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September 14, 2000

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

RE: Docket No. 00D-1335
Draft Guidance for Industry on Allergic Rhinitis: Clinical Development
Programs for Drug Products; Availability

Dear Sir or Madam:

Reference is made to the June 21st Federal Register notice (FR Doc. 00-15632 Filed 6-20-00; 8:45 am) announcing the availability of Draft Guidance for Industry on Allergic Rhinitis: Clinical Development Programs for Drug Products; Availability.

AstraZeneca has reviewed this guidance and our comments are as follows:

Comments to Guidance to Industry – Allergic Rhinitis

Line 35: Allergic Rhinitis refers to the nasal symptoms. Other symptoms such as conjunctival and bronchial or dermal are to me specific responses to allergen. If FDA wants to address rhinoconjunctivitis this should be more clearly explained. Prefer to address allergic rhinitis and limit the definition and efficacy evaluation to rhinal symptoms. Suggest that mucosal itchy feeling regardless of in the throat, nose or eye could be referred to as mucosal itchiness.

Line 68-70: If the emphasis is on identification of the lowest effective dose, is there a tendency to approve doses, which demonstrate an effect, but not the maximum effect, particularly for programs, which are based on subjective symptom scores?

Line 68-71: Lowest effective dose – the definition of this is difficult. Supposing a S-shaped dose-response curve depending on the interval between studied doses and the sample size it would seem possible to detect a small magnitude with a statistical significant difference to placebo in the absurd. Maybe in a population of 200,000 patients 10 µg of any nasal steroid could be defined as LED. Thus, further guidance regarding LED seems necessary. The lowest dose reaching maximal achievable efficacy maybe is more relevant och a guidance on what is a clinically relevant efficacy. Can not understand why this is "particularly important for intranasal steroids". Maybe this is true in todays environment but this guideline will cover also entirely new classes of drugs and combinations of drugs.

Line 124-127: Cortisol level testing: guidance suggests 12 hr or 24 hr urinary measures as acceptable. However, Pulmonary Division has not been willing to accept 12 hr measures.

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Line 127: Reference to oral prednisone, we find it ethically questionable to expose patients to weeks of cortisol suppression by systemic steroids typically 6 w with the only reason to get a positive control even if kids are exempt (L293).

Line 130: The incidence of cataract is very low and to study this vast numbers of patients are needed .

Line 133: Glaucoma is even more rare after systemic steroids and the link to inhaled GCS definitely not confirmed.

Line 301: Knemometry is an indicator of a systemic effect but highly questionable as a growth parameter. However, Knemometry and growth seems to be linked in FDAs reasoning.

Line 362: If this type of information should be of any value means of considering these aspects in the analysis should be at hand. At present we can only confirm that patients have been exposed and maybe grade it none, low moderate, severely. It will be tricky and add a lot of data maybe for no use. Regional or sitebased pollen counts and meteorological records should be sufficient.

Line 445-446: By requiring a description of the differences between the active and placebo treatment in the protocol, which is provided to each investigator, it seems that the agency is maximizing the possibility of unblinding the results. While information about the differences should be discussed with the agency, it seems that this discussion would be more appropriate between the sponsor and the agency in separate correspondence, which would not be available to all investigators in the trial.

Line 480: Instantaneous and reflective scores will not be independent variables. Instantaneous necessary for specific analyses like onset and duration of action.

Line 480: Weighing the itch/sneeze symptoms as 2/4, and blockage and secretion as ¼ each in a combined score to renders a rationale from the FDA.

Line 528: We have been informed we have freedom to pick 3.

Line 509: The issue of how to make reflective and instantaneous scoring independent variables is a problem.

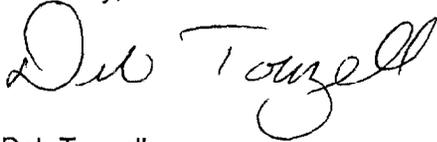
Comment on Sections VI B and VI D of the references draft FDA guidance:

Here, the Agency describes an analysis approach in which mean differences between active and placebo from serial measurements of symptoms would be used to make an inference about a "time to" variable. The suggested analyses are on the wrong scale to make an inference about timing. A more appropriate analysis would be to define "maximal effect" and "action" at an individual patient level and then perform a descriptive of formal statistical analysis on the "time to" scale, utilizing methods appropriate for data captured on a time scale (eg, survival analysis methodology). Attributes such as "time to maximal effect" and "onset of action" should describe the compound and should be invariant to the size of the study on which the claim is based (for example, consider how the half-life of a

compound is calculated). A larger study should provide greater confidence in an estimate of a compound's attribute, but it should never be allowed to more or less determine what the value of the estimate would be. As currently stated, the draft guidance risks allowing advantageous labeling for the compound involved in the largest trial - for the procedures recommended will reward the highest-powered study and not the compound with the best efficacy profile.

Thank you for your consideration.

Sincerely,

A handwritten signature in black ink that reads "Deb Touzell". The signature is written in a cursive style with a large, looped initial "D".

Deb Touzell
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Regulatory Affairs
AstraZeneca Pharmaceuticals
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PRC/dt