FDA BACKGROUNDER

U.S. FOOD & DRUG ADMINISTRATION

Cancer Therapies: Accelerating Approval and Expanding Access

The Food and Drug Administration is undertaking four new initiatives to improve patient access to promising new cancer therapies. FDA will:

- shorten approval times for cancer treatments by recognizing that tumor shrinkage is often an early indicator of a treatment's effectiveness
- work with pharmaceutical companies to make promising cancer therapies approved by foreign countries available to cancer patients even before the product is approved in the United States
- improve the therapy review process by ensuring that all FDA cancer-therapy advisory committee meetings include an *ad hoc* member who has personal experience with the illness for which a new product is being considered
- make it easier for investigators to test new uses for cancer therapies already on the market.

Until now, FDA has usually required that a cancer therapy's sponsor demonstrate improvements in survival time or quality of life before a therapy could be approved. Based on accumulating evidence, FDA now believes it is appropriate to approve products that show evidence of tumor shrinkage for patients who have no satisfactory alternative therapy. Companies can more quickly demonstrate tumor regression than improvements in survival time or quality of life and can do so in studies that are relatively easy to carry out. Allowing companies to provide additional evidence of increased survival or improved quality of life associated with that therapy after marketing approval may, in many situations, substantially shorten (sometimes by years) the total time needed for marketing approval.

Cancer patients and their families sometimes believe that they must travel to a foreign country to receive the newest cancer therapies. While this is rarely so, FDA will make it even less likely by actively encouraging companies to submit expanded access protocols in the United States for cancer therapies that have been approved by recognized foreign regulatory authorities.

FDA advisory committees play a critical role in product review. FDA will improve the review provided by its cancer-therapy advisory committees by adding on an *ad hoc* basis patient representatives, who have experience with the illness for which a therapy is under consideration.

FDA will reduce the number of investigational new drug applications filed for additional studies of already approved therapies. This change will make it easier for researchers to study new uses of already approved therapies.

FDA is undertaking these initiatives after careful consideration of suggestions and advice offered by patients and their advocates, pharmaceutical industry representatives, and physicians and researchers. FDA will continue to seek the views of these interested parties, as well as those of the agency's advisory committees and the National Cancer Institute. FDA's goal is to significantly improve patient access to promising cancer treatments. FDA recognizes that these initiatives may also apply to therapies for patients with other serious and life-threatening diseases.

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PRESIDENT CLINTON ANNOUNCES PLAN TO SPEED CANCER DRUGS

President Clinton today announced a major initiative to make promising new cancer therapies available sooner to American cancer patients. As part of Vice President Gore's National Performance Review, the Food and Drug Administration's report "Reinventing the Regulation of Cancer Drugs" proposes to shorten development and review times for cancer products and to make it easier for many cancer drugs approved elsewhere to be tested and used in the U.S.

"Cancer is a terrible tragedy for many families in this country. With our actions today, we give them new hope," said the President.

"These measures will bring safe and effective therapies to cancer patients sooner," he added. "As we search for new ways to make this happen, creativity and flexibility will be the rule, not the exception."

Joining the President in announcing the cancer drug initiative today were Vice President Al Gore, Secretary of Health and Human Services Donna E. Shalala, FDA Commissioner David A. Kessler, M.D., and _____ [name tk], _____ [title tk].

This cancer initiative represents another element of the Clinton Administration's efforts to streamline the regulatory process and to help the Federal government become more responsive to the needs of its citizens. It was developed with the cooperation and advice of cancer patients and their advocacy groups, representatives of the pharmaceutical industry, physicians and cancer researchers.

The initiative consists of four major proposals:

(1) Accelerated approval for cancer drugs. Although FDA now measures review times for cancer drugs in months, it can take years of testing before a marketing application for a cancer drug even reaches FDA. To speed the availability of cancer drugs, FDA will now rely on partial response (such as measurable but incomplete shrinkage of a tumor) to a therapy, instead of the current criteria such as survival and improved quality of life. By basing accelerated approval on surrogate markers such as tumor shrinkage, and by allowing more definitive data on survival or other criteria to be developed later, FDA believes that many cancer therapies will reach patients sooner.

