
Guidance for Industry

Cancer Drug and Biological Products — Clinical Data in Marketing Applications

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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**U.S. Department of Health and Human Services
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**Guidance for Industry¹
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This draft guidance, when finalized, will represent the Food and Drug Administration's current thinking on this topic. 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 statutes and regulations.

If you plan to submit comments on this draft guidance, to expedite FDA review of your comments, please:

- *Clearly explain each issue/concern and, when appropriate, include a proposed revision and the rationale/justification for the proposed change.*
- *Identify specific comments by line number(s); use the PDF version of the document, whenever possible.*

I. INTRODUCTION

This document is intended to provide recommendations for sponsors designing clinical trials to demonstrate efficacy and safety of cancer treatments on the collection of data that may be submitted to support marketing claims in new drug applications (NDAs), biologics license applications (BLAs), or applications for supplemental indications. This guidance is also intended for private investigators, cooperative cancer groups, contract research organizations, and others designing and conducting studies that subsequently may be used in a marketing application for an anticancer drug or biological product.

Because of the complexity of clinical trials and different needs for data 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 proposals for data collection, and discuss their proposals with the FDA at meetings such as end-of-phase-2 meetings. This guidance document is intended to enable sponsors to create plans for recording and reporting data prior to such meetings. Specification of these data should help avoid the collection of unnecessary information, allowing resources to be directed toward studying

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).

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40 important endpoints, while ensuring that the data collected and reported are adequate to support the
41 study.

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43 **II. BACKGROUND**

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45 **A. General Regulations and Guidance**

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47 This guidance is one in a series of regulations and guidances outlining special considerations for
48 evaluation of cancer treatment. In subpart E of the IND drug regulations (21 CFR 312 subpart
49 E), special procedures are outlined to expedite the development, evaluation, and marketing of
50 new therapies for life-threatening diseases, such as cancer. These procedures reflect the
51 recognition that physicians and patients are generally willing to accept greater risks or side
52 effects from products that treat life-threatening illnesses in view of the possible benefits of
53 therapy. Subpart H of the NDA regulations (21 CFR 314 subpart H) and subpart E of the
54 BLA regulations (21 CFR 601 subpart E) allow accelerated approval of new drugs that provide
55 meaningful therapeutic benefit over existing treatment for serious or life-threatening illnesses,
56 such as cancer, based on use of a surrogate endpoint that is reasonably likely to predict clinical
57 benefit. Several initiatives were announced in a 1996 initiative, *Reinventing the Regulation of*
58 *Cancer Drugs* (National Performance Review, March 1996). In a guidance for industry on
59 *FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological*
60 *Products* (December 1998), FDA addressed the number and type of studies recommended to
61 support a new oncologic use of a marketed drug or biologic product.

62

63 **B. Data Requirements and Guidance**

64

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

² SAS transport files are the preferred format for electronic data sets. Details on the 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).

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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 may request. Noncommercial sponsors, such as cancer cooperative groups, often perform important multicenter studies that are later used by commercial sponsors for regulatory submissions. Representatives from these noncommercial sponsors have told FDA that the commercial sponsors encourage collection of much more data than the investigators would normally collect. In fact, many of these data may not be required for 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 requirements that could be modified in many situations. We encourage discussion of specific data requirements at end-of-phase-2 meetings to minimize unnecessary data collection.

When evaluating what data are important for a particular trial, the investigator may be considering *what data will answer the objectives in this trial*. The Agency will also be considering *what data will support a marketing application for a drug for this indication*. Therefore, to understand what the Agency would like to see from a study, it is important to consider the entire drug development plan and how the study fits into the plan to provide the data to 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

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

122

B. Medical History

124

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

131

C. Cancer Diagnosis and Stage

132

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

139

D. Cancer Treatment History

140

141 Collection of data on previous adjuvant therapy is important because this can be prognostic for
142 response to treatment. In the metastatic disease setting, it is helpful to note the identities of
143 previous chemotherapies received, but other details are generally not necessary. Cancer
144 treatment history should be recorded for all patients in all trials when it is pertinent to the
145 indication being studied. For example, for the indication of second-line therapy, first-line
146 treatment should be documented.

