



Comments on Draft Guidance for Industry

Inhalation Drug Products Packaged in Semipermeable Container Closure Systems

(FDA Docket No. 02D-0254)

Submitted by the International Pharmaceutical Aerosol Consortium on
Regulation and Science (IPAC-RS)

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I. INTRODUCTION

The International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) is an association of companies that research, develop and manufacture aerosol drug products for oral inhalation or intranasal delivery. The importance of these drug products is growing with the expanding range of conditions they are used to treat, including asthma, chronic obstructive pulmonary disease (COPD), rhinitis, migraine, diabetes and others.

Current members of IPAC-RS are: Aradigm, AstraZeneca, Aventis, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Inhale Therapeutic Systems, Inc., Kos Pharmaceuticals, Norton Healthcare, Pfizer, and Schering-Plough Corporation. IPAC-RS companies and the Food and Drug Administration (FDA) share a common goal: to meet the medical needs of patients in a timely manner by facilitating the arrival of new drug products to the market while maintaining scientifically justified standards of safety, efficacy and quality.

II. GENERAL COMMENTS

IPAC-RS welcomes the opportunity to offer comments on the Draft Guidance for Industry entitled *Inhalation Drug Products Packaged in Semipermeable Container Closure Systems*.¹

IPAC-RS commends the Agency for developing guidance documents focused on a specific regulatory issue, which should facilitate timely discussion and efficient finalization of Draft Guidances. We hope that the Agency will continue this approach in the future by issuing topic-specific Guidances with a well-defined scope.

We are concerned, however, that this particular Draft Guidance is redundant to several other FDA Guidances, which address the issue of leachables testing as well as requirements for primary and secondary packaging, such as the following Guidances:

- Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation;²
- Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation;³ and
- Container Closure Systems for Packaging Human Drugs and Biologics Chemistry, Manufacturing, and Controls Documentation.⁴

The value of an additional Guidance that mostly repeats general statements made elsewhere, is questionable. Moreover, as elaborated in our specific comments below, the new language included in this Draft Guidance confuses rather than clarifies the matter (*e.g.*, do LDPE containers need secondary packaging or not?) or introduces vague but potentially

¹ See <http://www.fda.gov/cder/guidance/4168dft.pdf>.

² See <http://www.fda.gov/cder/guidance/2180dft.pdf>.

³ See <http://www.fda.gov/cder/guidance/4234fnl.pdf>.

⁴ See <http://www.fda.gov/cber/gdlns/cntanr.pdf>.

burdensome requirements without substantive justification (e.g., what analytes and methods should be used to assess the effectiveness of a secondary overwrap system to prevent environmental contamination?)

We also feel it is not appropriate for this Guidance to speculate on the medical implications of leachables, as there are no established facts on linkage between incidence and mortality of asthma and leachables.

III. SPECIFIC COMMENTS

In an effort to point out areas for improvement in the present Draft Guidance, we offer the following specific comments.

Clarify Applicability

Lines 23-31

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. ...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.

The Guidance should set a clear definition of when a container is considered semipermeable. It should also elaborate as to whether any material besides LDPE is considered "semipermeable" for the purposes of this Guidance.

Further, we request that the Guidance include an explicit statement that it applies only to liquid, aqueous-based inhalation drug products, and does not apply to metered dose inhalers (MDIs) and dry powder inhalers (DPIs). In addition, newer products for systemic delivery, which treat patients who do not necessarily have hypersensitive airways or have chronic disease, should be explicitly excluded from the applicability of this Guidance.

Furthermore, while the Agency specifically mentions that the Guidance applies to the products already approved and marketed in the U.S., it does not specify a process by which these products can comply with the Guidance. For example, it would be helpful if the Agency described in detail the information that should be submitted, as well as the timeframe and procedure (e.g., first submitting a proposed study protocol to the Agency for comment, and then submitting the data in the Annual Report).

Explain referenced FDA study

Lines 55-58

In an FDA study involving random sampling of a number of different inhalation products in non-overwrapped LDPE vials, the majority of these products were found to contain chemical contaminants of various types. The sources of these contaminants were the primary and secondary packaging and labeling components.

In light of the importance the Agency attributes to this study, the Guidance should describe in more detail what type of secondary packaging was involved if it was not overwrap. (The memorandum referenced in the Draft Guidance in footnote 2 does not provide such information). Clarifying this point is especially important because the Draft Guidance specifically recommends (in line 150) that each individual semipermeable container be overwrapped.

Better define and justify requirements

The Draft Guidance contains a number of open-ended recommendations, which should be clarified in order to provide better guidance for the industry as well as consistency in the regulatory review. Specific examples follow.

