
Guidance for Industry

FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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TABLE OF CONTENTS

- I. INTRODUCTION 1
- II. BACKGROUND 1
- III. DATA NEEDED TO SUPPORT SUPPLEMENTAL APPLICATIONS 2
 - A. Types and Quantity of Clinical Data Needed 3
 - B. Alternative Sources of Clinical Study Data 6
- IV. FDA INITIATIVES TO ENCOURAGE SUPPLEMENTAL APPLICATION SUBMISSIONS FOR PRODUCTS USED IN CANCER TREATMENT 8
 - A. Encourage Recommendations to the Agency 8
 - B. Provide Community Outreach 8
 - C. Help Identify Promising New Uses 9
 - D. Support Sponsors in Application Development 9
 - E. Continue to Prioritize Certain Supplemental Application Reviews 9
 - F. Designate Key Persons 10

GUIDANCE FOR INDUSTRY¹

FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products

I. INTRODUCTION

This document provides guidance to sponsors planning to file applications for new uses of marketed drug and biological products for the treatment of cancer. This guidance for industry is part of ongoing Agency efforts to encourage the submission of supplemental applications for new uses for approved drug and biological products. The guidance also is consistent with section 403 of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act), which specifies that the FDA will continue its efforts to encourage sponsors to submit supplemental applications for new uses for their products. This guidance for industry discusses the quality and quantity of data that may be adequate to add a new use to the prescribing information for a product used in the treatment of cancer. It also describes specific steps FDA is taking to foster the updating of labeling for products used in cancer treatment.

For additional information on this topic, sponsors are referred to the guidance for industry entitled *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998) and *Standards for the Prompt Review of Efficacy Supplements, Including Priority Efficacy Supplements* (May 1998).

II. BACKGROUND

Product labeling is intended to provide full prescribing information for a product and should include all clinical indications for which adequate data are available to establish the product's safety and effectiveness. Many newer uses of anticancer products are common in clinical practice, but are not listed in product labeling, despite the fact that they appear to be supported by published data from clinical studies.

Currently, both incentives and disincentives exist for holders of approved marketing applications to submit supplemental applications for new uses for their marketed products. In addition to the

¹ This guidance has been prepared by the Division of Oncology Drug Products in the Center for Drug Evaluation and Research (CDER) in collaboration with the Office of Therapeutics Research and Review, Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration with input from the Supplemental Indications Working Group, an Agency working group headed by the Deputy Commissioner for Operations. This guidance document represents the Agency's current thinking on FDA approval of new cancer treatment uses for marketed drug and biological products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

goal of giving patients and physicians the best, most up-to-date information about scientifically established uses of a product, incentives include (1) increased sales as a result of being able to promote a product for additional clinical indications and (2) the greater likelihood of reimbursement by third-party insurance payers. But there are substantial disincentives, including (1) the cost and effort involved in completing new research (where necessary) to verify whether a product provides patient benefit in a new indication; (2) the cost and effort involved in submitting an application for regulatory approval of new clinical uses; and (3) the lack of perceived commercial benefit of revised labeling if the product is already being used for the new indication — especially if it no longer has patent protection. To date, the net effect of the incentives and disincentives has been that relatively few supplemental applications have been submitted for new uses of marketed cancer treatment products.

Agency efforts initiated in 1997 and supported by requirements in section 403 of the Modernization Act of 1997 should improve the Agency's process for approving supplemental applications and facilitate the addition of safe and effective new uses for the treatment of cancer to drug labeling. The Agency believes that the outreach efforts specified in the Modernization Act of 1997 will encourage the submission of supplemental applications for new cancer uses to the Agency. As discussed in more detail in the following sections, the Agency's efforts in this regard include (1) clarifying what evidence should be provided in supplemental applications for new uses to treat cancer (this clarification will also be pertinent to assessing uses presented in initial applications), (2) identifying unlabeled uses of products that have become widespread in the treatment of cancer and that may be supported by existing data or newly developed data, and (3) working with industry and others (e.g., the National Institutes of Health) to minimize barriers to the submission of supplemental applications for new uses for the treatment of cancer.

