the protective foil pouch until ready to use. Also, most manufacturers recommend that containers removed from the foil pouch be used within one week.
- In an effort to keep medications in their original packaging, pharmacists should avoid dispensing partial boxes. If boxes must be “broken up,” ensure that plastic containers are dispensed in a clearly labeled package and that medications packaged in foil pouches are dispensed in an intact foil pouch.
- Counsel patients regarding the proper use and storage of their medication. Alert patients to the potential for misidentification with these products. To reduce this problem, stress the need to store medications in original, clearly labeled packaging.
- Be prepared for questions from patients related to identification of plastic containers as well as what to do if the wrong medication or too much of one medication is administered. Ensure that elderly patients and those with visual difficulty have some means of properly identifying their respiratory medication, especially if using more than one.

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Shake well before dispensing

Obviously, it is important to ensure that the active ingredient(s) in a suspension is properly dispersed throughout the vehicle before administration. "Shake well before use" is a common reminder (in the form of directions typed on the pharmacy label, an auxiliary label, or verbal instructions) given by pharmacists to patients who receive oral suspensions. But how often is this important reminder forgotten by pharmacy staff when preparing a smaller quantity of a suspension from a large stock bottle? And what happens if the stock bottle is not shaken or is inadequately shaken? One mother knows all too well. In a report, she explained that her son had been diagnosed with epilepsy and his seizures were well controlled with carbamazepine (**TEGRETOL**) oral suspension. His prescription called for 8 oz. of carbamazepine to be dispensed with each refill. Because the medication is available in a 16 oz. stock bottle, smaller bottles were prepared for each refill.

Several days after starting a new bottle, her son had a recurrence of seizures that lasted about a week. During this time, his mother noticed that the suspension had a different appearance than the previous prescription and mentioned it to the prescribing physician, who recommended getting a new refill. She was subsequently more aware of the appearance of the suspension whenever she had the medication refilled. Whenever the suspension looked different than expected, she would ask the pharmacist for a replacement, dispensed from an unopened manufacturer's bottle, and shaken in her presence. But after a few of these occurrences, she later insisted that the pediatrician write prescriptions instructing pharmacists to dispense the medication only in the 16 oz. unopened manufacturer's stock bottle. She saved several of the more suspicious-looking suspensions dispensed in 8 oz. bottles and sent them to the manufacturer. Assays performed by the manufacturer's Quality Control Division revealed that three of the bottles contained suspensions that were significantly less concentrated than the expected 100 mg/5 mL concentration and one bottle of suspension was three times more concentrated than would be expected!

The source of the problem appears to have stemmed from pharmacy staff not shaking or inadequately shaking the stock bottle of carbamazepine suspension before preparing a smaller bottle. If an unopened stock bottle of a suspension was inadequately shaken before preparing a smaller bottle, the suspension that was poured out could potentially be less concentrated than expected. This, in turn, would leave the remainder of the stock suspension more highly concentrated. Both situations could

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Accidental administration of Amaryl could pose a great danger to any patient, especially an older patient, who may be more sensitive to its hypoglycemic effects. Practitioners should be alerted to the potential for confusion between Amaryl and Reminyl. Prescribers should indicate the medication's purpose on prescriptions. Build alerts into computer order entry systems and add reminder labels to pharmacy containers. Patients (or caregivers) should be educated about all of their medications, so they are at least familiar with each product's name, its purpose, and its expected appearance. Most importantly, pharmacists and nurses should confirm that patients are diabetic before dispensing or administering antidiabetic agents. Look for a review of errors involving other diabetic medications in next month's issue.

■ **Name change.** Andrx Corporation has recently changed the name of their cholesterol-lowering drug **ALTOCOR** (extended-release lovastatin) to **ALTOPREV**. This change was made to reduce confusion with the Kos Pharmaceuticals product, **ADVICOR** (niacin and lovastatin sustained release). A Safety Brief in our February 2003 issue had previously highlighted the potential for confusion between the two medications. Be sure to alert patients who currently take Altocor that the name has been changed, but everything else about the medication is the same. Until physicians become familiar with the name change, mix-ups between Altocor and Advicor are still possible.

