
Guidance for Industry

Inhalation Drug Products Packaged in Semipermeable Container Closure Systems

DRAFT GUIDANCE

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**July 2002
Clinical/CMC**

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GUIDANCE FOR INDUSTRY¹

Inhalation Drug Products Packaged in Semipermeable Container Closure Systems

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- *Clearly explain each issue/concern and, when appropriate, include a proposed revision and the rationale/justification for the proposed change.*
- *Identify specific comments by line number(s); use the PDF version of the document, whenever possible.*

I. Introduction

This document provides recommendations for industry on inhalation drug products that are packaged in semipermeable primary container closure systems, such as low-density polyethylene (LDPE) containers. It is intended to provide guidance on (1) the appropriate protective secondary packaging, (2) the embossing and/or debossing of the primary container in lieu of paper labels, and (3) the number of unit-dose containers within each protective secondary package.

These recommendations apply to inhalation drug products (e.g., solutions, suspensions, sprays), both those in development and those already approved and marketed in the United States.

II. Background

Under FDA's Current Good Manufacturing Practice regulations, manufacturers must establish adequate acceptance criteria to ensure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release (21 CFR 211.165(d)). One purpose of such acceptance criteria is to avoid the occurrence of adverse reactions, such as toxicologic, irritant, or immunologic reactions from

¹ This guidance has been prepared by the Inhalation Drug Products LDPE Working Group of the Medical Policy Coordinating Committee (MPCC) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

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39 chemical impurities. In an inhalation drug product packaged in a semipermeable container, in
40 addition to chemical impurities that can accumulate over time as a result of the degradation of
41 formulation components or leaching from the container closure system, chemical impurities can
42 enter from the local environment. For example, volatile chemical components from the local
43 environment, particularly the secondary packaging, can react with the drug product to form
44 different impurities.

45
46 Drug substances used in the treatment of patients with asthma or chronic obstructive pulmonary
47 disease (COPD) are often formulated as inhalation solutions or suspensions. These drug
48 products can be packaged in either unit-dose vials or multi-dose vials. The unit-dose vials are
49 commonly manufactured from LDPE. LDPE vials are permeable to some volatile chemicals
50 (i.e., chemicals with moderate to high vapor pressure under typical climatic storage conditions).
51 As a result of this permeability, chemicals originating from packaging materials, such as
52 adhesives, varnishes, and solvents, have been found in inhalation drug products packaged in
53 LDPE. These findings have resulted in drug recalls.

54
55 In an FDA study involving random sampling of a number of different inhalation products in non-
56 overwrapped LDPE vials, the majority of these products were found to contain chemical
57 contaminants of various types.² The sources of these contaminants were the primary and
58 secondary packaging and labeling components. Careful choice of primary packaging can
59 address the risk of contaminants from the primary packaging. Overwrap protects against
60 secondary and other environmental contaminants. Thus, chemical contamination of inhalation
61 drug products can and has occurred as a result of entry through LDPE container closure systems.

62
63 For several reasons, it may not be possible to identify all potential chemical contaminants that
64 may be in a drug product formulation or to determine their toxicological profile:

- 65
- 66 • Toxicological data on many of the identified chemical contaminants are incomplete.
 - 67
 - 68 • The analytical procedures used may not detect unknown chemical contaminants. The
69 source of these chemical contaminants is likely to be the labeling and packaging
70 material. Changes in the composition of these materials may introduce new chemical
71 contaminants that may be difficult to identify, given proprietary considerations.
72 Moreover, some of these changes can be made without notification to FDA.
 - 73
 - 74 • Contaminants can enter into the drug product formulation as a result of variable
75 environmental conditions.
 - 76

77 The clinical consequences of chemical contamination of inhalation drug products are uncertain.
78 Although there are no data on the potential for the identified chemical contaminants to act as
79 spasmogens in the airways of patients with the target diseases for these medications (i.e., asthma
80 and/or COPD), many of these chemical contaminants are potential respiratory irritants. No

² Memorandum from Team Leader, ANDA Review Team 2, Division of Chemistry 1, Office of Generic Drugs, Center for Drug Evaluation and Research, “Summary report of FDA analytical survey of approved NDA/ANDA inhalation solutions marketed in Low Density Polyethylene (LDPE) containers without a protective overwrap,” October 17, 2000.

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81 previously reported adverse reactions can be conclusively attributed to chemical contaminants.
82 However, given the known sensitivity of these patients to respiratory irritants and sensitizers, it is
83 possible that these chemical contaminants may induce bronchospasm. The potential adverse
84 effect of these chemical contaminants (i.e., bronchospasm) is also the indication for which the
85 drug product is used. Therefore, in the clinical setting it is very difficult to establish whether
86 bronchospasm after the use of a drug product is due to chemical contaminants or to the disease
87 itself.

88
89 Data indicate that the asthma mortality rate is increasing in the United States. The reason for this
90 increase is unknown but is likely to be caused by a variety of factors. Since it is conceivable that
91 chemical contaminants in the inhalation solutions used to treat the most critically ill asthmatics
92 could play a role, it is important that preventive measures be taken to limit, to the extent
93 practicable, the leaching and entry of chemical contaminants into the drug formulation.

