Reinventing the Regulation of

CANCER DRUGS

PRESIDENT BILL CLINTON
VICE PRESIDENT AL GORE

MARCH 1996

REINVENTING THE REGULATION OF CANCER DRUGS

ACCELERATING APPROVAL AND EXPANDING ACCESS

President Bill Clinton
Vice President Al Gore

National Performance Review

March 1996

OVERVIEW

Introduction

The Food and Drug Administration has demonstrated a longstanding commitment to the prompt consideration and, when appropriate, early approval of new therapies for cancer patients. However, the overall process of developing a new agent is a complex one, and a substantial period exists between the first introduction of the agent into humans and the completion of clinical trials leading to formal submission of an application.

Faster Approvals

In order to speed up the entire process further, FDA is adopting a uniform policy that will permit accelerated approval of a significant number of new cancer therapeutics. In the past, FDA has approved cancer therapies on the basis of an agent's ability to produce an effect on the well-established and long-recognized criteria such as survival, improved quality of life, and relief of symptoms, as well as objective disease regression. When partial response of disease (measurable but incomplete tumor shrinkage) has been noted in patients who have extensive or metastatic cancer, it has often correlated with the other approval criteria. Because of this experience, FDA believes that for many cancer therapies it is appropriate to utilize objective evidence of tumor shrinkage as a basis for approval, allowing additional evidence of increased survival and/or improved quality of life associated with that therapy to be demonstrated later. By utilizing objective response as a surrogate endpoint in cancer clinical trials, FDA will decrease the total time needed for marketing approval in many situations.

Expanded Access

FDA is also committed to helping provide greater patient access to potentially effective cancer treatments even before full marketing approval, wherever possible. So-called "expanded access" mechanisms, such as Treatment Investigational New Drug (IND) protocol, the Group C Program, and "compassionate use" (single patient) protocols have been successfully utilized. They permit patients to receive promising but not yet fully studied or approved cancer therapies—that are undergoing clinical testing—when no other satisfactory options exist. To facilitate this availability even more, FDA is adopting a policy that will actively encourage the submission of expanded access protocols for U.S. patients for therapies that are approved in other countries. This policy will help ensure that

promising new therapies are available in the United States near the time of their availability in other countries and will ease the burden on commercial sponsors of preparing an expanded access protocol submissions.

Listening to Patients/Removing Barriers

FDA is undertaking two additional efforts that should positively affect the review of new cancer therapies. One policy will improve the representation of patients with disease-specific perspectives on FDA's cancer-related advisory committees. The second policy will reduce the number of IND Applications required for additional studies of already approved therapies.

FDA is undertaking these initiatives after carefully considering suggestions and advice offered by patients and their advocates, pharmaceutical industry representatives, physicians, and researchers. The Agency will continue to seek their views, as well as those of FDA advisory committees and the National Cancer Institute. FDA's intention is to foster expanded access to promising cancer treatments because cancer is among the greatest public health problems facing the United States. These initiatives are also prompted by the increasingly large number of cancer therapies being developed by the pharmaceutical and scientific communities and the demonstrated willingness of these communities to find the best use of new agents by continuing to study them after initial approval. FDA wishes to encourage the rapid development and availability of these and future therapies.

FDA'S PROPOSALS FOR REFORM

Accelerating Approval of Cancer Therapies For Primary and Secondary Indications

Background: Currently, FDA may utilize the "accelerated approval" process to allow marketing of therapeutics for patients with serious and life-threatening diseases. Under existing regulations, a new drug or biologic agent that is intended to provide a meaningful therapeutic benefit over existing therapies may be approved on the basis of:

> *adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty about the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.*
> (21 *CFR* § 314.510 and 21 *CFR* § 601.41.)

Although the accelerated approval provisions have been applicable to promising treatments for cancer patients who do not benefit from or cannot tolerate available therapy, this approval mechanism has not been frequently utilized, largely because general agreement on reasonable surrogate endpoints has been lacking.

Until now, therapies for cancer patients have usually been approved on the basis of objective response to the agent (tumor shrinkage) together with direct evidence that the therapy produces measurable clinical benefit. Typical approval endpoints have included response rate together with increased patient survival, decreased recurrence rate, increased disease-free interval, and/or improved quality of life. It has been assumed that durable, complete clinical response (complete disappearance of detectable tumor) is a valid surrogate for such clinical benefit, but it is only infrequently achieved. Much more commonly, partial tumor shrinkages are induced, and evidence has accumulated that such responses are often directly linked to longer or better patient survival. In fact, for certain new agents, FDA has already begun to rely on a reasonably high rate of verifiable objective partial response to the

therapy as a basis for approval of agents to treat refractory malignancies, without requiring evidence of improved survival or quality of life. Subsequently, additional trials have been conducted to confirm or expand the product's indications. While the predictive value of partial responses may still be a matter of discussion and study for all types of cancer patients, FDA has concluded that for patients with refractory malignant diseases or for those who have no adequate alternative, clear evidence of anti-tumor activity is a reasonable basis for approving the drug. In these cases, studies confirming a clinical benefit may appropriately be completed after approval.

