

EXECUTIVE SUMMARY

Safe Use of Drug Products Packaged in Low Density Polyethylene (LDPE) Containers

Many inhalation drug products, particularly those marketed in a unit-dose form, are packaged in plastic containers composed of low density polyethylene (LDPE). Although convenient, the use of LDPE containers introduces two potentially serious safety concerns.

The first concern that impacts on the purity of inhalation drug products relates to the permeability of LDPE containers. LDPE is described as a “semipermeable” material because it is known to be permeable to volatile chemicals (i.e., chemicals that have moderate to high vapor pressure). Volatile chemicals are often present in adhesives, varnishes, inks, and solvents used in labeling and packaging materials. Thus, the labeling and packaging materials surrounding LDPE containers contain a number of sources of volatile chemicals and there is evidence that contamination of inhalation solutions can occur as a result of ingress of these volatile chemicals through LDPE containers. In an FDA study involving random sampling of a number of different inhalation products packaged in LDPE containers, the majority of the products sampled were found to contain chemical contaminants, whose presumed source was the packaging and labeling materials. In addition, the identification of chemicals originating from packaging materials in inhalation drug products has resulted in drug recalls in the past.

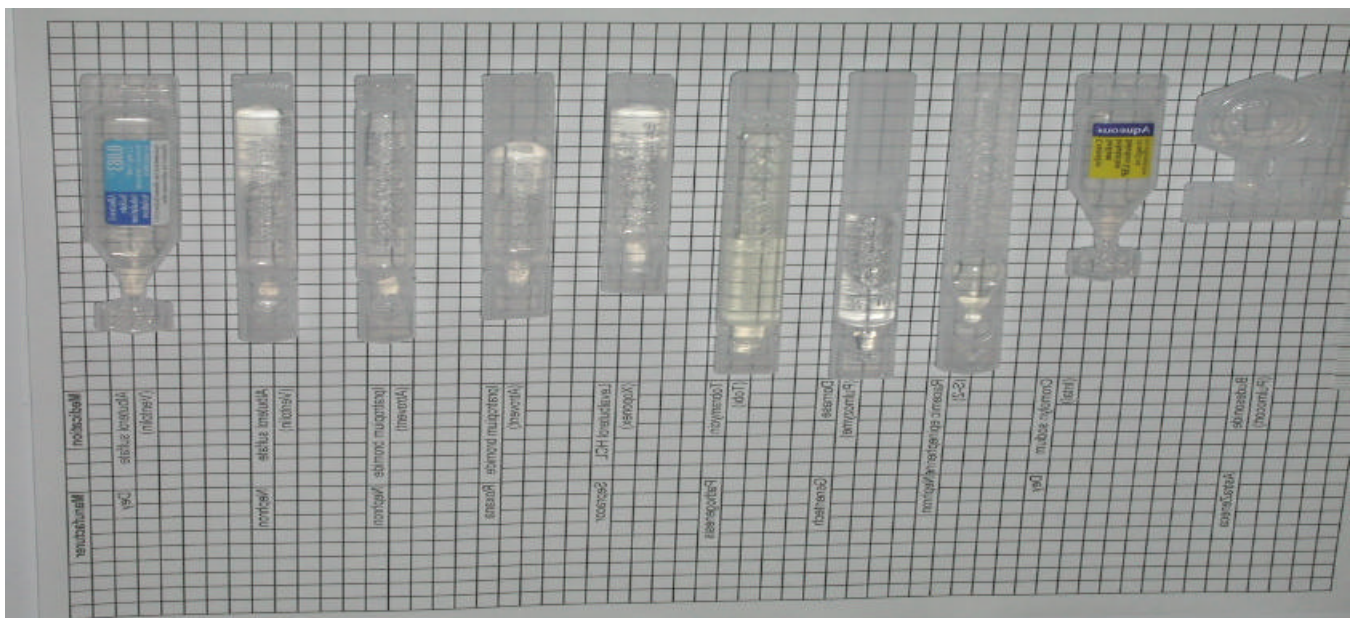
The clinical consequences of exposure to chemical contaminants of inhaled drug products are uncertain. It is not possible to establish the identity and toxicologic effects of all potential contaminants. However, given that patients with respiratory diseases, such as asthma and Chronic Obstructive Pulmonary Disease (COPD), are typically very sensitive to respiratory irritants and/or immunologic sensitizers, it is possible that the ingress of volatile chemicals into these vials may induce bronchospasm. Although there have been no specific reports of adverse reactions that could be conclusively attributed to chemical contamination of inhaled drug products, FDA is aware that physicians and patients are unlikely to suspect a drug-related phenomenon when the adverse effect mimics the disease being treated. Therefore, it is unlikely that bronchospasm due to a chemical impurity would be identified in a patient receiving the drug to treat bronchospasm.

