



Date: AUG 12 2002

Dockets Management Branch  
Food and Drug Administration  
HFA No. 305, Room No. 1061  
5630 Fishers Lane  
Rockville, MD 20852

Re: Docket Number 02D-0258  
Response to Food and Drug Administration Call for Comments

Dear Sir/Madam:

Reference is made to the Federal Register notice (Federal Register Vol. 67, No. 133, July 11, 2002) of the availability of the draft revised "Guidance for Industry on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations" for comments [Docket No. 02D-0258].

AstraZeneca Pharmaceuticals LP (AstraZeneca) has reviewed this draft revised guidance and offers the following comments:

- This revision to the final guidance published in the Federal Register on October 27, 2000 (65 FR 64449) reflects two major points:
  1. removal of the replicate design recommendation for extended release products;
  2. removal of the IBE and PBE criteria as a method for market access.

Overall, we welcome these changes and find this version of the guidance to be a significant improvement over the previously published October 2000 final guidance.

- In general, there is a lack of information and guidance given for statistical analysis and standards for bioequivalence. Does the FDA intend to promulgate such guidance in a separate guidance document on statistical approaches? Section IV of the revised draft guidance provides a few general principles, such as a criterion to allow the comparison, a confidence interval for the criterion, and a BE limit. Presumably the inclusion of the 90% confidence interval within 80-125% for AUC and  $C_{max}$  ratios will be the standards. However, this is not explicitly stated anywhere, with only indirect mention made under "Narrow Therapeutic Range Drugs" (Section VI.F) and rounding off principles (Attachment A).

02D-0258

C7

- It may not be appropriate to use the bioequivalence limits of 80-125% for  $C_{\max}$  (or partial AUC for early exposure) when we compare an immediate release solid dosage to other formulations such as solutions, capsules, suspensions, and various controlled release formulations.
- AstraZeneca noted the Agency's recommendation of single dose studies to demonstrate bioequivalence because they are *generally* more sensitive in assessing release of the drug substance from the drug product into the systemic circulation. The clinically most relevant exposure parameters for drugs that are chronically used are AUC and  $C_{\max}$  obtained after multiple dosing, especially if the pharmacokinetics are time-dependent. Furthermore, AUC estimates after a single dose will be less reliable, due to the need for extrapolation to infinite time. For drugs with long elimination half-lives and/or extended-release products, excessive blood collection may be needed for calculation of  $\geq 80\%$  of the total AUC. Steady state studies should therefore be an option even under circumstances other than those defined in §320.27(a)(3).
- The guidance should provide specific suggestions for the design of bioavailability and bioequivalence studies for highly variable drug products (either high inter- or intra-subject availability) and for parallel designs for drugs with a long half-life or large intra-subject variability.
- Please consider adding the following text to line 7, Section III.A.1 on page 7: "***Since the intra-subject variability is generally less than the inter-subject variability and a potential carry over effect is generally negligible, a crossover design is typically used for BA/BE studies.***"
- Please add "*crossover*" to the text in line 1, Section III.A.4 on page 7, so that the final text would read: "Non replicate ***crossover*** study designs are recommended ....."
- Please make the following change to the text in line 11 of Section V on page 8: "***Inferential*** statistical analysis of subgroups is not recommended."
- Please make the following changes to the text in lines 1 and 2 Page 24, lines 1 and 2: "Ratios of mean ***PK parameters***" and "Confidence intervals ***for the ratio of mean PK parameters.***"
- In Section III.A.8.a, it is not clear how the determination of an early exposure measure (partial AUC) will be treated. For compounds for which this parameter is deemed "informative," does early exposure determination impose an additional hurdle (i.e. establish equivalence in  $C_{\max}$ , AUC *and* the partial AUC?).

- In Section V.D.2, the use of replicate study design is recommended for a “highly variable” drug product. Please provide the Agency definition of a “highly variable” drug product.
- In Attachment A, it is stated that sampling should continue for “at least three *or more* terminal half-lives...” Please delete the phrase “*or more*.”
- In Attachment A, it is stated that “At least *three to four* samples should be obtained during the terminal log-linear ....” Please change to “At least *three* samples should be .....
- When considering data deletion due to vomiting in Attachment A, depending on the variability of the drug product, setting a window two (2) times the median  $T_{max}$  may not be appropriate to ensure that a subject has absorbed a product prior to vomiting. The Sponsor must have the option to omit a subject based on the Sponsor’s knowledge of the disposition of the compound.
- In Attachment A, please specify the confidence intervals desired (e.g. 95% confidence on estimates of arithmetic means, 90% confidence intervals on geometric mean ratios etc.)

Please contact me with any questions or requests for additional information.

Sincerely,



Philip E. M. Crooker  
Manager  
Technical Regulatory Affairs  
(302) 886-7144  
(302) 886-2822 (fax)

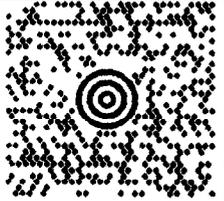
1 LBS 1 OF 1

ASTRA ZENECA PHARMA  
302 886-2806  
1800 CONCORD PIKE  
WILMINGTON DE 19803

SHIP

TO:

FOOD AND DRUG ADMINISTRATION  
5630 FISHERS LANE  
ROCKVILLE MD 20857

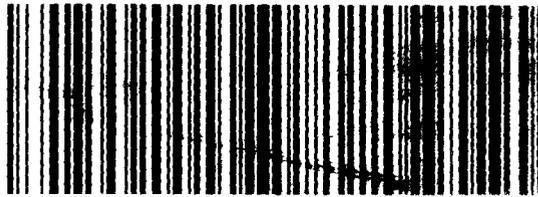


MD 207 9-06



UPS GROUND

TRACKING #: 1Z X29 W25 03 0018 9920



BILLING: P/P

INV#: 62657

ASC 05.00 J69X/164X 16.0A 01/2002