



February 1, 2002

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20857

Re: Docket Number 01D-0432
Response to FDA Call for Comments
Draft Guidance for Industry: Evaluation of the Effects of Orally Inhaled and Intranasal
Corticosteroids on Growth in Children

Dear Sir or Madam:

Reference is made to the draft guidance issued September 2001 (Federal Register Doc. 01D-0432) entitled, "Draft Guidance for Industry: Evaluation of the Effects of Orally Inhaled and Intranasal Corticosteroids on Growth in Children".

AstraZeneca LP has reviewed the draft guidance and our comments are outlined in the attached document. We hope that you find this information useful in clarifying and adding to the pending final guidance document. Thank you for your consideration.

Please direct any questions or requests for additional information to me, or in my absence to Robert Monaghan, Associate Director, at 302/885-4227 or to James Sullivan, Manager, at 302/885-1423 (please note new telephone numbers).

Sincerely,

A handwritten signature in cursive script that reads "Eric Couture".

Eric Couture, PhD
Director, Regulatory Affairs
302/885-1263

01D-0432

US Regulatory Affairs
AstraZeneca LP
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**Comments from AstraZeneca on the FDA Draft Guidance for Industry
Evaluation of the Effects of Orally Inhaled and Intranasal Corticosteroids on Growth in
Children**

Comments are summarized below:

- General Comment

The proposed study design does not provide any balance between the effects of the corticosteroid on growth versus the effects of more severe disease on growth. Presentation of data in labeling should contain a qualifying statement regarding the relative mismatch of disease severity to dose and that long-term implications and effects in other age groups are unknown.

Section	Line Number	Comment or proposed replacement text
Title		We suggest referring to "...Growth in Children" as "...Growth in Pre-pubertal Children". This more accurately reflects the population being studied.
I. Introduction	Lines 19-20	If the term "linear growth" is used in this guidance, it should be defined and used consistently.
I. Introduction	Lines 24-25	Please define "active moiety" and clarify if this refers specifically to steroids.
II. Background	Lines 56-57	We suggest revising "...however, many recommendations can be extended to include evaluation of possible growth effects with other therapies for asthma and allergic rhinitis." to read "...however, many recommendations can be extended to include evaluation of possible growth effects with other therapies for asthma and allergic rhinitis, in cases where effects on growth are anticipated based on pharmacological evidence."
II. Background	Lines 80-83	Please address the use of PK bridging in relation to combination products. For combination products that include a component for which there is no pharmacological evidence for growth suppression (e.g. beta-agonist), PK bridging to the corticosteroid mono-product can be considered.
III. General Study Design Recommendations for Growth Studies	Lines 92-93	Please note that double blinding of studies may be difficult and burdensome if an active control is necessary that would require double-dummy blinding. In these cases, open-label designs should be considered.

III. General Study Design Recommendations for Growth Studies	Lines 96-97	The Guidance refers to phase 3 or 4 studies. Growth studies should be considered as a phase 4 commitment for steroids that have a pediatric indication and not as a requirement for registration.
III. General Study Design Recommendations for Growth Studies	Lines 101-102	Patient stability criteria would be helpful during baseline period to help assure that patients complete the 12-month treatment period.
III. General Study Design Recommendations for Growth Studies	Lines 126-128	We suggest revising "...for patients who discontinue because of worsening symptoms..." to read "...for patients who discontinue for any reason – particularly because of worsening symptoms of the underlying disease - ..."
IV. Protocol Design B. Exclusion Criteria	Lines 187-189	Please cite references for the 3 rd and 97 th percentiles.
IV. Protocol Design E. Dose and Dosage Regimens	Lines 229-230	We suggest revising "Sponsors should include the proposed to-be-marketed or labeled starting pediatric dose of drug in the growth study." to read "Sponsors should include the highest proposed to-be-marketed or labeled pediatric dose of drug in the growth study."
IV. Protocol Design F. Data Quality	Line 235	We suggest revising "The protocol should specify..." to read "The protocol or prospective statistical analysis plan should specify..."
IV. Protocol Design H. Sample Size	Lines 255-269	We agree with the philosophy set forth in the 2nd paragraph of Section II. Background. In particular, we agree that "a clinically meaningful difference of 1-year growth velocities between treatment groups is difficult to define". Therefore, we do not understand how the Agency arrived at the recommendation stated twice in Section IV.H. that the width of the 95% CI for the estimated difference in mean growth velocities between treatments to be not "considerably wider than 0.5 cm". It appears that the rationale for the 0.5 cm interval width is based upon the minimal treatment difference that has been demonstrated for some steroids to date. The rationale for linking previously demonstrated mean differences to the current definition of acceptable precision is difficult to understand. Without knowing what degree of change in growth velocity should elicit concern from the clinician, there appears to be no scientific basis for proposing a minimal interval width as small as 0.5 cm. However, if this approach to sizing and analyzing the studies is kept in the guidance, then we propose that 0.5 cm be replaced with 1.0 cm - a more commonly reported treatment difference for inhaled

		steroids. The proposed sample size could be adjusted down accordingly, allowing multiple doses of the steroid to be more feasibly studied. A confidence interval width of 1.0 cm would provide sufficient precision to signal (or rule out) a reduction in growth associated with compounds, including those which have previously demonstrated mean treatment effects of 0.5 cm or greater per year.
V. Data Analysis	Lines 275-284	We note that "standard deviation scores" have been previously used. Please comment on the acceptability of this approach.

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