FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
ANTIVIRAL DRUGS ADVISORY COMMITTEE (AVAC) MEETING

QUESTIONS TO THE COMMITTEE

August 7, 2002

Holiday Inn, 8120 Wisconsin Avenue, Bethesda, MD

Topic: Clinical trial design issues in the development of products for the treatment of chronic hepatitis B infection

Patient Populations

1. Please identify patient populations that are appropriate targets for treatment studies (consider attributes such as stage of disease, viral genotype, co-morbidities, lamivudine resistance, IFN-experience, pediatrics, HBeAg-/HBV DNA+)? Please include demographics in your discussion, i.e. race and ethnicity.

2. Which of the aforementioned patient subgroups is essential in a marketing application? In particular, comment on race and ethnicity, disease stage and comorbidities.

Control Arms

3a. Discuss the role of the following controls in the compensated liver disease group:

- Placebo controls/delay of initiation of treatment; and of what duration?
- Lamivudine (or other antiviral drug) monotherapy
- Interferon

3b. Please also discuss controls for patients with decompensated liver disease or who have failed previous regimens.

Study Endpoints and Timing of Evaluations

4. Considering the patient populations identified in question #1, the information presented today, and the necessity that endpoints for registration be clinically meaningful, please answer the following:

   - Which endpoint (or combination of endpoints) should be the primary in clinical trials? Please discuss histologic, serologic (HBeAg loss vs. seroconversion; HbsAg loss vs. seroconversion), biochemical, and virologic endpoints.
   - When should the assessment of the primary endpoint be made?
   - List the most appropriate secondary endpoints and rank them in order of importance.

5. For histologic endpoints, what is the preferred method of histologic scoring? What degree of change in histologic score is clinically meaningful?

6. For virologic endpoints, which assay is best suited for clinical trials? What is the appropriate cutoff point for HBV DNA (eg. $<10^5$, $<10^4$, etc)? Should viral genotyping be done and why?

7. For patients with decompensated liver disease, please discuss the feasibility/validity of the following alternative endpoints:

    - mortality
    - change in Child Pugh or MELD score (or its components)
    - transplant/no transplant
    - occurrence of liver disease associated illness (variceal bleed, SBP, etc)

Long Term Follow-Up

8. Beyond the assessment of the primary endpoint for registration, what is the appropriate duration of studies for treatment of chronic hepatitis B infection, and what kind of information should be gathered?