Guidance for Industry

Cancer Drug and Biological Products — Clinical Data in Marketing Applications

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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I. INTRODUCTION

This document provides recommendations for sponsors on data collection for cancer clinical trials submitted to FDA to support marketing claims in new drug applications (NDAs), biologics license applications (BLAs), or supplemental applications for new indications. The data collected should be sufficient to evaluate the safety and effectiveness of the treatment but need not include other data. This guidance is also intended for private investigators, cooperative cancer groups, contract research organizations, and others designing and conducting studies that later can be used in a marketing application for an anticancer drug or biological product.

Because of the complexity of clinical trials and different data that should be included in different situations, the precise data for each trial cannot be specified in a guidance document. This guidance provides general principles for data collection and submission. Sponsors are strongly encouraged to begin with these principles, develop specific proposals for data collection, and discuss their proposals with the FDA at meetings such as end-of-phase-2 meetings. Specifying these data should avoid the collection of unnecessary information, allowing resources to be directed toward studying important endpoints, while ensuring that the data collected and reported are adequate to support the study.

II. BACKGROUND

A. General Regulations and Guidance

This guidance is one in a series of regulations and guidances outlining special considerations for evaluation of cancer treatment. In subpart E of the IND drug regulations (21 CFR 312 subpart E), special procedures are outlined to expedite the development,

[1] This guidance has been prepared by the Division of Oncology Drug Products in the Center for Drug Evaluation and Research (CDER) and the Oncology Branch of the Division of Clinical Trials Design and Analysis in the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA). Input was also received from the Cancer Treatment Evaluation Program (CTEP) at the National Cancer Institute (NCI).

evaluation, and marketing of new therapies for life-threatening diseases, such as cancer. These procedures reflect the fact that physicians and patients are willing to accept greater risks or side effects from products that treat life-threatening illnesses in view of the possible benefits of therapy. Subpart H of the NDA regulations (21 CFR 314 subpart H) and subpart E of the BLA regulations (21 CFR 601 subpart E) allow accelerated approval of new drugs that provide meaningful therapeutic benefit over existing treatment for serious or life-threatening illnesses, such as cancer, based on use of a surrogate endpoint that is reasonably likely to predict clinical benefit. Several initiatives were announced in a 1996 initiative, *Reinventing the Regulation of Cancer Drugs* (National Performance Review, March 1996). In a guidance for industry on *FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products* (December 1998), FDA addressed the number and type of studies recommended to support a new oncologic use of a marketed drug or biologic product.

B. Data Requirements and Guidance

The regulations at 21 CFR 314.50 require that supporting data be submitted with study reports from well-controlled trials but do not describe the amount and type of data that should be collected. The specifics are sometimes determined in meetings with the review division prior to submission of the application, but often they reflect established practices. Submission of case report forms (CRFs) is required for patients who died or dropped out during the study because of an adverse event (22 CFR 314.50(f)(2)), and submission of individual patient safety data from all studies and individual efficacy data from controlled trials supporting effectiveness is required in case report tabulations (21 CFR 314.50(f)(1)). These tabulations include the data on each patient from each study, except that the applicant can delete those tabulations the Agency agrees in advance are not pertinent to a review of the drug's safety or effectiveness. More recently, the Agency stated that case report tabulations can be submitted as electronic data sets.[2] This is the preferred form of data submission for most oncology submissions, because data submitted electronically can generally be reviewed more rapidly and thoroughly.

C. General Considerations

The Agency recognizes that the collection, quality control, and entry of data in a database is an expensive and time-consuming process. Some sponsors collect large amounts of information to be certain they have all the data the Agency can request. Noncommercial sponsors, such as cancer cooperative groups, often perform important multicenter studies that are later used by commercial sponsors for regulatory submissions. Representatives of these noncommercial sponsors have told FDA that commercial sponsors often encourage collection of much more data than the investigators would normally collect. In fact, many

[2] SAS transport files are the preferred format for electronic data sets. Details on the recommended format of electronic data may be found in two guidances: *Providing Regulatory Submission in Electronic Format — NDAs* (January 1999) and the companion guidance, *Regulatory Submissions in Electronic Format — General Considerations* (January 1999).

of these data may not be called for in a marketing application for cancer therapy. It is possible that industry representatives are using data submission standards for marketing applications for less serious diseases or assuming standards that could be modified in many situations. We therefore encourage discussion of specific data requirements at end-of-phase-2 meetings to minimize unnecessary data collection. Ideally, the background documents for these meetings should include annotated CRFs indicating the data elements that will be collected for the database to facilitate this discussion. When the sponsor and FDA agree on the scope of data collection, the agreement should be reduced to writing and become part of the administrative record.

