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GlaxoSmithKline

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Re: Docket Number 02D-0254, Comments on Draft Guidance for Industry on Inhalation Products Packaged in Semipermeable Container Closure Systems

Dear Sir or Madam;

Enclosed please find comments from GlaxoSmithKline on the Draft Guidance for Industry on Inhalation Products Packaged in Semipermeable Container Closure Systems. The comments are provided for consideration by the FDA. The comments are listed in order by the line number in the attachment.

GlaxoSmithKline appreciates the opportunity to provide feedback and suggestions for this guidance. I am submitting this document both electronically and by hardcopy. Therefore, you will receive a copy of this letter and two copies of the comments through the USPS. If you have any questions about these submitted comments, please feel free to contact me at (919) 483-5857. Thank you for your consideration.

Sincerely,

Mary Faye S. Whisler, Ph.D.
Assistant Director
New Submissions, North America

02D-0254

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Specific comments from GSK relating to the Draft Guidance for Industry on Inhalation Drug Products Packaged in Semipermeable Container Closure Systems include the following.

I. Introduction:

Line 25 should be changed to "It is intended to provide guidance on (1) the considerations for selecting appropriate protective..."

II. Background

Lines 39- 53 should be changed to clarify and eliminate redundancy. The first paragraph in this section should end with the statement that ends on line 39 (statement ending in "...chemical impurities."). The next paragraph (lines 46 to 53) should be changed to the following.

"Drug substances used in the treatment of patients with asthma or chronic obstructive pulmonary disease (COPD) are often formulated as inhalation solutions or suspensions. These drug products can be packaged in either unit-dose vials or multi-dose vials. In an inhalation drug product packaged in a semipermeable container, in addition to chemical impurities that can accumulate over time as a result of the degradation of formulation components or leaching from the container closure system, chemical impurities can enter from the local environment. For example, LDPE vials are permeable to some volatile chemicals (i.e., chemicals with moderate to high vapor pressure under typical climatic storage conditions). As a result of this permeability, chemicals originating from packaging materials, such as adhesives, varnishes, and solvents, have been found in inhalation drug products packaged in LDPE. These findings have resulted in drug recalls."

Lines 77 – 93 should be deleted. The information in these two paragraphs are speculative (as to the link of chemical contaminants, asthma, and asthma mortality) and should not be included in a CMC guidance document.

III. Chemistry, Manufacturing and Controls Considerations

Lines 96 to 110 should be rewritten because it is hard to assess the risk of the different types of contamination. Specific information follows. Lines 96 to 107 are confusing. We would agree that the extent of leaching should be limited, but limits do not keep the levels down. The issues with secondary packaging are confusing because we would increase the risk of one form of contamination (from the secondary packaging) to minimize the risk of other contamination (from the environment). The opening phrase in line 107 indicates that secondary packaging is optional, whereas lines 96 and 97 mandate

the use of secondary packaging. Additionally, lines 104-105 ("Controls are also important to prevent loss of water from the formulation.") is not really a part of the problem and is not mentioned again.

Lines 122-129 seem to require a lot of information for secondary packaging, that are not necessary for performance purposes. This information should be deleted. If these lines are not deleted, the guidance suggests a significant permeation study should be performed with multiple analysts. If this is required, the agency should give guidance on the type of analyst studies required.

Lines 146 to 153 should also be deleted because the information is not necessary for performance purposes.