III. DATA NEEDED TO SUPPORT SUPPLEMENTAL APPLICATIONS

To add new use information to the labeling of a marketed product, a holder of an approved marketing application must submit a supplemental marketing application that provides data establishing the safety and effectiveness of the product for the proposed new indication (21 CFR 314.70, 21 CFR 601.2). The application should include all relevant data available from pertinent clinical studies, including negative or ambiguous results as well as positive findings. Data can come from pharmaceutical company-sponsored clinical trials intended to test the safety and effectiveness of a new use of a product, or from a number of alternative sources (see section B, below).² To support approval, the data submitted should be sufficient in quality and quantity to establish the safety and effectiveness of the product with a high level of confidence, as required by law and scientific expectations.

² Sponsors conducting research on products for use in treating cancer patients are strongly encouraged to consult with the Agency for specific advice on study designs and product development plans, especially prior to initiating resource-intensive or marketing application-directed studies.

A. Types and Quantity of Clinical Data Needed

The types and quantity of data needed to support product effectiveness and safety claims in a supplemental marketing application depend on what already is known about the product (see *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*). In many cases, the results of prior clinical studies of a product can be used to support the findings of subsequent clinical studies.

The types and quantity of clinical data that should be provided will also vary depending on the cancer indication under study, the availability and acceptability of other therapies, and the specific observations in the studies. In the refractory cancer setting, for example, where therapies with meaningful benefit are unavailable, nonrandomized studies showing that a new treatment provides a significant objective response rate with tolerable treatment toxicity may be adequate to support approval under the accelerated approval regulations. In this setting, objective response rates are considered a surrogate endpoint reasonably likely to predict a clinical benefit; evidence to confirm that clinical benefit can be obtained after approval. In those cases where durable complete responses can be attained, non-randomized studies showing a significant rate of durable complete responses can be persuasive evidence of effectiveness (not requiring further confirmation).

In cases where an existing therapy offers benefit, partial response rate alone would not usually be a basis for approval. In such cases, concurrently controlled randomized studies with clinical endpoints (e.g., survival and/or symptomatic benefit) would generally be needed.

In the adjuvant setting, where all known tumor has been effectively treated (e.g., by surgical removal) and many or most patients may enjoy long-term survival without a recurrence even if they receive no further therapy, risks of serious treatment toxicities are much less acceptable and relatively large randomized studies are typically necessary to assess the benefits and risks of a new treatment.

As indicated in *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, the additional clinical data needed to support a new use of an already-marketed product may be less extensive than the clinical data needed for an initial approval (which would generally consist of independent substantiation of a finding in more than one controlled trial), since existing controlled trial data may provide significant support for the new use. Listed below are examples illustrating the types and quantity of clinical data that may be adequate to establish the effectiveness and safety of a product in a

new cancer indication.³

1. If a product already has been shown to be safe and effective in the treatment of patients with a given type of cancer, a single, adequate and well-controlled, multicenter study demonstrating acceptable safety and effectiveness in another form of cancer that is known to have a generally similar pattern of responsiveness to chemotherapy may support labeling for that additional form of cancer. For example, if a product is currently approved for use in the treatment of advanced squamous carcinomas of the head and neck and approval is sought for use in treatment of another advanced aerodigestive squamous carcinoma (e.g., squamous lung cancer or esophageal cancer), a single, adequate and well-controlled, multicenter study may be sufficient.⁴

Similarly, with an advanced, refractory-stage solid tumor, if a product already has been shown to be safe and effective in treating patients, a single, adequate and well-controlled, multicenter study in patients with another type of advanced, refractory-stage solid tumor (with appropriate endpoints, depending on the benefits that have been demonstrated with other available therapies) may be sufficient to support approval for treating this additional type of refractory-stage solid tumor.

2. If a product already has been shown to be safe and effective in treating a given type of cancer in adults, then the additional data needed to establish safety and effectiveness of the product in children with that same type of cancer may be limited. If the effects of the drug and the type of cancer under study appear to be biologically similar in children and adults and the proposed use in children is in a setting where known curative treatments are unavailable, a single study demonstrating the safety of the product in children (typically with pharmacokinetic data that can be compared with pharmacokinetic findings of previous studies in adults and including response rate observations) will usually be sufficient.⁵ In disease settings where established curative treatments are available for children, however, a randomized, controlled trial of ethically and scientifically appropriate design (with a survival and/or time to progression endpoint, depending on the exact circumstances) would usually be necessary before a new treatment can be labeled for use as an *alternative* to the established curative treatments.