(2) Expanded Access Programs for Drugs Approved Elsewhere. For patients with serious and life-threatening illnesses such as cancer and AIDS, FDA has devised several programs that provide access to promising but unapproved therapies even as they are being studied. To make even more cancer drugs available before formal approval, FDA will encourage sponsors of drugs approved elsewhere and being studied in the U.S. to apply for expanded access here.

(3) Placing Cancer Patients on FDA Advisory Committees. FDA relies on advisory committees to provide outside expertise on agency policy and product decisions. Each advisory committee typically includes one consumer member. Because cancer is not one disease but many, FDA will improve the review process by

including on each cancer-therapy advisory committee a patient who has experienced the cancer that therapy is designed to treat.

(4) Fewer Applications for Additional Uses of Approved Cancer Drugs. Currently, many researchers and pharmaceutical firms ask FDA to review "supplemental" applications to study unapproved uses for the approved cancer drugs, even if they do not intend to market the drug for the new use. In many circumstances these additional applications are unnecessary. FDA will no longer accept such applications, freeing investigators from unnecessary paperwork and allowing them to devote more of their time to cancer research.

FDA currently has the authority to carry out these initiatives, and it will begin to do so immediately.

In a related initiative, the FDA will soon publish a series of five proposals designed to establish a uniformly high level of standards for mammography centers nationwide. These proposals, which cover such issues as quality assurance, equipment, facilities, and personnel, are expected to be published in the next two weeks.

Mammography remains the single best means of fighting breast cancer, which is expected to strike approximately 185,000 American women in 1996. It is currently estimated that women in the U.S. have a one-in-nine lifetime risk of breast cancer.

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Reinventing the Regulation of

CANCER DRUGS

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NATIONAL PERFORMANCE REVIEW

DETERMINED TO BE AN
ADMINISTRATIVE MARKING
INITIALS: MA DATE: 12-18-13

PRESIDENT BILL CLINTON
VICE PRESIDENT AL GORE

MARCH 1996

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REINVENTING THE REGULATION OF CANCER DRUGS

ACCELERATING ACCESS AND APPROVAL

President Bill Clinton
Vice President Al Gore

National Performance Review

March 1996

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OVERVIEW

Introduction

The Food and Drug Administration has demonstrated a long-standing commitment to the prompt consideration and, when appropriate, early approval of new therapies for cancer patients. Currently, when new product applications are submitted by commercial sponsors, the FDA reviews them rapidly, and such agents are usually reviewed in about 1 year (mean = 12.4 months, median = 13 months, from 1990 to 1995). However, the overall process of developing a new agent is a complex one, and a substantial period of time 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, the 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, time to progression, improved quality of life, and relief of symptoms, as well as objective disease regression. Often, partial response of disease (measurable but incomplete tumor shrinkage) has been noted in patients who have extensive or metastatic cancer and correlates 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

The Food and Drug Administration 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 approved cancer therapies—that are undergoing clinical testing—when no other highly satisfactory options exist. To facilitate this

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availability even more, FDA is adopting a policy that will actively encourage the submission of expanded access protocols for experimental therapies for United States (U.S.) patients if they are first approved in other countries. If the foreign approval data are adequate, FDA will approve the expanded access protocol. This policy will help ensure that promising new therapies are available in the U.S. near the time of their availability in other countries and will ease the burden on commercial sponsors of preparing an expanded access protocol submission.

Listening to Patients/Removing Barriers

The Food and Drug Administration is undertaking two additional efforts which should positively affect the review of new cancer therapies. One policy will improve the representation of disease-specific patient 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. We will continue to seek their views as well as those of our advisory committees and the National Cancer Institute (NCI). FDA's intention is to foster a medical environment of improved access to cancer treatments because cancer is among the greatest public health problems facing the U.S. These initiatives are also prompted by the increasingly large number of cancer therapies being produced and studied in the pharmaceutical and scientific communities and the demonstrated willingness of the relevant participants to find the best use of new agents by continuing to carefully study them after initial approval. FDA wishes to encourage the rapid development and availability of these and future therapies.

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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 new treatments for cancer patients who do not benefit from or cannot tolerate available therapy, as well as to treatments that are superior to existing therapy, this approval mechanism has not been frequently utilized. This has been largely because a general agreement on acceptable surrogate endpoints has been lacking.

