FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

March 13, 2006

Oncologic Drugs Advisory Committee (ODAC) Meeting

Gaithersburg Hilton, Gaithersburg, MD

FDA Questions for the ODAC
AM session: Non-clinical and Phase 1 Issues

FDA and the International Conference of Harmonization (ICH) Guidance documents provide recommendations for non-clinical testing of small molecule drugs and biologics under development for human use. These guidances outline general principles and are not tailored to drug development for a specific medical condition. While the ultimate goal of all non-clinical testing is to characterize adverse drug effects and the pharmacokinetic profile in order to guide safe use in human subjects, the amount of non-clinical safety data needed to support initiation of clinical testing differs, based on the proposed use and patient population(s). The non-clinical data must be sufficient to permit FDA to conclude that the patients are not exposed to unreasonable risks.

Not only will the patient population dictate the amount of non-clinical data necessary to support clinical testing, but the product class is also a factor in determining both the type of studies conducted, and the amount of non-clinical data required to initiate clinical testing. Biotechnology-derived drugs such as monoclonal antibodies differ from small molecular weight drugs in their biology, pharmacodynamics, pharmacokinetics, and potential for cumulative toxicity. Moreover, the pharmacologic and potential toxic effects of biologics may differ qualitatively and/or quantitatively from effects seen with small molecular weight drugs, may be more apparent with increasing exposure, may not be identified by routine non-invasive tests typically used to monitor toxicity in clinical trials (e.g., urinalysis, chemistry profile, or ECG), and may not be readily reversible. The FDA considers all these factors when advising sponsors about the design of their non-clinical safety programs for oncology drugs and biologics. The Agency believes an individualized, science-based approach to non-clinical testing requirements across different product classes of anti-tumor therapies is appropriate.

FDA seeks the Committee's advice regarding approaches to non-clinical safety data that will facilitate development of drugs and biological products for the treatment of cancer while safeguarding patient safety.

1. For most drug development programs, FDA recommends that the duration of non-clinical studies match the duration proposed for the clinic, an approach supported by the ICH M3 Guidance document. However, an abbreviated duration of non-clinical testing is generally acceptable for small molecule drugs under development as anti-tumor therapies. An abbreviated dosing duration has also been proposed for selected biological products intended as anti-tumor treatments. Please discuss scenarios where the duration of non-clinical studies:

   a. may be abbreviated relative to the clinical duration.
   b. should match the duration of the proposed clinical study.

   In your response, please address the anticipated non-clinical parameters (*e.g.*, PK/PD, toxicity profiles) that should be considered in determining the minimum duration of toxicity testing.

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2. The FDA has received applications that do not provide adequate non-clinical data to support continuation of dosing for an extended duration in a phase 1 clinical study. Please discuss the following:

    a. In what clinical setting and/or patient population (*e.g.*, refractory disease, indolent disease status, no prior treatments) would the risk of continued treatment in the absence of long-term non-clinical safety data be considered acceptable?

    b. Where extended non-clinical safety data are unavailable for long-acting biologic therapeutics (e.g., monoclonal antibodies), FDA believes that continued dosing in the phase 1 study is appropriate only in patients who have demonstrated an acceptable benefit:risk (*e.g.*, objective tumor responses or symptomatic improvement). Should extended non-clinical testing be available prior to allowing continued dosing in patients who have not had clear evidence of benefit? Please discuss the following scenarios: the patient with stable disease, the patient with progressive disease. [Voting]

    c. How should patients who continue dosing in the absence of supporting non-clinical data be informed of the limitations of the non-clinical data and potential risks? Should they sign a new consent form, and if so, what should be conveyed (*e.g.*, the lack of information about cumulative/delayed onset toxicity, the lack of information on how best to monitor patients, the potential for irreversible toxicity)? What additional information should the sponsor obtain during the clinical study to minimize the risks to the study subjects in the absence of supporting non-clinical safety data (e.g., interim reports of ongoing non-clinical studies)?