³ In each example, it is assumed that clinical trials are adequately designed and well conducted, that trial outcomes are favorable, and that data from other studies do not contradict the observed favorable results. In some settings, trials that do not include a concurrent, randomized control group may still be adequate and well-controlled clinical trials, with external groups serving as control. Conversely, clinical trials that include a concurrent control group may not always constitute adequate and well-controlled trials (e.g., if there are serious deficiencies in the design or conduct of a study or the selected control group is not appropriate).

⁴ In this document *approval* may indicate either conventional approval or accelerated approval, depending on the specific cancer indication under study, study endpoints, and the details of the study findings.

⁵ This reflects the current FDA CDER/CBER guidance for industry, *Content and Format for Pediatric Use Supplements*. See also final rule, 59 Federal Register 64240, December 13, 1994.

3. For certain products used to ameliorate an adverse effect of a cancer treatment, there is often a concern that the product could also significantly reduce the effectiveness of the treatment. When such a product has been shown to ameliorate adverse treatment effects without significantly compromising the effectiveness of treatment for patients with one specific type of cancer, it would usually be labeled for use only in that type of cancer. Expanded claims for use in other settings would depend on whether there were specific concerns that the product might not alleviate toxicity or might significantly reduce treatment effectiveness in other cancer treatment settings. If there were such concerns, a single, additional, adequate and well-controlled, multicenter study showing that the product can similarly reduce adverse treatment effects in patients with a second type of cancer without significantly reducing the effectiveness of cancer treatment would usually be sufficient to support labeling of the product for use to ameliorate adverse treatment effects in all similar palliative settings. However, it would not support use in settings where treatment is known to be potentially curative or is associated with a substantial survival benefit. In those settings, where preservation of effectiveness is especially important, additional studies to verify preservation of treatment effectiveness would usually be needed.

4. New dosing regimens (including changes in the range of doses administered for approved indications and changes in the schedule of administration) can lead to improved effectiveness, tolerance, or convenience. A single, adequate and well-controlled study demonstrating the safety and effectiveness of the product when administered for an approved indication using a different dosing regimen will generally be sufficient to support the addition of the new dosing regimen to product labeling.

5. If a product already has been shown to be safe and effective for treatment of patients with a given type of cancer in advanced, refractory stages, support for a claim at an earlier stage of the same type of cancer may be provided by a single, adequate and well-controlled, multicenter study demonstrating effectiveness and safety. For example, for a product that is already approved for use in the treatment of metastatic colorectal cancer or breast cancer after failure of first-line treatment, a single, randomized, controlled trial of the product in first-line treatment (with a survival endpoint or possibly a carefully assessed time to disease progression endpoint) could be sufficient to support approval for first-line treatment of the same condition.

6. If a product already has been shown to be safe and effective as part of a combination treatment regimen for a given type of cancer, then a single, adequate and well-controlled study providing evidence of safety and effectiveness when the product is administered as part of a different combination or as monotherapy in the same clinical setting may be sufficient to support the addition of a new combination regimen or a new monotherapy dosing regimen to product labeling.

Similarly, if a product already has been shown to be safe and effective when administered alone in the treatment of a given type of cancer, then a single, adequate and well-

controlled study providing evidence of safety and effectiveness of the product when administered together with other products that have established safety and effectiveness in treatment of that condition may be sufficient to support the addition of the new combination dosing regimen to product labeling.

7. If the safety/toxicity profile of a product has been well established in prior studies, the safety data needed to support additional clinical indications for the product may be limited, provided that there are no significant changes in the product's dosing regimen, in concurrent therapies, or in the patient populations to be treated that would require additional safety data.

8. Depending on the data previously submitted to FDA in prior marketing applications and on the degree of similarity between the patient populations evaluated in prior applications and the patient populations included in the proposed new uses for the product (including use of concomitant medications), applications for new uses of a product often do not require additional data concerning pharmacokinetics (PK); concomitant medications and possible drug-drug interactions; or evaluation of product safety as a function of age, sex, race, or co-existing diseases.

