Endocrinologic and Metabolic Drugs Advisory Committee
January 13, 2003

Preliminary Discussion Topics
Agalsidase beta for the treatment of Fabry Disease
Genzyme Corp., Inc.

1) The primary measure of outcome in study AGAL-002 was the effect of the enzyme on renal histopathology. Among the secondary outcomes were measures directly associated with clinical benefit, including the effect of the enzyme on pain and renal function. AGAL-002 was not specifically designed or powered to show an effect on these secondary outcomes. The eligibility criteria did not specifically focus on patients who might be likely to demonstrate an effect on these measures. Nevertheless, an assessment of the treatment-associated effect on important secondary outcomes is useful in lending strength to the findings on the primary endpoint. When compared to placebo, agalsidase treatment did not affect these clinical outcomes.

   Please comment on the relevance of the clinical measures studied and the importance of the observed results. To what extent should the results on these outcomes be considered in evaluating the potential efficacy of this product as predicted by the histologic results?

2) The controlled study AGAL-002 conducted by Genzyme was designed with the primary objective of demonstrating a treatment associated effect on a histologic endpoint of "near-normalization" of renal capillary endothelium on light microscopic examination. Additional histologic analyses of other cell types have also been submitted.

   a) Please discuss the quality and strength of the histology data. Please include discussion of the importance of substrate accumulation in the renal capillary endothelium to the pathophysiology of the kidney dysfunction, and the possibility that "near-normalization" is likely to predict a clinically meaningful effect.

   b) To what extent is it important to show that histologic results are not limited to a particular cell type?

3) Antibody formation against agalsidase beta occurs in a substantial number of patients. In Study AGAL-002 and -005 (the extension study) nearly all patients develop positive antibody assays at some time, and most are persistant, at least at low titer levels. There exists the theoretical potential for these antibodies to impair the activity of the enzyme, either by direct neutralization or by altering the pharmacokinetics and cellular/organ distribution of enzyme uptake. Direct neutralization was not observed.

Longer-term bioactivity data is available in Study AGAL-005 in skin biopsies. Genzyme observed that in 6 of 20 patients who had near-absence of substrate deposition at 5 months of enzyme treatment in skin deep vessel endothelium had increased deposition after 23 months of enzyme treatments. No longer term biopsies were obtained in other tissues. A similar finding had been seen in month 23 superficial skin capillary histology, but was observed to have returned to near-normalization appearance by month 29. No month 29 deep vessel endothelium biopsies are available for these subjects. No diminishment of treatment-associated response in urine or plasma substrate levels associated with antibody formation was discerned.

a) Please discuss your interpretation of these data. To what extent do these findings suggest a waning of enzyme activity.

b) In light of the need for long term, and likely life-long treatment, please discuss how important it is to obtain, and with what degree of rigor (e.g., degree of precision in ruling out a loss of activity) an evaluation of potential antibody-related loss of efficacy and/or activity.

c) If you view this as a critical requirement,

i) Is it reasonable to permit these data to be generated and evaluated after marketing approval, or should the data be available and integrated into a decision about marketing approval? Please bear in mind that rigorous assessment may be more difficult in the post-marketing situation.

ii) Please discuss what types of outcomes would be most useful for assessing persistence or loss of enzyme activity related to antibody formation, and the time frame duration for assessment that you view as important to evaluation of this issue.

4) This product is intended for long term use by patients with Fabry Disease. If marketed on the basis of an accelerated approval, the product must be studied further to describe and verify the clinical benefit. If the verification study were to yield inconclusive results, there would be uncertainty as to the clinical benefit of the product, and FDA would need to consider withdrawal of approval of a product that might, in fact, be beneficial.

   a) Please discuss how FDA should approach verification studies, including the degree to which sensitivity to important, but small amounts of benefit should be sought.

   b) Consider the situation of a post-marketing verification study where the result is inconclusive; e.g., an inability to complete the study as designed due inability to recruit or retain study subjects, or a study result that is not statistically significant but compatible with a worthwhile benefit smaller than the design goal.

      Please discuss what issues FDA should consider in this circumstance and what actions you would advise FDA to take regarding the marketed product.

5) Genzyme is currently conducting a randomized, controlled study to provide the verification of clinical benefit that they believe the histologic measure predicts. Genzyme proposes to change this study design to a single arm, open label study of treatment with agalsidase beta. In order to support this proposal, they have provided a database of information on creatinine levels in patients with Fabry Disease. Genzyme proposes that this database can form an external, historical control group for comparison with the data in the proposed open label treatment study.

   a) Please discuss the quality and strength of data in this database, particularly as regards the intended use as a historical control.

   b) Please discuss whether Genzyme's completed analysis (and/or the newly proposed analysis) provides a sufficiently accurate and precise prediction of the renal progression rate.

   c) Is this database, as analyzed, sufficient to serve as a comparator group to judge the efficacy of the product?