Proposal and Justification: Under this initiative, FDA will substantially expand the use of the accelerated approval process for cancer treatments, based upon verified and recognized demonstration of objective tumor shrinkage. For approval, the potential effectiveness of the treatment should outweigh its toxicities. FDA will also apply the accelerated approval provisions to certain products intended to remove a serious or life-threatening toxicity of cancer treatment.

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.

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.

A post-approval study will not necessarily be required in the exact population for which the approval was granted. For example, 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.

In many instances, additional studies would be already under way at the time the accelerated approval is granted. If such studies are adequate and well-controlled (either utilizing proper historical controls or randomization), they may fulfill the accelerated approval requirements for post-approval studies. All required post-approval studies should be carried out with due diligence. Failure to do so would constitute grounds to withdraw approval of the product application. (21 *CFR* § 314.530(a) or 21 *CFR* 601.43(a).) FDA may also withdraw approval of the application if studies fail to demonstrate clinical benefit. *Id.*

Supplemental Applications: The greater utilization of the accelerated approval provisions for cancer treatments should have an important impact not only on original applications but also on supplemental applications for secondary indications. FDA recognizes that the actual use of cancer agents may be far

broader than the approved indications, and that, because of the nature of cancer therapy, the approved label does not necessarily convey all the medical conditions for which the agent is used and may be useful. Nevertheless, for a variety of reasons, the FDA-approved label should accurately convey as many of the agent's uses as are properly supported by data. FDA encourages the submission of supplemental applications for secondary indications and believes that this initiative will significantly expedite the time to marketing approval.

Impact: This new policy is designed to make it easier to study cancer therapies and shorten the total time for first and subsequent marketing approvals for a wide range of cancer therapeutics. The broader use of accelerated approval will provide an important benefit to patients by permitting the marketing of promising cancer therapies at an earlier time than was previously possible. Although the complete success of this initiative depends upon the commitment of product sponsors, clinical investigators and patients to complete crucial studies after marketing, it is FDA's experience that in the field of oncologic therapy there is a tradition of continuing to study approved products.

Implementation and Timeline: This initiative is effective immediately.

Expanded Access to Investigational Cancer Therapies That Have Been Approved in Other Countries

Background: FDA recognizes that many cancer patients who have exhausted standard therapeutic options, or who do not have such options available, seek access to new treatments that may offer some hope of benefit. They may be willing to accept some risk from products still under study and with potentially dangerous toxicities. While most new agents are available in the United States at about the same time as in other countries, if not earlier, there are occasional exceptions. Cancer patients may feel particular frustration when new cancer treatments are approved elsewhere in the world before they are approved in the United States.

Although the primary purpose of the investigational use of a new product is to generate sufficient data to establish safety and effectiveness, several mechanisms currently exist to allow patients "expanded access" to such products (i.e., to allow patients access to the experimental agent primarily for the purpose of treatment rather than data gathering). These mechanisms include Treatment INDs, Group C drugs made available through the National Cancer Institute, and "compassionate use" (single patient) protocols. Ordinarily, these expanded access options become available after the product has been studied in the United States in a substantial number of patients.

Proposal and Justification: FDA believes that when a cancer therapy is under study in the United States in a controlled clinical trial and has been approved by an identified regulatory authority in a foreign country, there may be an adequate basis to allow early expanded access based on the data package submitted to the foreign regulatory authority. Therefore, whenever a cancer therapy for patients who are not curable or well-treated by currently available therapies is approved by a recognized foreign regulatory authority, FDA intends to contact the U.S. sponsor and encourage the submission of an expanded access protocol, regardless of the length of time that the product has been studied in the United States.[1] The expanded access protocol will be directed at the same general type of patient condition and similar dosage and schedule as formed the basis for the foreign approval. An English-language version of the relevant data submitted to the foreign regulatory authority will be accepted as providing the information needed to consider the expanded access protocol application. If these data are adequate, FDA will permit use of the therapy for appropriate patients under the expanded access protocol.