All of these examples are intended to illustrate in a general way the quantity and types of data that should be provided to support typical labeling changes. However, the specific data needs may vary substantially from case to case, depending on what is already known about the product and the specific cancer indications under study. Sponsors are strongly encouraged to consult with the Agency for specific advice on the design of research programs intended to support new product labeling before proceeding with such programs.

B. Alternative Sources of Clinical Study Data

Although clinical studies conducted by pharmaceutical companies generally are carefully monitored, are subjected to quality control audits, and can achieve very high quality, alternative approaches, such as those described below, also may provide reliable data to support the effectiveness and safety of a product in cancer treatment. For example, most of the data pertaining to the adjuvant therapy of breast and bowel cancers have come from studies that were performed independently of pharmaceutical companies (see *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*). Listed below are some examples of alternative approaches to data gathering.

1. Data, including individual patient data, study reports, and statistical analyses may be obtained from experienced, independent cancer clinical trials organizations that have well-established and publicly available procedures for research data management, monitoring, and auditing, and a track record of high-quality research (e.g., U.S. National Cancer Institute-sponsored cooperative cancer research groups or other highly credible organizations that have no commercial interest in study outcomes). Such data can be

submitted to FDA without additional data collection, auditing, or analyses by a pharmaceutical company submitting a supplemental marketing application as long as (1) the clinical trials organization can provide the data necessary for FDA to examine and verify the data and analyses that support all major study findings (e.g., stratification and randomization data, and tumor measurements in studies that use objective response rate as a primary efficacy variable) and (2) the clinical trials organization is willing to work with FDA to resolve any issues that may arise during FDA review.

Although these organizations usually do not carry out the monthly on-site monitoring that is often performed in company-sponsored studies, they do have established audit procedures. FDA has had extensive experience in the review of data and analyses from such independent organizations during the past several years and has found the data and the analyses generally to be highly credible and reliable.

2. In situations where several reports of controlled studies from multiple centers, published in adequate detail in peer-reviewed journals, provide consistent support for the effectiveness and safety of a product in a cancer indication, such reports may form the primary basis for establishing the safety and effectiveness of a product in a cancer indication. The centers and investigators generating these data should have substantial experience in clinical cancer investigations and no commercial interest in the study outcomes.

In most cases, unless numerous published confirmatory reports are available, such literature reports should be supplemented by selected additional information (e.g., copies of study protocols, computer databases giving relevant baseline and outcome information, and/or case records of individual patients reported as having critical efficacy or safety findings). These types of additional information are often readily obtainable for recently conducted studies and may substantially enhance the usefulness of a study in supporting product labeling. A single published report supplemented by such additional information may be persuasive.

The general request for this additional information is based on prior experiences where, following review of study records, FDA has sometimes been unable to confirm major findings of published studies (including multicenter studies published in high-quality, peer-reviewed journals).

IV. FDA INITIATIVES TO ENCOURAGE SUPPLEMENTAL APPLICATION SUBMISSIONS FOR PRODUCTS USED IN CANCER TREATMENT

Treatment of many forms of cancer is in continuous and sometimes rapid evolution due to the efforts of many researchers in private, academic, and government sectors. After a product receives initial marketing approval, it will be used in a variety of settings, especially where available treatments prove unsatisfactory. Product labeling, therefore, may not include the very latest information about promising new uses for products. In many cases, early promise is not borne out by subsequent definitive studies. It is important, however, for the labeling of products used in cancer treatment to include information on all scientifically proven uses. FDA has made a number of efforts to enhance the quality of labeling for products currently approved for use in cancer treatment. Consistent with the Modernization Act, additional efforts are planned:

A. Encourage Recommendations to the Agency

FDA will consider recommendations from any source regarding promising new cancer treatment indications for currently marketed products that should be examined for possible inclusion in labeling. Recommendations for new uses for drugs or biologics, respectively, can be submitted to:

Division of Oncology Drug Products (HFD-150)
Center for Drug Evaluation and Research, FDA
5600 Fishers Lane, Rockville, MD 20857

or

Oncology Branch, Division of Clinical Trials Design and Analysis (HFM-573)
Center for Biologics Evaluation and Research, FDA
1401 Rockville Pike, Rockville, MD 20852.