To understand what data should be submitted, it is important to consider the entire drug development plan and the role the study will play in providing data that demonstrate safety and effectiveness. Data submitted could vary, depending on factors such as:

- The type of regulatory submission (new marketing application versus efficacy supplement using a drug with well-established adverse effects)
- The similarity of the proposed new use of drug to already approved uses of drug
- The population being studied (patients in the surgical adjuvant setting, patients getting first-line treatment, or patients with refractory disease)
- The amount of available supplemental information from other sources on the safety of the drug, such as data from trials in a similar patient population

III. RECOMMENDATIONS FOR DATA COLLECTION

Experience in reviewing oncology applications in CBER and CDER leads to the following recommendations for data collection for trials supporting marketing applications for oncologic drug or biologic products. Data collection plans should be discussed with the Agency prior to their implementation.

A. Demographic Data

Demographic data on study participants should include date of birth, race, and sex. Each patient should be assigned an identifying number unique to the study. The date of randomization should be recorded.

B. Medical History

Information on major diseases that might affect function of critical organs (e.g., renal failure, hepatic insufficiency, heart disease) should be collected at baseline in a specified number of patients for each new population studied. Such data can be useful for determining whether certain diseases predispose patients to particular adverse reactions. Collection of additional historical data on diseases affecting specific organ systems can be appropriate for some drugs and should be specified in the protocol.

C. Cancer Diagnosis and Stage

Data that verify the diagnosis and stage of cancer treated in the study are important. Other details vary according to the specific protocol objectives and planned analyses. Important prognostic factors for the primary efficacy outcome should be collected. The protocol should specify all baseline data that should be included to adequately characterize the population, to evaluate the success of randomization in achieving balance of important prognostic factors, and to allow for consideration of adjusted analyses.

D. Cancer Treatment History

Collection of data on previous adjuvant therapy is important because this can be prognostic for response to treatment. In the metastatic disease setting, it is helpful to note the identities of previous chemotherapies received, but other details (e.g., doses of drugs, response to treatment) are generally not necessary. Cancer treatment history should be recorded for all patients in all trials to the extent warranted to document that patients are eligible. For example, for the indication of second-line therapy, details of first-line treatment should be documented. Specific data on cancer treatment history should also be recorded when there are safety concerns (e.g., the history of anthracycline use will be important for a drug suspected of being cardiotoxic).

Occasionally, approval of a new drug is sought under the accelerated approval regulations based on demonstration of tumor responses in patients with tumors refractory to all available therapies. Usually these applications involve single-arm studies rather than randomized comparative studies. In such cases, when the proposed indication is for treatment of *refractory disease*, the protocol should specifically define the meaning of *refractory disease*, and sufficient treatment history should be collected to document the refractory state of the patients entered. Depending on the protocol definition of *refractory*, this can include name of drug, dose of drug, dates of starting and stopping, best response to drug, date of progression, and/or reason for stopping drug.

E. Laboratory Tests

Protocols should carefully detail the laboratory tests that should be conducted for full evaluation of the drug. All new NDAs or BLAs should contain a sample of patients for which a full laboratory evaluation has been carried out that would be a subset of all patients studied. (New efficacy supplements may call for less data depending on the specific circumstances and what is already known, as discussed in section C.) For the intensively monitored group, it is important to collect both scheduled and unscheduled laboratory data. The number of patients in this data sample should be determined in consultation with the reviewing oncology division at the FDA. This complete collection of laboratory data might be warranted, for example, in only one of the trials submitted or in a subset of patients from a large trial, assuming that a sufficient number of patients is studied and that relevant demographic groups are included.

1. Baseline Tests

Initial applications for marketing a new drug product should contain detailed data from a routine battery of laboratory tests collected at baseline in a specified number of patients. The number of patients should be determined in discussions with FDA during design of the protocol. In these patients, the baseline data are important to interpret subsequent abnormal values. Such baseline studies should include electrolytes, creatinine, hemoglobin, granulocyte count, platelet count, liver enzymes, alkaline phosphatase, bilirubin, and urinalysis. Additional baseline laboratory tests and other tests (such as EKG) that are specific to the drug being evaluated should be enumerated in the protocol.