Recognized Acceptable Regulatory Authorities: For consideration under this policy, a foreign regulatory authority is to be identified as having review practices, review standards, and access to

[1] If there is currently no U.S. sponsor, the FDA will contact the foreign sponsor and encourage it to file an IND. Once the IND is filed, FDA will encourage submission of an expanded access protocol.

specialized expertise in the evaluation of agents for use in cancer treatment that are sufficient to allow FDA to conclude that a marketing approval action by that authority is likely to provide an adequate basis for proper consideration of an expanded access protocol for U.S. patients.[2]

Types of Treatments to Which This Policy Applies: FDA will encourage submission of expanded access protocols for therapeutic products under study in the United States that have been approved in a foreign country for treatment of patients with forms and stages of cancer that are not adequately treated by therapies currently approved in the United States. The route, dose and schedule of administration of the agent will generally be similar to that approved by the foreign regulatory authority, unless the sponsor is able to provide data supporting the safety and potential efficacy of an alternate dosing regimen.

Pursuit of Marketing Approval: To ensure that this process does not become a substitute for obtaining full marketing approval, the sponsor of the product will be required to demonstrate that it is pursuing marketing approval—accelerated or otherwise—with due diligence. (See 21 *CFR* §312.42(b)(4)(vii).) Due diligence requires that the sponsor has begun, or made credible plans for, the early initiation of studies designed to obtain data needed for submission of a marketing application. Such studies should be designed in conjunction with FDA to optimize study designs. There is a risk that the availability of expanded access protocols for an unapproved cancer agent may interfere with the enrollment of patients in the trials intended to support marketing approval. It is therefore imperative that the trials intended to support marketing approval be designed to efficiently enroll patients. FDA believes that one of the best mechanisms for ensuring adequate enrollment is to design the trials so that they offer a hope of personal benefit to the patient-volunteers that is at least equal to the hope of benefit associated with treatment under the expanded access protocol.

Impact: This policy will help make experimental cancer therapies available to patients shortly after they are approved in other countries even if they are early in their U.S. development. Reliance on the data submitted to the foreign authority could also ease the burden on sponsors of preparing a U.S. expanded access application. Under an expanded access protocol, the required data collection from the enrolled patients would usually be relatively limited. Nonetheless, this information has sometimes in the past provided important data for marketing applications. To ensure that this process does not become a substitute for obtaining marketing approval, the sponsor of the therapy will be required to demonstrate that it is pursuing marketing approval—accelerated or otherwise—with due diligence. FDA will work with the sponsor to develop an expanded access protocol that does not interfere with the enrollment of patients in the studies that will support approval.

---

[2] For purposes of initiating this policy, countries which use the English language and are identified in Section 802(b)(4)(A) of the Federal Food, Drug and Cosmetic Act will be contacted first.

Implementation and Timeline: To implement this initiative, FDA will establish a system to monitor the approval of new cancer therapies by foreign countries with identified regulatory review authorities. Information from the U.S. FDA about U.S. approvals of new cancer therapeutics will be communicated to them to foster a bilateral exchange. FDA will make initial contact with the identified foreign regulatory authorities within 30 days.

Patient Representation on FDA's Cancer-Related Advisory Committees

Background: FDA relies on several advisory committees to provide the Agency with advice on the consideration of cancer treatments. These panels are composed of individuals from outside the Agency, whose training, skills, and/or experience enable them to offer the Agency needed expertise in making decisions about new medical treatments. Currently, many of these committees include a "technically qualified" public representative who is identified broadly with consumer interests and has been nominated and recommended by a consumer-oriented organization. This individual serves as a liaison with interested consumers and their organizations, as well as other potential constituencies served by FDA, and attempts to represent the perspectives of these groups on issues and actions that come before the committee.

Because there are so many different cancers, the number of appropriate perspectives is larger than a single consumer can represent. As a result, organized patient advocacy groups have requested that their interests be more specifically represented on the advisory committees that consider cancer therapies by the addition of ad hoc representatives who have experience with the specific cancer for which a therapy is under consideration. For certain other advisory committees that review products for other life-threatening diseases, FDA already includes an ad hoc patient representative for the specific condition for which a product is indicated.

Proposal and Justification: It has been FDA's experience that well-informed and motivated representatives of the patient's perspective provide a valuable contribution to the decision making associated with the review of new cancer therapies. FDA has therefore concluded that an ad hoc patient representative with experience in the specific malignancy for which a therapeutic product is under consideration should be included in the advisory committee deliberations concerning that product. This individual will be screened in the same manner as other full members. In order to properly develop a system for selection and service of patient representatives for all future advisory committee meetings on cancer therapies, the agency has enlisted the assistance of an external consultant with expertise in this area.