147

148 Occasionally, approval of a new drug is sought under the accelerated approval regulations
149 based on demonstration of tumor responses in patients with tumors refractory to all available
150 therapies. Usually these applications involve single-arm studies rather than randomized
151 comparative studies. In such cases, when the proposed indication is for treatment of *refractory*
152 *disease*, the protocol should specifically define the meaning of *refractory disease*, and sufficient
153 treatment history should be collected to document the refractory state of the patients entered.
154 Depending on the protocol definition of *refractory*, this may include name of drug, dose of
155 drug, dates of starting and stopping, best response to drug, and/or reason for stopping drug.
156 Specific data on cancer treatment history should also be recorded when there are safety
157 concerns (e.g., the history of anthracycline use will be important for a drug suspected of being
158 cardiotoxic).

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E. Laboratory Tests

Protocols should carefully detail laboratory tests for full evaluation of the drug. All original applications should contain a database of all laboratory tests from a specified number of patients. It is important to collect both scheduled and unscheduled laboratory data for this group of patients. The number of patients in this detailed data collection should be determined by statistical and/or epidemiological factors. This complete collection of laboratory data might be needed 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, only those laboratory tests the investigator feels are needed to allow safe administration of the drug may be important. Again, during design of the protocol, the sponsor should discuss with the Agency any additional follow-up laboratory tests.

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.

F. Physical Examination

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

G. Efficacy Data and Tumor Measurements

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211 The schedule for collection of baseline and follow-up data for full evaluation of efficacy should
212 be specified in the protocol. In addition to the investigator's evaluation of efficacy, all raw data
213 collected for evaluating efficacy should be recorded on the CRF and submitted to FDA. These
214 data allow FDA to verify efficacy assessments. When tumor response or progression are
215 important regulatory endpoints, submission of tumor measurement data is critical. On the other
216 hand, when survival is the main efficacy endpoint, evaluation of tumor response may not be
217 critical for a determination of efficacy, and recording tumor measurements for the database may
218 not always be important. When response and progression are evaluated, criteria for these
219 endpoints should be detailed in the protocol, and data should be carefully collected at specified
220 intervals. The following are important considerations for tumor measurement data.

- 221
222 • The protocol and the corresponding CRF should make clear which tumor evaluations are
223 intended to be used to evaluate response and progression. Missing data has been a chronic
224 problem for FDA in evaluating these endpoints.
- 225
226 • The CRF should document the target lesions identified during the baseline visit, or at least
227 prior to treatment. Retrospective identification of such lesions would rarely be considered
228 reliable.
- 229
230 • Tumor lesions should be assigned a unique identifying letter or number. This allows
231 differentiating among multiple tumors occurring at one anatomic site and matching of tumors
232 measured at baseline and tumors measured during follow-up.
- 233
234 • It is desirable to have a mechanism that ensures complete collection of data at critical times
235 during follow-up. The CRF should ensure that all target lesions are assessed when
236 response and progression are noted. One approach would be to use an evaluation form to
237 display data at the three time points in a traditional response pattern: baseline, response,
238 and verification visit.

H. Cancer Drug Dosing

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241
242 Detailed data on dosing of anticancer drugs should be collected in at least a sample of patients
243 in each important study to adequately characterize the dose intensity of therapy in each study
244 arm. It is important to demonstrate whether the proposed dose of the study drug is tolerated
245 and whether an adequate dose of therapy was given in the control arm. In all patients, data
246 should be collected to document whether the initial dose of drug was decreased and, if so, the

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247 date and the reason for the dose decrease. These data can be collected in the form of check
248 boxes corresponding to the expected reasons for dose decrease, with a separate box for *other*,
249 together with a space for comment.

250

251 **I. Toxicity**

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253 Data on National Cancer Institute (NCI) grade 4-5 hematologic toxicity and grade 3-5
254 nonhematologic toxicity should be collected. Marketing applications for a new regimen should
255 also collect data on grade 1-2 nonhematologic toxicity and grade 1-3 hematologic toxicity for
256 an adequate number of patients from one or more studies or from a subset of these studies. The
257 number of patients adequate for a marketing application should be determined with FDA at an
258 end-of-phase-2 meeting. In supplemental efficacy applications that propose a new use for an
259 already marketed drug in a similar population, additional data on grade 1-2 nonhematologic
260 toxicity and grade 1-3 hematologic toxicity may not be important and may not need to be
261 collected. Data on serious adverse events associated with the use of a drug, or adverse events
262 leading to discontinuation or dose reduction of treatment should be collected.

263

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

269

270 Unless previous applications have fully characterized the toxicity of a regimen, documented
271 toxicities should be followed until resolution. Follow-up visits should record whether the toxicity
272 has been reevaluated and/or has resolved. Similarly, unless previous applications have fully
273 characterized the toxicity of a regimen, major actions taken should be recorded and categorized
274 (e.g., treatment delayed, dose reduced, hospitalized). Data on investigator attribution of toxicity
275 is not necessary.