■ **Two pneumococcal vaccines are available in the US.** Pneumococcal 7-valent vaccine (**PREVNAR**) is used for the routine immunization of infants and toddlers against pneumococcal bacteria that can cause life-threatening meningitis and blood infections. A pharmacist recently reported that this product was confused with pneumococcal polyvalent vaccine (**PNEUMOVAX 23** or **PNU-IMUNE 23**), which is used for adults over 65 years of age; patients who are at increased risk of pneumococcal disease or its complications because of chronic illnesses; children over 2 years of age with chronic illnesses; and those with asymptomatic or symptomatic HIV infection. In this case, three adult patients received Prevnar in error. The pharmacist read only the top line of the Prevnar label, which reads Pneumococcal 7-valent, and thought it was the correct vaccine product. The brand name does not appear until the fourth line of the label and it is italicized, making it difficult to read. The first line of the Pneumovax

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Shake well (cont'd from previous page)

potentially lead to significant variability in doses, which could affect disease control (i.e., recurrence of seizures resulting from less concentrated carbamazepine suspension dispensed). This is particularly significant for drugs with a narrow therapeutic index. However, even if the suspension is adequately shaken prior to dispensing, if patients do not shake the medication properly, similar variability in doses could occur. Shown below are carbamazepine suspensions from two different manufacturers. Settling of the active ingredient (shown by the arrows) can be seen in both clear containers although it may be more difficult to notice in the amber stock bottles.



*Photo courtesy of NeighborCare

In order to prevent such problems, pharmacy staff should be sure to adequately shake all suspensions. Keep in mind that education may be required for pharmacy technicians and students who may not be aware of the difference between a solution and suspension. Visually check that the suspension is uniformly dispersed before it is transferred from its original container. Pharmacists involved in the final check of a suspension should verify with the individual who prepared it that this important step was performed before allowing the suspension to be dispensed. Consider making auxiliary labels that read, "Shake well before dispensing" and add them to appropriate pharmacy products. In addition, attention could be drawn to suspensions by highlighting or circling the word "suspension" on product labels. Make sure that patients receiving suspension preparations are counseled so that they fully understand the need to shake the medication well before each use. The "Shake Well" auxiliary label, which commonly accompanies the pharmacy label on suspension preparations being dispensed, should not be used as the only means of communicating this important information, but rather as a reminder for patients, since it could easily be overlooked.

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product reads pneumococcal, and, like the Prevnar label, the brand name does not appear until the fourth line. Both vaccines are stored under refrigeration, which may add to the risk of confusion. In each of the above cases, the prescribers and patients were notified of the error and an infectious disease consultant recommended revaccination with the adult product. The pharmacy now stores the vaccines in separate bins in different locations in the refrigerator. Also, they label the Prevnar bins, "For pediatric administration only." The vaccine manufacturers have been made aware of these errors.

■ **A new suffix.** Drug name suffixes are confusing enough without coining our own. A physician assistant recently wrote a prescription for a patient that was misread by a pharmacy technician as **VICODIN ES** (hydrocodone 7.5 mg, acetaminophen 750 mg). Upon closer examination, the pharmacist thought that the suffix looked more like RS. The pharmacist called the prescriber's office and learned that the physician assistant had used "RS" to indicate "regular strength." Vicodin (hydrocodone 5 mg, acetaminophen 500 mg) was subsequently dispensed. Because numerous brand and generic combinations of hydrocodone and acetaminophen products are available, there is a large potential for confusion. In order to minimize confusion, prescribers could include the strength of each ingredient on prescriptions for brand name products, as is done for prescriptions written using the generic drug names.

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