Impact: This proposal will make more uniform FDA's policy of including patient perspectives on new cancer treatments and responds to public interest in increased participation in the advisory committee process. In addition, the proposal is responsive to a recommendation of the Institute of Medicine's 1992 *Report on FDA Advisory Committees* "that the concept of consumer be expanded to include patients and patient-oriented organizations." Adding participation of ad hoc patient representatives to cancer-related advisory committees will also increase consistency with some other committees that consider products for life-threatening illnesses.

Implementation and Timeline: In order to establish an equitable and efficient framework, FDA is working with an external consultant to develop a model system for recruitment, assessment, selection, and utilization of patient representatives. In the interim, while this report is being considered, the cancer liaison staff in FDA's Office of AIDS and Special Health Issues (OASHI) will:

- Publish a notice in the *Federal Register* to seek greater patient representation on advisory committees that consider cancer therapies, and send letters to individuals and organizations on its cancer mailing list, which includes organizations representing cancer survivors. The letters will invite nominations for candidates to serve as ad hoc representatives to FDA's cancer-related advisory committees. Nominees will be asked to provide copies of their resumés with a brief statement of the disease-related topic for which they would be most appropriate and the details of any financial relationships that they have/had with the persons or companies involved in the manufacture or sale of drugs, biologics and devices.

- When it is decided which products will be considered at an upcoming meeting, the FDA Cancer Liaison Program staff will select appropriately screened and approved nominees for each meeting. The Cancer Liaison Program staff will contact the nominee for each topic, notify the nominee of the general topic to be discussed, and request that the nominee reserve the date of the meeting.

- When specific meeting dates are announced by FDA, the Cancer Liaison Program staff will notify the nominees of the meeting details, ask about conflicts of interest, and confirm availability. The staff will notify the executive secretary of the advisory committee and relevant FDA officials which nominee has been selected.

Clarification of Policy on INDs for Studies of Marketed Cancer Products

Background: Currently, FDA does not require the submission of an IND to study a new use of a marketed drug or biological product, where the agent will be used in generally the same patient population and in generally the same manner for which the agent was approved, and the study is not intended to support approval of the new use or to support a significant change in the labeling or advertising of the product. (21 *CFR* §312.2(b).) Notwithstanding this regulatory exemption, physician-investigators frequently submit INDs for exploratory studies of marketed drugs and biological products for so-called "off-label" uses in situations where an IND is not strictly required. There seem to be two major reasons for these unnecessary submissions: (1) the physician-investigator or Institutional Review Board incorrectly believes that an IND is required, or (2) the pharmaceutical manufacturer agrees to provide the product free-of-charge, but is mistakenly concerned that, unless there is an IND, FDA will view the manufacturer's donation of the product as a promotional activity.

Proposal and Justification: FDA intends to reduce the effort of the clinical investigator by refusing to accept INDs for exempt studies of marketed drugs and biological products. Moreover, FDA will reemphasize that the provision, by a sponsor of a marketed drug or biological product for a study, does not, in and of itself, constitute promotional activity if the product is provided for a physician-initiated, bona fide clinical investigation.

(1) FDA will not accept an IND for the study of a lawfully marketed drug or biological product if the proposed study meets all the criteria specified in 21 *CFR* §312.2(b)(1), as follows:

- The study is not intended to support approval of a new indication or a significant change in product labeling or advertising.

- The study does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with use of the product. Information from previously conducted clinical trials that contain prior human experience relevant to the safety and effectiveness of the drug for a proposed use (*e.g.*, use of larger than usual doses, or use in new combination) can be used to determine the degree of increased risk and the overall acceptability of the risk for the intended study population.

- The study meets the requirements for institutional review and informed consent, and does not commercialize the investigational product.

It is the responsibility of the investigator to determine whether an IND is necessary. Upon request, FDA will provide guidance to physician-investigators about the need for an IND in particular cases.

(2) FDA does not view the supply of a marketed product by the manufacturer or distributor for use in a study, in and of itself, as promotional activity, if the product is provided for a physician-initiated, bona fide clinical investigation. To assess the adequacy of a proposed study, the commercial manufacturer may request review of the investigator's proposed investigational plan. Nothing in this policy prevents FDA from finding that certain subsequent uses of physician-initiated studies by the manufacturer or distributor constitute promotional activity.

Impact: Clinical research will be fostered somewhat by the relief of burdens associated with filing and maintaining an IND. In addition, by not reviewing INDs for exempt studies, FDA will conserve resources that can be redirected to reviewing other applications for promising new therapies.

Implementation and Timeline: This initiative is effective immediately.