Lines 125-129

Additionally, if secondary packaging is added, appropriate data must be provided in NDAs, ANDAs, or their supplements to demonstrate that the specified foil-laminate can provide adequate protection from reactive gases, volatile compounds, and foreign chemicals that can enter into the drug products from the packaging materials and/or from the local environment (see 21 CFR 314.420).

The Guidance should include a specific list of “reactive gases, volatile compounds and foreign chemicals” against which the packaging should be tested. Otherwise, the number of chemicals to test is limitless. The Guidance should identify gases, chemicals and compounds the Agency views as most relevant for these drug products (21 CFR 314.420 does not provide such guidance). Moreover, the Agency should clarify what types of tests are required and what constitutes “appropriate data.”

The Guidance would be improved if such specific recommendations were linked to available scientific data and documented studies of potential safety concerns. For example, a method of toxicity classes similar to that adopted by the International Conference on Harmonization for organic solvents,⁵ could be used to provide substantive guidance and inform decisions about details of recommended packaging testing.

⁵ International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, *Q3C: Impurities: Guidelines for Residual Solvents*. Internet: <http://www.ich.org/pdf/ICH/Q3C.pdf> (1997).

Without further specificity, there is a real potential for the scope of the required testing to grow out of proportion and impose unjustifiable regulatory burden on the developers and manufacturers of these types of drug products.

Lines 129-132

...any leaching of contaminants into the formulation...be adequately documented, quantified, and qualified.

The Guidance should include the threshold levels at which the leachables are to be identified, quantified, and qualified. Otherwise, the amount, scope, intensity and associated costs of the required testing will be driven by the ever-increasing detection capabilities of analytical technology and not by any clinical or quality concern.

The industry has repeatedly requested that the threshold approach to leachables in orally inhaled and nasal drug products be adopted by the Agency.^{6, 7, 8} This approach received positive comments during a 2000 meeting of the FDA Advisory Committee for Pharmaceutical Science.⁹ Most recently, FDA, industry, USP and academic representatives have undertaken an evaluation of the details of this approach and associated methods through the Product Quality Research Institute.¹⁰ We also note that use of thresholds has a well established precedent in general guidelines developed by the International Conference on Harmonization for impurities in new drug products.¹¹

To consolidate best scientific regulatory approaches to leachables testing, we strongly urge the Agency to acknowledge and use the concept of identification, quantification and qualification thresholds in this and future Guidances. Moreover, based on its extensive data base, the Agency could propose a practicable set of

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- ⁶ CMC Leachables and Extractables Technical Team of the ITFG/IPAC-RS Collaboration, *Leachables and Extractables Testing: Points to Consider*. Internet: http://ipacrs.com/PDFs/Points_to_Consider_FINAL.PDF (2001).
- ⁷ IPAC, *Comments on a draft Guidance for Industry Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation (Docket No. 98D-0997)*. Internet: http://ipacrs.com/PDFs/IPAC_Final_Comments_on_CMC.PDF (1999).
- ⁸ IPAC, *Comments on a draft Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation (Docket No. 99D-1454)*. Internet: http://ipacrs.com/PDFs/IPAC_Final_Comments_on_CMC.PDF (1999).
- ⁹ Advisory Committee for Pharmaceutical Science. *Transcripts of the Meeting on November 15, 2000*. Internet: <http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3657t1.pdf> (2000).
- ¹⁰ PQRI Leachables and Extractables Working Group, *Development of Scientifically Justifiable Thresholds for Leachables and Extractables*. Internet: <http://www.pqri.org/minutes/pdfs/dptc/lewg/workplan02.pdf> (2002).
- ¹¹ International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, *Q3B(R): Impurities in New Drug Products*. Internet: <http://www.ich.org/word/Q3Brstep2.doc> (1999).

identification, quantification and qualification thresholds for leachables in orally inhaled and nasal drug products.

Lines 146-153

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

We request that the Agency provide further guidance on what would be considered an acceptable “limited” number of units per pouch.

Furthermore, in view of the study referenced by the Guidance in lines 55-61, it would be interesting to know if an evaluation of chemical contamination was performed on inhalation products using both secondary packaging and overwrap, to justify the recommendation of individually wrapping containers within secondary packaging. Since no material is entirely free of compounds that can potentially migrate, it should be evaluated whether use of overwrap significantly diminishes contamination from the environment, has little effect, or adds new contaminants to the immediate environment of the primary semipermeable container.

IV. CONCLUSIONS

We sincerely hope that our comments will be helpful to the Agency. We believe our suggestions will help clarify and further strengthen the Draft Guidance and increase its usefulness and scientific relevance.

We look forward to the publication of a final Guidance that will effectively serve the current and future needs of the inhalation drug product industry and ultimately the consumers of these important drug products.