
Guidance for Industry

Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations

DRAFT GUIDANCE

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**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)**

**February 2012
Clinical Medical**

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**U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research (CDER)
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February 2012
Clinical Medical**

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1 **Guidance for Industry¹**
2 **Determining the Extent of Safety Data Collection Needed in Late**
3 **Stage Premarket and Postapproval Clinical Investigations**
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7 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current
8 thinking on this topic. It does not create or confer any rights for or on any person and does not operate to
9 bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of
10 the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA
11 staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call
12 the appropriate number listed on the title page of this guidance.
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17 **I. INTRODUCTION**
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19 This guidance is intended to assist sponsors of clinical trials of investigational drug and
20 biological products in determining the amount and types of safety data to collect during late
21 stage premarket and postmarket clinical investigations. The guidance emphasizes a selective and
22 better targeted approach to safety data collection during late stage development or during the
23 postmarket stage based on what is already known about a medical product's safety profile.
24 Although many of the general principles discussed in this guidance apply to clinical development
25 of oncology drugs, there is a separate guidance that pertains specifically to collection of clinical
26 data needed to support oncology product marketing applications.² This guidance document is
27 not intended to affect reporting of postmarketing adverse events that occur with use of an
28 approved drug as required by 21 CFR 314.80 and 600.80.
29

30 FDA's guidance documents, including this guidance, do not establish legally enforceable
31 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should
32 be viewed only as recommendations, unless specific regulatory or statutory requirements are
33 cited. The use of the word *should* in Agency guidances means that something is suggested or
34 recommended, but not required.
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¹ This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

² FDA guidance for industry, *Cancer Drug and Biological Products – Clinical Data in Marketing Applications*
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II. BACKGROUND

A robust safety database is critically important to a meaningful assessment of the potential risks of a new drug so that these can be weighed against its benefits. For this reason, extensive safety-related data are collected throughout the course of drug development to characterize the safety profile of a drug. That drug profile continually evolves as the data accumulate from premarket testing through postmarket surveillance and risk management. However, in late stages of development or during the postmarket period, a selective, and better targeted, approach to safety data collection may be warranted. In some cases, for example, when certain aspects of the safety profile are well established prior to the completion of clinical development, it may no longer be necessary to collect certain types of safety data (see section III.A). Similarly, if there is generally a well established safety profile for a marketed drug being used in a postmarket clinical trial, it may not be necessary to collect certain types of safety data in such a trial.

In some cases, collection of data that are no longer useful for characterizing the safety profile of a drug may even have negative consequences. Arduous and excessive data collection may be a major disincentive to investigator participation in clinical trials. There is also growing interest in and a need for larger, simpler trials to obtain outcome data, data on long-term effects of drugs, and comparative effectiveness and safety data, but excessive data collection requirements may deter the conduct of these types of trials by increasing the difficulty, time, and cost of conducting the trials.

In such cases, more selective safety data collection may (1) improve the quality and utility of the safety database and safety assessment without compromising the integrity and validity of the trial results or losing important information, (2) ease the burden on investigators conducting and patients participating in a study, and (3) lower costs, thereby facilitating increased use of large, simple trials and better use of clinical trial resources generally. For these reasons, more selective safety data collection is generally advisable in the appropriate situations (see Section III).

In the past, selective or specifically targeted data collection and reporting during clinical trials have been implemented on a case-by-case basis. However, there has been little public discussion of this practice. It is common, for example, in large outcome trials (generally conducted postmarket, but in some cases during late phase 3) for FDA to agree to selected or targeted collection of adverse events—specifically, those with important effects on treatment, such as events leading to discontinuation of therapy, change in dose, or need to add concomitant therapy— and more limited collection of routine laboratory data. It has also been common for FDA to agree to the collection of data only on concomitant therapy that was of a particular concern (e.g., because of a pertinent pharmacologic effect or potential interaction), rather than data on all concomitant therapy. This more targeted approach to collection of safety data reflected the view that less serious, less severe, and more common events (e.g., headache, nausea) had been adequately evaluated and characterized in earlier data collection and that little would be gained from further collection of these events. However, it is important to note that data from serious adverse events must always be collected and reported.