2. Follow-Up Tests

Similarly, in a specified number of patients for each drug application, routine follow-up tests should include hemoglobin, granulocyte count, platelet count, creatinine, liver enzymes, alkaline phosphatase, and bilirubin. If a drug has been adequately studied for toxicity in previous applications or other studies, the protocol can specify only those laboratory tests the investigator and the sponsor agree should be included to allow safe administration of the drug. Again, during design of the protocol, the sponsor should discuss with the Agency additional follow-up laboratory tests that can be indicated considering the known or suspected toxicities of the drug and the specific population to be studied.

3. Tests Corresponding to Severe Toxicities

Scheduled and unscheduled laboratory tests for abnormalities, corresponding to grade 4-5 hematologic toxicities and grade 3-5 nonhematologic toxicities, should be collected and entered into the database for all regulatory settings. These data should also document whether the abnormality resolved and the date of resolution.

F. Physical Examination

Other than body weight and performance status, which should be recorded at baseline, most significant findings noted on the prestudy physical exam will be reflected in the prestudy medical history, so such data need not be routinely collected. Physical findings associated with adverse reactions should be recorded with the toxicity data.

G. Efficacy Data and Tumor Measurements

The schedule for collection of baseline and follow-up data for full evaluation of efficacy should be specified in the protocol. In addition to the investigator's evaluation of efficacy, all raw data collected for evaluating efficacy should be recorded on the CRF and submitted to FDA. (Usually, actual tumor images need not be submitted, although tumor images should always be available at the investigative site for FDA audit. If there is a need for such images, the sponsor and the reviewing division should discuss this at end-of-phase-2

or presubmission meetings.) These data allow FDA to examine the basis for efficacy assessments. When tumor response or progression are important regulatory endpoints, submission of tumor measurement data is critical. On the other hand, when the primary endpoint is survival and the sponsor anticipates demonstrating a survival advantage in two trials, evaluation of tumor response may not be critical for a determination of efficacy, and recording tumor measurements for the database may not always be important. When response and progression are evaluated, criteria for these endpoints should be detailed in the protocol, and data should be carefully collected at intervals specified in the protocol. The following are important considerations for tumor measurement data:

- The protocol and the corresponding CRF should make clear which tumor evaluations are intended to be used to evaluate response and progression. Missing data has been a chronic problem for FDA in evaluating these endpoints.

- The CRF should document the target lesions identified during the baseline visit, or at least prior to treatment. Retrospective identification of such lesions would rarely be considered reliable.

- Tumor lesions should be assigned a unique identifying letter or number. This allows differentiating among multiple tumors occurring at one anatomic site and matching of tumors measured at baseline and tumors measured during follow-up.

- It is desirable to have a mechanism that ensures complete collection of data at critical times during follow-up. The CRF should ensure that all target lesions are assessed at each follow-up visit, and especially at the visits when response and progression are noted. For documenting tumor response, one approach is to add an evaluation form to display data from three time points: the baseline visit, the visit first demonstrating tumor response, and the visit verifying that response.

H. Cancer Drug Dosing

Detailed data on dosing of anticancer drugs should be collected on all patients in each important study to adequately characterize the dose intensity of therapy in each study arm. It is important to demonstrate whether the proposed dose of the study drug is tolerated and whether an adequate dose of therapy was given in the control arm. The reasons for decreasing the dose should be documented. These data can be collected in the form of check boxes corresponding to the expected reasons for dose decrease, with a separate box for *other*, together with a space for comment.

I. Toxicity

Data on National Cancer Institute (NCI) grade 4-5 hematologic toxicity and grade 3-5 nonhematologic toxicity should always be collected. Marketing applications for a new regimen should also collect data on grade 1-2 nonhematologic toxicity and grade 1-3 hematologic toxicity for an adequate number of patients from one or more studies or from a subset of patients in these studies. In studies including a large number of patients, it may be

sufficient to collect detailed data such as laboratory and grade 1-2 toxicity data from only a sample of patients studied. Complete data collection might be performed in only one of the principal trials or only in a sample of patients from a large trial, assuming that enough patients are studied and that relevant demographic groups are included. FDA and the sponsor should determine at an end-of-phase-2 meeting the number of patients with complete data that should be included for a marketing application. In supplemental efficacy applications that propose a new use for an already marketed drug in a similar population, additional data on grade 1-2 nonhematologic toxicity and grade 1-3 hematologic toxicity may not be important and may not need to be collected. Data on serious adverse events associated with the use of a drug, or adverse events leading to discontinuation or dose reduction of treatment should always be collected.