B. Provide Community Outreach

In the past, FDA has surveyed private, academic, and professional groups involved in cancer research and treatment for their views regarding appropriate uses of products in cancer treatment not described in current product labeling. Where appropriate, FDA has met with commercial sponsors of marketed products and has encouraged the submission of supplemental marketing applications.

As specified in the Modernization Act, FDA will continue its outreach efforts to survey major groups in the cancer research and treatment community (including professional societies, cancer patient and research advocacy organizations, other government agencies, and other interested groups and individuals) for their views regarding new cancer treatment indications that should be examined for possible inclusion in labeling for currently marketed products. These groups and individuals will be asked to identify published and unpublished studies that may support a supplemental application. They will be asked to collaborate with FDA to encourage sponsors (1) to prepare supplemental

applications in cases where definitive studies have been completed or (2) to conduct further research that may be needed to provide support for a supplemental application that is suggested by preliminary research findings.

The Agency will contact the commercial sponsor(s) of a promising product and encourage the sponsor(s) to evaluate the available data and, if the data appear adequate, to submit a supplemental marketing application.

C. Help Identify Promising New Uses

FDA will institute a program to encourage Agency professional staff to review regularly the labeling of each product used in cancer treatment with the goal of identifying uses or dosing regimens that appear to be well supported by the results of clinical studies, but are not yet included in labeling. Although the magnitude of this effort will depend on workload and availability of staff, FDA will endeavor to conduct such reviews of labeling of 10 to 20 percent of marketed cancer treatment products each year.

D. Support Sponsors in Application Development

In some cases, commercial sponsors of a product may be unable to accommodate an FDA request to evaluate the data regarding a currently unlabeled indication for a product used in cancer treatment or to consider filing a supplemental marketing application. In such cases, FDA may pursue other avenues, depending on specific circumstances and in accordance with applicable laws and regulations. For example, FDA may provide public notification of the Agency's interest in receiving a supplemental application for review. FDA may request a summation and analysis of the data from staff of other governmental agencies (e.g., staff of the National Cancer Institute), for review by FDA staff. If necessary, FDA may directly approach study investigators and request study data for summary and analysis by Agency staff.

E. Continue to Prioritize Certain Supplemental Application Reviews

Supplemental applications will continue to be assigned a review priority based on the importance of the new use of the product.⁶ As with original marketing applications, supplemental applications for new cancer treatment uses will receive priority review if, based on preliminary review of the application, it appears that the new product use may represent a significant improvement (compared to other marketed products) in the treatment, diagnosis, or prevention of a disease. The fact that a product is already marketed for another indication does not affect FDA's determination of whether a new supplemental application will receive priority review.

⁶ See also guidance for industry, *Standards for the Prompt Review of Efficacy Supplements, Including Priority Efficacy Supplements*, May 1998.

F. Designate Key Persons

Consistent with section 403(c) of the Modernization Act, CDER and CBER have designated key persons who will (1) encourage the prompt review of supplemental applications for approved products and (2) work with sponsors to facilitate the development and submission of data to support supplemental applications.

Within CDER, the Associate Director for Medical Policy, Center for Drug Evaluation and Research, FDA, 5600 Fishers Lane, Rockville, MD 20857, is fulfilling the requirements of section 403(c) by working with sponsors to facilitate the development of supplemental applications. Within the Division of Oncology Drug Products, the Special Assistant to the Division Director is working with sponsors to facilitate the development and submission of data to support supplemental applications for drug products used in cancer treatment. Efforts include managing initiatives to seek the views of major groups and of individuals in the cancer research and treatment community; managing and monitoring actions regarding possible labeling revisions; and preparing regular progress reports.

Within CBER, supplemental applications are being facilitated by the Deputy Director, Medical, 1401 Rockville Pike, Rockville, MD 20852 in accordance with section 403(c). Review activities for most oncologic product applications are managed by the Office of Therapeutics Research and Review, HFM-500, Center for Biologics Evaluation and Research, FDA, 1401 Rockville Pike, Rockville, MD 20852. The Oncology Branch of the Division of Clinical Trials Design and Analysis will work with sponsors to facilitate the development and submission of data to support supplemental applications for biologics used in cancer treatment.