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84 Encouraging more selective or targeted safety data collection in certain clinical trials and
85 postmarket safety evaluations is also consistent with FDA’s evolving overall approach to safety
86 assessment, which emphasizes quality over quantity. For example, the recently revised
87 regulations for reporting of serious, unexpected, suspected adverse reactions to FDA and all
88 investigators (the IND safety reporting rule) address a similar concern.³ FDA determined that
89 the old regulations on IND safety reports needed to be revised because large numbers of 15-day
90 safety reports submitted to FDA under the old regulations did not reflect true signals of adverse
91 reactions, but rather were background events that occur commonly in the study population, or
92 study endpoints, and not interpretable as single events. Therefore, FDA modified the IND safety
93 reporting regulations to require that single events, uninterpretable in isolation, not be reported,
94 but be examined in the aggregate as safety data accumulate and be reported only when there are
95 sufficient data to determine there is a reasonable possibility that the drug caused the adverse
96 event.

97
98 The goal of this guidance is to provide advice on how and when to simplify data collection to
99 maintain a balance between eliminating the collection of data that will not be useful and
100 collecting sufficient data to allow adequate characterization of a drug’s safety profile given the
101 potential benefits. A sponsor considering a simplified data-collection approach should consult
102 with the relevant FDA review division on the feasibility and acceptability of the plan before its
103 implementation.

III. TARGETED SAFETY DATA COLLECTION — RECOMMENDATIONS

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108 The amount and types of safety data collected during clinical trials and observational safety
109 evaluations will vary based on a range of factors, including the disease, patient population,
110 subgroup of interest, preclinical findings, prior experience with the drug, experience with the
111 drug class, phase of development, and study design, among other factors. Safety data collected
112 could include some or all of the following, among other information:

- 113
- 114 • Serious, unexpected adverse events
- 115 • Serious expected adverse events
- 116 • Adverse events that cause discontinuation of treatment or dose modification
- 117 • Nonserious, unexpected adverse events
- 118 • Nonserious, expected adverse events
- 119 • Routine laboratory data (basic blood and urine analyses)
- 120 • Laboratory data limited to specific tests of interest or specialized laboratory data (e.g.,
- 121 radiographic tests, EKGs, pulmonary function tests, lipid fractions)
- 122 • Physical examination findings
- 123 • New concomitant medications (post-enrollment)
- 124

³ 21 CFR 312.32. See also *75 Federal Register* 59935, Investigational New Drug Safety Reporting for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans, for discussion of the rationale for more selective use of IND safety reports. See also *75 Federal Register* 60129, including a reference to the FDA draft guidance for industry, *Guidance for Industry and Investigators, Safety Reporting Requirements for INDs and BA/BE Studies*.

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Certain aspects of patient history may also be relevant to safety, including:

- Concomitant illnesses at baseline
- Concomitant medications at baseline
- Prior treatment history
- Prior medical history
- Cardiovascular risk factors (history or laboratory)

Information on serious adverse events should generally be collected during all clinical trials, even for expected serious events, as collection of these events may change conclusions about the rate of occurrence or severity of an event. Adverse events leading to discontinuation or dose modification are also of interest, as such outcomes could vary by indication and population. Laboratory tests of particular interest for the study or population should also be collected. As discussed in more detail below, it may be appropriate in later phases of drug development or in postmarket studies to not collect some or all of the remaining types of data identified, or to collect such information at lower frequency or from only a fraction of the total study enrollment (e.g., 10% in a study with large population), depending on the extent to which a drug’s safety characterization is already established.