Toxicity duration should be recorded unless the toxicity of the regimen has been well characterized in previous applications. Depending on how well toxicity has been evaluated in previous studies, duration information may be needed only for a list of selected toxicities and/or only in a subset of patients in very large studies. This should be discussed with the Agency during design of the protocol.

Unless previous applications have fully characterized the toxicity of a regimen, documented toxicities should be followed until resolution. Follow-up visits should record whether the toxicity has been reevaluated and/or has resolved. Similarly, unless previous applications have fully characterized the toxicity of a regimen, major actions taken should be recorded and categorized (e.g., treatment delayed, dose reduced, hospitalized). Data on investigator attribution of toxicity is not usually necessary for the marketing submission, because there is usually a randomized control arm for comparison.

In some settings (e.g., for drugs anticipated to provide only marginal clinical benefit) quantifying the incidence of certain known toxicities may be important for making a risk-benefit assessment. In such cases, preplanned data on selected toxicities, including grade 1-2 toxicities, should be collected. Such toxicities should be specifically identified in the protocol and individually reported in the CRF.

J. Concomitant Medications

If data on concomitant medications are collected, the quality of these data will be improved by designing protocols to ask specific questions about specific concomitant medications. It is not necessary to record every drug use. For example, antihistamines, hypnotics, and analgesics are regularly used by patients and should be recorded only if they might reflect responses to drug toxicity or if there is concern about possible interactions. It may be sufficient to collect information only on certain classes of medications and record whether a particular class of drugs was used, omitting the name and dose of each drug. Data should be collected, however, for a list of targeted medications when such medications could affect assessment of efficacy (e.g., dexamethasone use in applications for treating brain tumors or narcotic use when reduction of pain is an important endpoint).

If protocol-specific information on targeted concomitant medications is important because of special efficacy or safety concerns, the specific medications (or classes of medications) should be identified in the protocol. CRFs should be designed to gather data on these specific medications or classes of medications to facilitate preplanned analyses.

K. Further Anticancer Therapy

When survival is an important study endpoint, anticancer therapy given after study therapy should be recorded. This is especially true when the subsequent therapy represents crossover in a randomized study. Only the names of the drugs should generally be recorded, not doses or outcomes other than survival. This will allow an evaluation of the potential effect of subsequent therapy on survival. It is generally adequate to collect data only on the first regimen given after study therapy. Therapy beyond the first regimen is less likely to have a survival impact.

IV. DATA COLLECTION DURING THE DEVELOPMENT OF A CANCER DRUG: A HYPOTHETICAL EXAMPLE

The following illustrates how data collection can vary at different stages of cancer drug development. It is a purely hypothetical example of development of Drug A, a new cancer drug. During the development of Drug A, comparisons were made to drugs B, C, and D in the treatment of cancers E, F, and G.

Drug A was initially studied in small phase 1 studies. It was then evaluated in three single-arm phase 2 studies in patients with refractory E cancer, a cancer of elderly men. Based on an impressive objective tumor response rate from treatment with Drug A, accelerated approval was granted under subpart H (21 CFR 314 subpart H) for *treatment of refractory E cancer*. Accelerated approval, with its reliance on a surrogate endpoint (response rate), was possible because no other therapies were available for treatment in this refractory setting. For this limited indication and for these patients with no other available therapy, the data from only 200 patients were sufficient for approval. Critical to FDA's decision to approve Drug A were (1) the company's careful documentation of previous cancer treatments, (2) demonstration that tumors were refractory to available therapy, (3) tumor measurements verifying the claimed tumor response rate, and (4) collection of detailed safety data on all patients, including toxicity and/or adverse drug reactions of all severity.