Until now, therapies for cancer patients have been approved on the basis of objective response to the agent (tumor shrinkage) together with direct evidence that the therapy produces appreciable 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 directly linked to longer or better patient survival. In fact, for certain new agents, FDA has begun to rely on a reasonable rate of verifiable objective partial response to the therapy as a basis for approval of refractory malignancies, without requiring direct explicit evidence of an improved

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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 those with refractory malignant diseases or 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 postponed until after approval. This should allow the submission of a marketing application as soon as verified evidence of reasonable clinical activity is available.

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. The agency has concluded that it is now appropriate to approve applications utilizing the accelerated approval provisions for drugs and biological products that demonstrate reasonable rates of verifiable objective tumor shrinkage for patients with refractory disease or those with incurable cancer without satisfactory options. For approval, the effectiveness of the treatment should outweigh its toxicities. The FDA will also apply the accelerated approval provisions to certain products intended to ameliorate a serious or life-threatening toxicity of cancer treatment.

For products approved on the basis of verified and accepted objective evidence 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, alone or in combination with other agents.

For accelerated approval of products that ameliorate 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 surrogate measures of amelioration 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 be as useful as randomized, controlled trials in a previously untreated or an adjuvant population.

In many instances, additional studies would be already underway at the time the accelerated approval is granted. Such studies must be adequate and well-controlled (either utilizing proper historical controls or randomized). 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 21CFR 601.43. FDA may also withdraw approval of the application if studies fail to demonstrate clinical benefit. Id.

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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.

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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 the risk of unknown and potentially dangerous toxicities from treatments that have not yet been shown to be safe and effective. 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" protocols. Ordinarily, these expanded access options become available after the product has been studied in the United States for a significant period in a substantial number of patients and is being considered for approval.

Proposal and Justification: FDA believes that when a cancer therapy is under study in the U.S. in a controlled clinical trial(s) 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 acceptable foreign regulatory authority, FDA intends to contact the United States 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 for the expanded access protocol application. If these data are adequate, the FDA will permit use of the therapy 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.

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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 products under study in the U.S. 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 that are currently approved in the U.S. The route, dose, and schedule of administration of the agent will generally be similar to that which was 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 §312.14 (b)(4)(vii)). Due diligence requires that the sponsor have 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 the 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 and for products already approved in other countries but early in their U.S. development, sooner than now typically occurs. 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. The 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.

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[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.

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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.

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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 decision making 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 cancers are many, 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 illness 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 specific illnesses for which a product is indicated.

Proposal and Justification: It has been FDA's experience that well-informed and motivated representatives of patient perspectives 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 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 contracted with the Citizen Advocacy Center.

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.

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Implementation and Timeline: In order to establish an equitable and efficient framework, the FDA contracted with the Citizen Advocacy Center for preparation of an advisory report which proposed 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 cancer-survivor organizations. 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 resumes 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 and devices.

- When it is decided which products will be considered at upcoming meetings, the cancer liaison staff will select appropriately screened and approved nominees for each meeting. The cancer liaison will contact the nominee for each topic and notify them 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 will notify the nominees of the meeting details, ask if there are any obvious conflicts of interest, and confirm availability. The cancer liaison will notify the executive secretary of the committee and relevant FDA officials which nominee will participate.

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Clarification of Policy on INDs for Studies of Marketed Cancer Products

Background: Currently, FDA does not require the submission of an IND for a study of 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, 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 seems 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 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 make it clear and 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 of 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., larger than usual doses) can be used to determine the degree of increased risk and the overall acceptability of the risk for the intended study population.

- consent requirements, 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. Consistent with current policy, a study of a product whose pharmacological properties are represented

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to have been altered from the approved form continues to require an IND. DRAFT

(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 sponsor constitute promotional activity.

Impact: Clinical research will be fostered by the relief of burdens associated with filing and maintaining an IND. Patients will benefit from the lessening of barriers to conducting research in areas that might not be perceived by the commercial manufacturers as profitable or even interesting. Commercial manufacturers may also gain insights into new or safer uses of marketed drugs from the results of physician-investigator studies. 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.

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