A. Circumstances in Which Targeted Data Collection May be Appropriate

Although it is reasonable and appropriate to limit collection of additional data on well-characterized adverse events and certain other types of safety data, it is also important not to compromise the ability to identify important new safety problems (new serious events or events more prominent in a new population) or to start selective data collection before the safety profile of the drug has been adequately characterized at the doses being studied. In general, selective or specifically targeted safety data collection is appropriate when the following conditions are present:

- The number of subjects exposed to the drug in previous studies is sufficient to characterize the safety profile for all but rare events
- The occurrence of adverse events has been generally similar across multiple studies
- There is a reasonable basis to conclude that occurrence of adverse events in the population to be studied will be similar to previously observed rates

These criteria are most likely to exist in the following types of clinical studies.

1. Postmarket studies

Studies of new indications: Targeted data collection will often be appropriate in postmarket studies for new indications or other purposes because the existing safety database will often be relevant to the study population in the postmarket study. The extent to which the existing safety database will be relevant will vary depending on the nature of the new study population, disease, dose, and duration of treatment and other factors (see section D.2).

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172 **Postmarketing Requirements (PMRs):** For clinical trials conducted to meet PMRs, the
173 enrolled population is often the same or very similar to the population from which the
174 premarket safety database was derived, and the purpose of the trial is often to assess a
175 particular concern. In such studies, safety data collection may be significantly
176 abbreviated. Safety data collection can often be focused on the primary safety endpoint
177 or endpoints of interest (e.g., the outcomes that are the basis for a composite
178 cardiovascular endpoint in a postapproval trial of an oral hypoglycemic). However, it
179 will still be important to collect data on other serious events and any adverse events
180 associated with trial discontinuation.

181
182 **Large outcome trials:** Large outcome trials (e.g., trials that evaluate uncommon
183 mortality or major morbidity events such as cardiovascular death, AMI, stroke, cancer
184 recurrence) are generally conducted postmarket and usually in the same type of
185 population from which the premarket safety database was derived. Therefore, these trials
186 are also often good candidates for selective safety data collection. The safety profile with
187 respect to frequent, non-serious adverse events is generally well established, and further
188 safety data collection can usually be limited to events of particular interest, serious
189 events, or other events that lead to discontinuation.

190
191 In unusual cases, a drug cannot be marketed on the basis of a short-term effect, and it is
192 necessary to conduct large outcome trials during phase 3 to obtain marketing approval
193 (e.g., most uses of anti-platelet therapy, anti-coagulant therapy to prevent stroke in
194 patients with atrial fibrillation). These trials typically involve quite large populations
195 relative to typical phase 3 trials and may be appropriate for selective safety data
196 collection methods. For example, it may be sufficient to collect safety data for the more
197 common, non-serious events in only a planned subset of the study population.

2. *Late phase 3 studies*

200
201 If a large safety database already exists before the initiation of a phase 3 trial, that
202 database may contain safety information adequate to characterize certain aspects of a
203 drug's safety profile. For example, a clinical trial safety database derived from one or
204 more randomized trials may be sufficient to provide a relatively precise estimate of
205 relatively common non-serious events (e.g., those that occur in 5% or more of
206 exposures). In these situations, it may not be necessary to collect further data for these
207 types of events. For certain medical imaging agents (e.g., radiopharmaceuticals
208 administered at tracer doses), there is existing guidance that provides for more targeted
209 safety data collection later during clinical development.⁴

210
211 If an applicant is considering selective safety data collection, the safety data collection plan
212 should be discussed with the relevant review division (e.g., at the end of a phase 2 meeting for
213 targeted data collection in a phase 3 trial).

⁴ FDA guidance for industry, *Developing Medical Imaging Drug and Biological Products Part 1: Conducting Safety Assessments*

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B. Safety Data That May Be Appropriate for Abbreviated Collection or Non-Collection

In the circumstances specified in section A above, it may be acceptable to limit collection of certain types of safety data or not collect certain types of data, including the following.

1. Non-serious adverse events not associated with drug discontinuation

Generally, these events are well characterized by the time a product is far along in development or has obtained marketing approval, and additional data would be likely to add little to what is already known.