276

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

282

283 In studies including a large number of patients, it may be appropriate to collect detailed data
284 such as laboratory and grade 1-2 toxicity data from only a sample or subset of patients studied.
285 Complete data collection might be performed in only one of the principal trials or only in a
286 sample of patients from a large trial, assuming that enough patients are studied and that relevant
287 demographic groups are included.

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J. Concomitant Medications

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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 need be recorded only if they might reflect responses to drug toxicity. 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 affect verification of efficacy (e.g., dexamethasone use in applications for treating brain tumors or narcotic use when reduction of pain is an important endpoint).

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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.

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K. Further Anticancer Therapy

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When survival is an important regulatory endpoint, anticancer therapy given subsequent to 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 be recorded, not doses or outcomes. 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 subsequent to study therapy. Therapy beyond the first regimen is less likely to have a survival impact.

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

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The following illustrates how data collection can vary at different stages of cancer drug development. It is a purely hypothetical example of drug 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.

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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

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331 decision to approve Drug A were (1) the company's careful documentation of previous cancer
332 treatments, (2) demonstration that tumors were refractory to available therapy, (3) tumor measurements
333 verifying the claimed tumor response rate, and (4) collection of detailed safety data, including
334 toxicity/adverse drug reactions of all severity.

335

336 The sponsor then planned trials to support an indication of *first-line therapy for metastatic E cancer*.
337 The sponsor performed two randomized studies comparing Drug A to Drug B, the standard first-line
338 therapy for this cancer. Four hundred patients were randomized to Drug A in each study. The
339 objective of the first study was to demonstrate that survival was improved in patients treated with Drug
340 A relative to those treated with Drug B. In the second study, reduction of symptoms was the primary
341 endpoint and tumor response was a supportive endpoint. FDA noted that most of the detailed data
342 needed for the application for first-line treatment of E cancer could be collected in the second study and
343 that the first study could be relatively simple, with efforts focused on collecting data on survival and
344 serious toxicities. Data on cancer treatment given subsequent to treatment with Drug A were also
345 collected in the first study to assess its potential effect on survival. Data on tumor response,
346 concomitant medications, and routine laboratory values were not necessary for the first study.

347

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

358

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

368

369 Data from phase 3 trials in Europe suggested the effectiveness of Drug A in the *treatment of*
370 *metastatic cancer G*, a cancer of young and middle-aged women, but these data were unavailable for
371 submission to FDA. The sponsor designed large randomized studies to evaluate efficacy of Drug A in
372 the adjuvant setting (a setting where chemotherapy is given after surgical removal of all known tumor).
373 The large study was designed to include 4000 patients to determine the disease-free survival and

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374 survival rates of Drug A versus Drug D, the standard approved adjuvant treatment with a well-
375 characterized survival effect. Because comparative safety data were important and because the
376 population was new, detailed toxicity data of all grades and routine laboratory data (those specified in
377 section III.E.1 of this document) were taken from an adequate sample of patients, the first 400 patients
378 and the last 200 patients enrolled. In addition, because the possibility of cardiac toxicity was still an
379 issue, serial cardiac ejection fraction was determined in this sample of patients. An interim toxicity
380 analysis was performed after evaluation of the first 400 patients. Efficacy data on tumor recurrence and
381 survival were collected for all patients. Concomitant cardiac medications were collected for all patients
382 but other concomitant medications were not collected. Again, for this new population and new study
383 design, specific data on dosing of the study drug and the control drug was recorded in a sample of 200
384 patients in each arm to allow calculation of relative dose-intensity on the two study arms. The CRF for
385 all patients recorded starting dose, dose reductions, and reasons for dose-reductions. Serious toxicities
386 and duration of toxicity were recorded in all patients in this trial.

387
388 The above fictitious drug development history shows that data collection recommendations can depend
389 on the stage of drug development, the indication sought, and clinical trial design. Taking these factors
390 into consideration can decrease collection of unnecessary data, allow sponsors to include more patients
391 in clinical trials, and improve the quality of the data that are collected. Sponsors should evaluate their
392 drug development plan, consider the principles outlined in this guidance, and develop a data collection
393 proposal. Given the complexity of the drug development process for cancer drugs, we encourage
394 sponsors to discuss their plans for data collection with the Agency prior to their implementation.