

April 19, 2002

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GlaxoSmithKline

Dockets Management Branch  
Food and Drug Administration  
HFA-305, Room 1-23  
5630 Fishers Lane, Rm 1061  
Rockville, MD 20852

**GlaxoSmithKline**  
PO Box 13398  
Five Moore Drive  
Research Triangle Park  
North Carolina 27709  
Tel. 919 483 2100  
www.gsk.com

**Re: Draft Guidance for Industry: Exercise-Induced Bronchospasm (EIB) – Development of Drugs to Prevent EIB  
Federal Register 67(34):7704 (February 20, 2002)  
[Docket No. 02D-0003]**

Dockets Management:

Enclosed please find comments from GlaxoSmithKline on the draft guidance for industry entitled *Exercise-Induced Bronchospasm (EIB) – Development of Drugs to Prevent EIB*. Notification of availability of this guidance for comment was published in the *Federal Register* on February 20, 2002 (Docket No. 02D-0003).

GlaxoSmithKline fully endorses the development of this guidance for the study of drugs to prevent exercise-induced bronchospasm and we appreciate the opportunity to provide comments for consideration by the Agency.

These comments are provided in duplicate. If you have any questions regarding these comments, please contact me at (919) 483-5121.

Sincerely,

A handwritten signature in cursive script that reads 'Lorna C. Wilson'.

Lorna C. Wilson  
Director  
Regulatory Affairs

02D-0003

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**Comments on the Draft Guidance for Industry:  
Exercise-Induced Bronchospasm (EIB) – Development of Drugs to Prevent EIB  
[Docket No. 02D-0003]**

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**1. Line 26 and 128 - 140**

Line 26 of the Introduction, clearly defines the scope of the draft guidance to be for drugs given acutely to prevent EIB. However, Lines 128-140 discuss the study of drugs used semi-regularly or regularly for the maintenance treatment of asthma, and as needed for the prevention of EIB, and suggest that it may be appropriate to study the degree of EIB protection over time with chronic administration. It would be helpful if the guidance clarified what would be considered semi-regular maintenance therapy. In addition, it is not clear whether this section applies only to maintenance drugs given semi-regularly/regularly or whether it would also apply to as-needed drugs that are used chronically.

**2. Line 44**

The recommendation “should be administered just before exercise” is unclear. Short-acting beta-agonists are recommended to be given 15 minutes prior to exercise and long-acting beta-agonists are recommended to be given 30 minutes prior to exercise. We suggest wording such as “should be administered *at the appropriate interval* before exercise” be added to the guidance.

**3. Lines 53 – 56**

It would be helpful if the guidance addressed whether or not a full EIB program is necessary in the case of a reference product that is formulated in a combination product.

**4. Lines 61 – 63**

In cases where the product is approved for the treatment of asthma in adults and children, we question the requirement to conduct two trials in adults and a single trial in children. We suggest that the guidance acknowledge that there may be cases where one study in adults and one study in children would be appropriate for an EIB indication.

**5. Line 67**

While we understand the recommendation that EIB trials should be placebo-controlled, we wish to point out that this makes it very difficult to conduct an EIB study in the pediatric population, especially when studying drugs used regularly for the maintenance treatment of asthma. A placebo arm may also lead to confounded results since placebo patients may require study withdrawal or albuterol rescue due to a lack of asthma control or protection from EIB challenges. In the case of serial challenges, the use of albuterol is likely to confound subsequent challenges on the same day.

**Comments on the Draft Guidance for Industry:  
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[Docket No. 02D-0003]**

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**6. Line 68**

We request the Agency clarify the requirement to include dose ranging in a pediatric EIB study. As written, it suggests that dose ranging is required for all pediatric EIB studies. We suggest that in cases where an appropriate dose has been established for the primary indication in children, there is no need to repeat dose ranging in the study of EIB.

**7. Lines 73 – 74**

We suggest that the guidance be revised to indicate that dose-ranging in a pediatric EIB study would not be required in cases where the dose is already defined for the treatment of asthma in the population being studied.

Also, establishing an appropriate dose for asthma via standard dose-ranging trials is sufficient for establishing a dose for EIB. To our knowledge, no data exists to indicate that a dose appropriate for asthma is different (i.e., higher or lower) than the dose appropriate for EIB.

**8. Lines 128 – 139**

It would be helpful if the guidance defined what is meant by “semi-regularly” and what period of time is considered to be appropriate to study drugs for EIB which are used chronically.

**9. Line 158 – 160**

Excluding patients who need rescue will simplify the analysis, but will limit the study population, and potentially be seen by patients as a deterrent to study consent.

**10. Lines 195 – 202**

We agree the primary analysis should compare maximum percent fall in FEV<sub>1</sub> from baseline following exercise challenge and an important secondary analysis is a categorical analysis of the percentage of patients who demonstrate a fall in FEV<sub>1</sub> from baseline by a pre-specified amount. Repeating exercise challenge tests following study drug administration can be performed to assess duration of protection. However, confounding issues for a subsequent exercise challenge test (i.e., patients treated with rescue medication after the first exercise challenge test), should be given consideration in analysis planning.

**Comments on the Draft Guidance for Industry:**  
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**11. Lines 207-209**

We suggest clarifying that ‘response’ in this section is in relation to the exercise challenge and not to the study treatment.