AstraZeneca

October 5, 2001

Dockets Management B
(HFA-305)
Food and Drug Admini
12420 Parklawn Drive
Room 1-23
Rockville, MD 20857

Dear Sir or Madam:

Section Number, Page Number	**Comment or proposed replacement text**
Section II, A., Page 2	*Studies that should be included in the Clinical Trials Section* This section of the guidance should provide more detail and clarity regarding the types of clinical studies that would provide important information about the limitations of effectiveness of a drug or biologic. The guidance should also indicate how information regarding pediatrics and other special populations should be included in the Clinical Studies section.
Section II, B, Page 2, Bullet point #2	*Studies that should not be included in the Clinical Trials Section* Information from comparative studies that provide support for the effectiveness of a drug should be included whether or not particular "claims" about the data may be supported by substantial evidence. Limitations regarding these data can be readily described in the labeling and/or promotional materials. See comments to Section III, A-4.
Section III, A-2, Page 4 Bullet point #4	*Amount of Detail* The guidance states that in cases where a new drug appears to have effects that are typical of its class, less detail is needed in describing the study. This is a subjective standard that may be difficult to apply consistently. It is the opinion of many in the medical community that efficacy differences between agents in the same class are meaningful. The FDA's comments on this point imply that in evaluating in-class product effects, the assessment of efficacy across clinical trials (ie, non-head-to-head studies) may be used, which is not a scientifically valid standard for comparison. Also, the lack of detail in clinical trial labeling information may put later market entries into a drug class at an unfair disadvantage when formulary committees, etc. are considering these products
Bullet point #8	The comment regarding needing less detail for clinical

	endpoints that are not readily measurable or applicable in clinical practice is questionable. Data that are meaningful to prescribers should not be minimized. The product labeling should be an authoritative informational document and the potential promotional implications of the inclusion of certain data should not result in the exclusion of information that is helpful to health care providers.
Section III, A-3 *Page 4*	*Endpoints, Closely Related Endpoints* Information describing secondary endpoints, whether they are identified as such, can be extremely useful to prescribers. Distinguishing primary from secondary endpoints is likely to be helpful to the understanding of a drug's effect in many cases. Although a product approval is most likely to be based on primary endpoint findings, a strongly positive outcome on secondary endpoints indicates that the results of the trial are robust. Depending on individual patient needs, information about secondary endpoints may be of particular interest to a practitioner and may hint at limitations of effectiveness in cases where the primary endpoint is positive, but the secondary endpoints fail to show efficacy.
Section III, A-4 *Page 5*	*Comparative Data* In many therapeutic areas, including oncology, psychiatry, and congestive heart failure for example, it is very difficult to randomize patients to a placebo unless the new therapy is given in a background of underlying standard therapy. The identity of an active comparator and the results from an active comparator arm are important to a clinician's understanding of a drug in these situations. Whether the standards are met for making certain comparative claims in the promotional setting should not dictate whether helpful clinical trial information will be included in product labeling. The guidance should provide clarification regarding statements concerning "substantial evidence" in the context of active control clinical studies. The provisions of the FDA Modernization Act allow that data from one adequate and well-controlled clinical investigation and confirmatory evidence may provide substantial evidence

	to obtain approval to market a drug product. This standard should also apply to an active control study that provides the primary support for effectiveness. The guidance should make clear that in these instances the absence of a second confirming study will not prohibit the inclusion of information from this type of study regarding the identity of the active control and the active control arm. The second paragraph in this section describing a clinical trial with three treatment arms (study drug, active control, and placebo) and how to describe the trial in the label seems directed toward those types of primary care products where placebo trials are typically done. Placebo controlled studies would exclude information from the vast majority of cancer studies and psychiatric studies where placebo's may not be appropriate or ethical. In addition, for reasons other than establishing non-inferiority, it may be useful to include information on the active comparator used in the trials that establish efficacy of a drug. For example, a more complete understanding of the results of a trial of an antidepressant drug in special populations may be possible if it is known whether a tricyclic antidepressant or an SSRI was used as a comparator.
Section III, C-2 *Page 7* *Bullet point #2* *Bullet point #4*	*Treatment Effect* This paragraph appears to confuse the concepts of treatment effect and the effect within each treatment group. Accordingly, the first sentence should be replaced with the following sentence: "The treatment effect should be represented, typically, by an estimate of the central tendency of the treatment effect (eg, a least squares mean difference) with a corresponding measure of the variability of that treatment effect (eg, the 95% confidence interval for the estimated mean difference)." It is stated that a confidence interval is typically more informative than a p-value and is the preferred method for describing uncertainty of the treatment effect. It is our opinion that prescribing physicians have a better understanding of p-values than of confidence intervals. The Agency should provide more information to support the conclusions made in this paragraph.

Section III, C-4 *Page 8* *Bullet point # 3*	*Demographic Subgroups* This part of the guidance states that summary statements about the results of treatment effects in age, gender, or racial subgroups should be included in the clinical studies section labeling. Bullet point number 3 provides a summary statement that "examination of age and gender subgroups suggested a larger treatment effect in women...but no age-related differences. There were too few black patients to adequately assess differences in effects in that population". This type of information is speculative in nature and should not be included in the labeling.
Section III, D-2 *Page 9*	*Continuous Variables* As currently written the third sentence in this paragraph is confusing because means and medians are not designed to adequately convey the variability of responses. Accordingly, the sentence should be revised to read as follows: "When typical measures of central tendency and variability (eg, mean with standard deviation) do not adequately convey the distribution of the responses...."
Appendix, II-B *Page 12*	*Histogram* Typically, histograms present grouped responses on the x-axis, and are therefore not presentations of individual patient data in these cases. In addition, when the x-axis represents grouped responses, these graphs can be misleading.
Appendix, II-B *Page 12*	*Line Graph* The addition of error bars to line graphs is not helpful. Standard error bars and within-group confidence intervals can be misinterpreted as indicative of significant between-group differences. Instead of within-group standard errors, confidence intervals for the between-group treatment effect should be provided.
Appendix, II-B *Page 13*	*Cumulative Distribution Plot* It is questionable whether a prescribing physician or healthcare professional would be able to make use of such a plot.

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