The second concern with LDPE containers is the legibility of the container label. Due to the potential for ingress of volatile chemicals and potential for bronchospasm, many of the vials do not bear a printed label. Instead, the label consists of the product name and dosage strength of the drug product debossed (sunken lettering) and/or embossed (raised lettering) on the LDPE container itself. While the use of debossed/embossed label information addresses the concern for drug product contamination by ingress of volatile chemicals, it introduces a second area of concern specifically relating to the legibility of the container label. The FDA and others are of the opinion that the difficulties

experienced in reading the embossed/debossed labeling may be likely one of the contributing factors in almost every medication error reported to FDA for these products. This opinion has been voiced by numerous health care practitioners, patients, and caregivers.

Patients and practitioners have experienced problems distinguishing one drug product from another because the product name and strength embossed/debossed on the container label may be difficult to read or illegible. Furthermore, the LDPE containers of many different drug products look very similar to each other (see figure 1). Difficult-to-read labels and look-alike containers have contributed to medication errors involving the administration of the wrong dosage strength or wrong drug product.

Figure 1 – Various Drug Products Packaged in LDPE Containers



As of July 9, 2003, FDA has received 121 cases of medication errors relating to these issues. 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 in breathing”. Since many of these medications are used to treat respiratory conditions, there is the potential for an error to result in life-threatening respiratory complications.

Additionally, in recent years LDPE containers have been used with other drug products such as injectables, ophthalmologics, oral solutions, and topical products. The introduction of these products into the marketplace in this type of container has increased the risk of potential of confusion between an inhalation product and a product with a different route of administration. For example, Gastrocrom® is administered orally and is packaged in LDPE vials. In one medication error report, an error occurred when pharmacy staff returned unused medications from the patient care area to the pharmacy stock. In many inpatient pharmacies, medications available in LDPE containers are stored loosely in bins either on the pharmacy shelf

or in the refrigerator. In this reported error, the wrong drug was placed in the wrong storage bin and it was possible the wrong medication would be dispensed.

There is also the potential for confusion between the inhalation drug products and injectable solutions (e.g., Naropin®, Xylocaine®, and Heparin) now available in plastic vials. Multiple medication error reports warn of the potential for confusion with injectable medications packaged in similar plastic vial containers. The main concerns expressed were the readability of the labels on the containers and the potential for confusion with inhalation solution products.

Given these dual concerns, FDA has encouraged manufacturers to take preventive measures to limit the potential for ingress of chemical contaminants into inhalation drug products packaged in semipermeable containers. In order to protect the containers from volatile chemicals that are often present in other secondary packaging materials (e.g. cartons), FDA has encouraged manufacturers to develop appropriate protective secondary packaging, such as foil overwrap pouches. At present a few manufacturers individually foil overwrap each unit-dose container. Most manufacturers overwrap multiple vials of the drug product (e.g., 4 to 25 vials) in foil. Many institutions remove the vials from the larger overwrap in order to disseminate the medication via a unit-dose system. Once the overwrap is removed, the name and strength of the drug product are difficult to read. Furthermore, few characteristics are available to distinguish the LDPE containers visually. Although the overwrap labeling could prevent medication errors, there is still the problem of unused vials stored as loose items with labels that may be difficult-to-read and prone to cause errors.

In summary, inhalation drug products packaged in semipermeable containers (e.g., LDPE vials) may become contaminated with volatile chemicals found in labeling and packaging materials. These volatile chemicals may pose a safety risk for patients. Therefore, FDA has encouraged manufacturers to take appropriate measures to prevent ingress of chemical contaminants from labeling (e.g., embossed vials) or other source. Individual foil overwrap has been considered as a mechanism to decrease the likelihood for removal of the product prior to patient administration and thus minimize the potential for confusion and errors relating to the embossed/debossed vial labeling and look-alike vials. However, there may be other ways to address the issue. We invite discussion of other methods of packaging or labeling that will address the legibility of LDPE containers while controlling the possible ingress of contaminants. Due to the challenging and complex nature of the issues explored and described above, FDA acknowledges that input from patients, care-givers and practitioners is vital to the identification of mechanisms to address the current concerns while not creating new problems for those who use these medications. In addition, it is vital for the industry to be involved in the process to be sure that the solutions identified are viable. Therefore, FDA believes it will be beneficial to discuss the issues surrounding safe use of drug products in semipermeable containers (e.g., LDPE vials) in this public forum.

To assist you in your deliberations, we have prepared the following items for your review:

1. Issues for Discussion
2. Division of Medication Errors and Technical Support (DMETS) review on medication errors with LDPE containers
3. Congressional Letter
4. ISMP Article on LDPE labeling
5. USP Letter on LDPE labeling
6. Draft Guidance on Inhalation Drug Products Packaged in Semipermeable Container Closure Systems
7. Comments received on the Draft Guidance on Inhalation Drug Products Packaged in Semipermeable Container Closure Systems
8. Labeling Regulations for:
 - *A drug packaged in a container too small or otherwise unable to accommodate a label with sufficient space.
 - *Location of Expiration Date