

**Aventis Pharmaceuticals**



October 24, 2002

Via fax and UPS

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**Re: Docket No. 02D-0254**

Draft Guidance for Industry on Inhalation Drug Products Packaged in Semipermeable Container Closure Systems [67FR 48920, July 26, 2002]

Dear Sir/Madam:

Aventis Pharmaceuticals Inc. appreciates the opportunity to comment on the above-referenced draft guidance entitled "Inhalation Drug Products Packaged in Semipermeable Container Closure Systems".

This draft guidance provides recommendations on the appropriate protective secondary packaging, the embossing and/or debossing of the primary container in lieu of paper labels, and the number of unit-dose containers within each protective secondary package. The development of the draft guidance on inhalation drug products packaged in semipermeable container closure systems is welcomed. The underlying principles are generally sound and acceptable. We offer the following comments/clarification for your consideration.

02D-0254

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## I. Introduction

Page 1, lines 23 to 31

*This document provides recommendations for industry on inhalation drug products that are packaged in semipermeable permeable 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.*

**We would like to have further clarification of the scope of this guidance and definition of semipermeable.**

The guidance refers to semipermeable container closure systems such as LDPE containers. We feel that this is an inadequate definition of the material covered by this guidance as many other polymers, such as medium density polymers are also semipermeable. It would be also helpful if semipermeable is further defined.

Further, reference is made that the guidance applies to inhalation drug products e.g. solutions, suspensions, sprays. We understand that this does not refer to products given nasally as these are dealt with in other guidance (July 2002 Guidance for Industry on Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation). Similarly, lines 46 and 47 refer to asthma and chronic obstructive pulmonary disease (COPD), which is the current practice, but newer inhaled therapies, especially for systemic diseases, would also be covered by this guidance.

We propose rewording this paragraph as follows:

***"This document provides recommendations for industry on ~~inhalation~~ orally inhaled unit and multi-dose drug products that are packaged in semipermeable polymer primary container closure systems. ~~such as low density polyethylene (LDPE) containers.~~ Semipermeable refers to those polymers through which chemical contaminants either from the container closure system or the environment can permeate. 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~~ orally inhaled drug products (e.g., solutions, suspensions, ~~sprays~~), both those in development and those already approved and marketed in the United States.'***

*Page 1, paragraph 2, lines 30 to 31*

*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.*

This guidance refers to those drug products already approved and marketed in the United States without reference to the process, including timeframe, by which manufactures should ensure and demonstrate those drug products currently marketed and not complying with the guidance become compliant.

**We believe that guidance is required to inform manufacturers of currently marketed drug products on the process that they should follow to ensure that the marketed drug products become compliant with the requirements of this guidance.**

## **II. Background**

*Pages 2-3, paragraph 5, lines 77 to 87*

*The clinical consequences of chemical contamination of inhalation drug products are uncertain. Although there are no data on the potential for the identified chemical contaminants to act as spasmogens in the airways of patients with the target diseases for these medications (i.e., asthma and/or COPD), many of these chemical contaminants are potential respiratory irritants. No previously reported adverse reactions can be conclusively attributed to chemical contaminants. However, given the known sensitivity of these patients to respiratory irritants and sensitizers, it is possible that these chemical contaminants may induce bronchospasm. The potential adverse effect of these chemical contaminants (i.e., bronchospasm) is also the indication for which the drug product is used. Therefore, in the clinical setting it is very difficult to establish whether bronchospasm after the use of a drug product is due to chemical contaminants or to the disease itself.*

We agree with the purpose of the guidance but feel that arguments supporting the clinical consequences for chemical contamination controls are overstated. The draft guidance recognizes that there is no previously reported adverse reactions conclusively attributed to chemical contaminants, nor that it would be "very difficult" to establish whether bronchospasm after the use of a drug product was due to chemical contaminants. A more rationale basis should be made on the potential of chemical contaminants to cause adverse events, and that these proposals would remove or even further reduce the risk.

### III. Chemistry, Manufacturing, and Controls Considerations

Page 3, paragraph 1, lines 99 to 105

*Special consideration should be given to the components and composition of the materials used in the protective secondary packaging and the manufacturing processes involved (e.g., adhesive lamination, heat-seal lamination, various temperature conditions). Adequate control of each of these components and manufacturing processes is critical to prevent the entry of volatile environmental contaminants and volatile chemical constituents from packaging components into the drug product. Controls are also important to prevent loss of water from the formulation.*

**We believe that this refers to the selection process of the components and materials.**

We propose rewording this paragraph as follows:

***“Special consideration should be given to the selection of components and composition of the materials used in the protective secondary packaging and the manufacturing processes involved (e.g., adhesive lamination, heat-seal lamination, various temperature conditions). Adequate control of each of these components and manufacturing processes is critical to prevent the entry of volatile environmental contaminants and volatile chemical constituents from packaging components into the drug product. Additionally, formation of volatile substances during the heat sealing process should be investigated and controlled. Controls are also important to prevent loss of water from the formulation.”***

Page 4, paragraph 1, lines 129 to 132

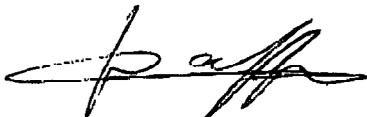
*FDA recommends that any leaching of contaminants into the formulation from the primary container, any entry of chemical contaminants from protective secondary packaging components or other packaging components (e.g., the carton) be adequately documented, quantified, and qualified.*

**It would be helpful here to refer to any other guidance or procedures that provide information on qualification and quantification of the contaminants, and what likely action levels should be in place for various contaminants classes.**

The activity should be linked with the Product Quality Research Institute (PQRI) Working Group that is considering leachables and extractables in orally inhaled and nasal drug products. We strongly suggest that the PQRI activity includes inhalation drug products packaged in semipermeable container closure systems, and that more specific recommendations on qualification and quantification with action limits are provided in this guidance.

On behalf of Aventis Pharmaceuticals Inc. we appreciate the opportunity to comment on the draft Guidance for Industry on Inhalation Drug Products Packaged in Semipermeable Container Closure Systems and are much obliged for your consideration.

Sincerely,



Steve Caffé, M.D.  
*Vice President, Head US Regulatory Affairs*