DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Memorandum

Date: October 12, 2005

To: Oncologic Drugs Advisory Committee (ODAC) Members and Guests

From: Richard Pazdur, M.D.
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Subject: FDA Background Package for November 8, 2005 ODAC Meeting on Accelerated Approvals

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Applicants submitting New Drug Applications (NDAs) and Biologics License Applications (BLA's) to the FDA are required to demonstrate the products to be safe and effective. The safety requirement is derived from the Federal Food Drug and Cosmetic Act of 1938 (FD&C Act). The effectiveness requirement stems from a 1962 amendment to the Act. Subsequent judicial rulings established that effectiveness means an effect that is clinically meaningful (e.g., improved survival, decreased rate of important events such as stroke, heart attack, beneficial effect on symptoms, etc,) or there is an effect on a "surrogate endpoint." A surrogate endpoint is a laboratory measure or physical sign used as a substitute for a clinically meaningful endpoint. Treatment-induced changes in a surrogate endpoint are expected to reflect proportional changes in a clinically meaningful endpoint.

In 1992, the NDA and BLA regulations were amended (Subparts H and E, respectively) to allow for "accelerated approval" in diseases that are serious or life-threatening. Under accelerated approval regulations, for indications where the new product appears to provide benefit over available therapy, accelerated approval may be granted on the basis of a surrogate endpoint that is "reasonably likely" to predict clinical benefit. The preamble to the rule is clear in identifying this as a lower standard of evidence than would support regular approval based on a surrogate. The applicant is required to perform studies to demonstrate that treatment with the product is indeed associated with clinical benefit. These trials may be either a new trial or completion and final follow-up of patients on an existing trial. In either case, the required post-marketing study must show an effect on an endpoint that reflects clinical benefit. If those studies fail to demonstrate clinical benefit, or if the applicant does not show "due diligence" in completing the trial(s), the regulations describe a process for removing the product from the market.

In March 1996, a U.S. presidential document entitled 'Reinventing the Regulation of Cancer Drugs' announced how the FDA would apply the accelerated approval rule to new cancer treatments, specifically by basing approval on demonstration of objective tumor shrinkage in patients with refractory disease or whose disease had no useful

therapy. The approach toward approval and subsequent verification studies outlined in that document is summarized below:

1. For products approved on the basis of tumor shrinkage, post-approval studies will usually be required to further define the utility of the new agent for the approved and/or other indications, either alone or in combination with other agents.

2. For accelerated approval of products that remove treatment-associated toxicities, post-approval studies will be required, as appropriate, to study the effect of the therapy on survival, and/or to demonstrate that the surrogate measures correspond to clinical benefit

3. A post-approval study will not necessarily be required in the exact population for which approval was granted. Where a product was approved to treat patients with refractory malignancy, additional information from that population may not, for example, be as useful as randomized, controlled trials in a previously untreated population.

This initiative has been successful in promoting the approval of cancer products with anti-tumor activity prior to verification of clinical benefit. In March of 2003, an ODAC meeting was held to review and discuss past oncology product accelerated approvals and progress with the associated phase 4 commitments. At that meeting, 8 products that received accelerated approval prior to May 2001 were discussed. Those discussions are summarized in Dagher R, et al. Accelerated Approval of Oncology Products: A Decade of Experience. J Natl Cancer Inst 2004; 96:1500-1509 (item 6 in this briefing material).

The purpose of this ODAC meeting is to provide an update on the status of the accelerated approval program. We are reviewing products that received accelerated approvals prior to 2002 and have not completed their confirmatory trials. Specifically, progress with associated phase 4 commitments will be discussed, and further input on improving the process will be solicited.