As part of its obligations resulting from subpart H approval, the sponsor then planned trials to support an indication of *first-line therapy for metastatic E cancer*. The sponsor performed two randomized studies of *add-on* design comparing Drug B, the standard first-line therapy for this cancer, to Drug A in combination with Drug B. Eight hundred patients were randomized in each study. The objective of the first study was to demonstrate that survival was improved by treatment with Drug A plus Drug B relative to treatment with Drug B alone. In the second study, which was a double-blind trial, reduction of symptoms was the primary endpoint, and tumor response was a supportive endpoint. FDA noted that most of the detailed data that should be included in the application for first-line treatment of E cancer could be collected in the second study and that the

first study could be relatively simple, with efforts focused on collecting data on survival and serious toxicities. Data on cancer treatment given after treatment with study drugs were also collected in the first study to assess the drugs' potential effect on survival. Data on tumor response, concomitant medications, and routine laboratory values were not necessary for the first study.

The primary endpoint of the second study was reduction of tumor-associated pain. Relevant efficacy data included pain scores, narcotic medications, and tumor measurements. Routine laboratory tests included tests described in section III.E.1 of this document. Data were collected on dosing of drugs A and B for all patients to allow calculation of relative dose-intensity on the two study arms. The CRF for all patients recorded starting dose, dose reductions, and reasons for dose reductions. Toxicity duration and all grades of toxicity were collected in this trial to allow a full assessment of the added toxicity resulting from Drug A. Analgesic medications were carefully documented on the CRF to assist in the evaluation of their potential effect on pain, the primary endpoint. Since there was concern about cardiac toxicity from phase 2 studies, cardiac medications were recorded for all patients, and serial left ventricular ejection fractions were determined in a sample of 100 patients taking Drug A. Survival data were collected for analysis as a secondary endpoint.

The drug was approved for *first-line therapy of metastatic E cancer*. Later results from phase 2 studies suggested activity in cancer F, a cancer of elderly men with no approved therapy. The sponsor did two randomized controlled studies comparing Drug A to Drug C, an unapproved therapy for cancer F. Because the efficacy of Drug C had not been established, both trials were designed to show that treatment with Drug A produced a longer survival than treatment with Drug C. Because Drug A had already been carefully evaluated in an elderly population, data collection for these studies focused on survival and serious toxicities. At a meeting the Agency agreed that data on laboratory tests, tumor measurements, mild adverse events, concomitant medications, and further anticancer treatment were not necessary for this study.

Data from phase 3 trials in Europe suggested the effectiveness of Drug A in the *treatment of metastatic cancer G,* a cancer of young and middle-aged women, but these data were unavailable for submission to FDA. The sponsor designed large randomized studies to evaluate efficacy of Drug A in the adjuvant setting (a setting where chemotherapy is given after surgical removal of all known tumor) for cancer G. The large study was designed to include 4,000 patients to determine the disease-free survival and survival rates of Drug A versus Drug D, the standard approved adjuvant treatment with a well-characterized survival effect. Because comparative safety data were important and because the population was new and potentially tumor-free, detailed toxicity data of all grades and routine laboratory data (those specified in section III.E.1 of this document) were taken from an adequate sample of patients, the first 400 patients and the last 200 patients enrolled, with serious toxicity recorded for all patients. In addition, because the possibility of cardiac toxicity was still an issue, serial cardiac ejection fractions were determined in this sample of patients. An interim toxicity analysis was performed after evaluation of the first 400 patients. Efficacy data on tumor recurrence and survival were collected for all patients. Concomitant cardiac medications were collected for all patients, but other concomitant medications were not collected. Specific data on dosing of the study drug and the control drug was recorded in all patients to allow calculation of relative dose-intensity on the two study arms and to allow

exploration for possible dose-related benefits and toxicity. The CRF for all patients recorded starting dose, dose reductions, and reasons for dose reductions. Serious toxicities and duration of toxicity were recorded in all patients in this trial.

The above fictitious drug development history shows that data collection recommendations can depend on the stage of drug development, the indication sought, and clinical trial design. Taking these factors into consideration can decrease collection of unnecessary data, allow sponsors to include more patients in clinical trials, and improve the quality of the data that are collected. Sponsors should evaluate their drug development plan, consider the principles outlined in this guidance, and develop a data collection proposal. Given the complexity of the drug development process for cancer drugs, we encourage sponsors to discuss their plans for data collection with the Agency prior to their implementation.