94

95 **III. Chemistry, Manufacturing, and Controls Considerations**

96 Because of the clinical concerns cited above, FDA recommends that inhalation drug products in
97 semipermeable primary container closure systems (e.g., LDPE vials) be further protected with
98 secondary packaging to minimize and control the entry of chemical contaminants from the local
99 environment into the drug product. Special consideration should be given to the components and
100 composition of the materials used in the protective secondary packaging and the manufacturing
101 processes involved (e.g., adhesive lamination, heat-seal lamination, various temperature
102 conditions). Adequate control of each of these components and manufacturing processes is
103 critical to prevent the entry of volatile environmental contaminants and volatile chemical
104 constituents from packaging components into the drug product. Controls are also important to
105 prevent loss of water from the formulation.

106

107 If secondary packaging is added, pertinent information on the manufacture and controls of the
108 protective secondary packaging must be included in new drug applications (NDAs), abbreviated
109 new drug applications (ANDAs), or their supplements to ensure reproducible lot-to-lot
110 performance characteristics (see 21 CFR 314.50(d)(1)). The qualitative as well as the
111 quantitative composition and physical characteristics (e.g., thickness) of all container closure
112 system components are critical to ensure the quality and purity of the drug product and must be
113 included in the NDA, ANDA, or supplement (see 21 CFR 314.70(b)(2)(vii)).³ This information
114 can also be incorporated by reference from type III drug master files (DMFs), if the holder of the
115 DMF authorizes the incorporation in writing (see 21 CFR 314.420).

116

117 The typical protective secondary packaging materials used for inhalation drug products packaged
118 in semipermeable containers are overwrap pouches made of flexible foil-laminates. The foil-
119 laminates usually contain multiple layers of various types of plastic films fused together by heat
120 or adhesives applied to one or both sides of an aluminum foil. Because adhesives are a possible
121 source of chemical contaminants, alternative approaches to adhesives should be considered for

³ Additional recommendations on inhalation drug products will be provided in the guidance on *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products* when it is finalized. A notice of availability for a draft version of this guidance published in the Federal Register on June 2, 1999 (64 FR 29657).

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122 the fusion of the multiple layers of a foil-laminate (e.g., a heat seal process). Testing of foil-
123 laminate and application of appropriate acceptance criteria (e.g., thickness of aluminum foil,
124 number of pinholes per unit area) are crucial for ensuring a consistent barrier to permeability.
125 Additionally, if secondary packaging is added, appropriate data must be provided in NDAs,
126 ANDAs, or their supplements to demonstrate that the specified foil-laminate can provide
127 adequate protection from reactive gases, volatile compounds, and foreign chemicals that can
128 enter into the drug products from the packaging materials and/or from the local environment (see
129 21 CFR 314.420). FDA recommends that any leaching of contaminants into the formulation
130 from the primary container, any entry of chemical contaminants from protective secondary
131 packaging components or other packaging components (e.g., the carton) be adequately
132 documented, quantified, and qualified. This information will ensure the identity, strength,
133 quality, purity, and potency of the drug product (see 21 CFR 314.50(d)(1)(ii)(a)).
134

135 Another potential source of chemical contamination for the inhalation drug products packaged in
136 semipermeable primary container closure systems are paper labels applied directly to the primary
137 container (e.g., the LDPE vial). The typical chemical components of paper labels are adhesives,
138 varnish or overlacquer, printing inks, and other chemicals used in the manufacturing of the paper
139 label itself. Each of these components is a proprietary formulation of many other chemicals and
140 solvents, some of which can have significant potential to leach and enter the drug product
141 formulation. Therefore, FDA recommends that direct application of paper labels to
142 semipermeable containers be avoided. Instead, the Agency recommends alternative approaches
143 to paper labels, including direct embossing or debossing of the semipermeable containers or
144 other means to display the requisite labeling information.
145

146 FDA also recommends that the number of semipermeable containers packaged within a single
147 protective secondary package (e.g., a foil-laminate overwrap pouch) be limited to restrict the
148 exposure of unused containers to environmental contaminants if the protective secondary
149 packaging should be compromised. To prevent such environmental contamination of the drug
150 product, the ideal approach would be to overwrap each semipermeable container individually
151 within the protective secondary packaging. However, if more than one unit is packaged per
152 pouch, the number of units per pouch should be limited so that the amount of time the vials are
153 exposed to the unprotected environment before use is kept to a minimum.

154 **IV. References**

155 For additional guidance, applicants can refer to the appropriate sections of the two guidance
156 documents listed below. PDF versions of these guidance documents are posted on the Internet at
157 <http://www.fda.gov/cder/guidance/index.htm>.

158
159 Draft guidance for industry on *Nasal Spray and Inhalation Solution, Suspension, and Spray*
160 *Drug Products, Chemistry, Manufacturing, and Controls Documentation*, May 1999.

161
162 Guidance for industry on *Container Closure Systems for Packaging Human Drugs and*
163 *Biologics*, May 1999.