2. Routine lab monitoring

In many cases, if medically appropriate for patient care, it may be possible to eliminate routine lab monitoring that occurred solely to collect and submit these data to the FDA. It may also be possible to decrease the frequency of any monitoring considered necessary (e.g., less frequent liver function testing when a drug's evolving safety profile diminishes concerns about hepatotoxicity).

3. Information on concomitant medications

Information on concomitant medications, particularly those used only short term, may add little information if the drugs are pharmacologically unrelated to the study drug, provided that drug-drug interactions and metabolic pathways are fully characterized. Information about the dose and frequency of administration of such concomitant medications is not likely to be useful and is an additional burden to collect. However, information about concomitant medications in specific cases should be collected to facilitate evaluation of serious adverse events or drug-drug interactions that are not fully characterized.

4. History and physical exams

Less detailed histories and more targeted physical exams may be acceptable in some circumstances, especially in outcome studies.

C. Methods for Targeted or Selected Collection of Safety Data

A targeted safety data collection plan should be clearly described in the study protocol.

1. Pre-identification of data that need not be collected

It may be appropriate to identify certain types of safety data that need not be collected at all. Identified safety data should be listed in the study protocol.

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2. *Collection of data in subset of study population*

It may also be appropriate to collect certain safety data (e.g., non-serious adverse events) from only a sample of the entire study population. Methods for selecting the subpopulation may include selecting patients randomly, selecting study sites randomly, or targeting only the larger population sites. When targeting patient subsets or sites, it may be important to ensure representation from important demographic subgroups and patients with compromised renal function in the sample from which data is collected. For example, targeted recruitment efforts for geriatric subjects may be warranted, particularly for drugs likely to be used in the elderly, unless the sponsor can establish that an adequate geriatric safety database exists for the drug.

3. *Decreased frequency of data collection*

Less frequent collection of data may be appropriate for trials with lengthy follow-up periods. For example, laboratory studies and physical examination data may be collected at less frequent intervals than might ordinarily be the case with telephone follow-up in between study visits to maintain patient contact.

D. *When Comprehensive Data Collection is Generally Needed*

Although a more focused collection of data is appropriate in some circumstances and stages of development, there are circumstances when comprehensive data collection would be expected.

1. *Development programs for original applications*

In general, comprehensive data collection is expected throughout premarket clinical development for trials intended to support an original NDA or BLA approval. In these trials, it is important to collect sufficient data to determine the occurrence, dose-response, and subset (demographic, concomitant illnesses, concomitant therapy) variations for the full range of adverse events of the drug, not just serious events. However, even in a development program for a novel agent, there may be cases when sufficiently comprehensive safety data are available before the completion of clinical development to permit selective data collection (see sections B.1 and B.2).

2. *Marketed drugs with differences in patient population, dose, or other conditions of use*

Although it may be appropriate to use selective safety data collection in many postmarket trials (see section B.1), it is typically not appropriate when there are important differences in the patient population, dose, dosage regimen, duration of use, or route of administration compared to the conditions of use in the approved labeling. For example, comprehensive data collection would generally be needed in a development program for the prevention of cancer or for use as adjuvant therapy in the treatment of cancer for a drug that is already approved for the treatment of active cancer, including collection of important long-term events. The development program supporting the approval of the

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306 drug for treatment of existing cancer would have gathered information on the usually
307 significant toxic effects of the drug in acute use, but would not have provided the
308 information needed to support use of the drug in a longer duration adjuvant regimen in an
309 essentially healthy population. Even in this setting, however, it may be acceptable to
310 collect common, non-serious adverse events, such as headache, in only a subset of the
311 overall study population.

312

313 3. *Development programs for orphan indications*

314

315 Orphan indications have limited patient populations available for study. Therefore, it is
316 important in general to obtain comprehensive data on each patient to best inform product
317 labeling.

318

319 4. *Assessing specific adverse events and baseline risk factors*

320

321 In some situations, the magnitude of the incidence or the relative risk of an adverse event
322 is related to baseline factors, and it is useful to identify these factors to manage risk. In
323 such situations, sufficient sample sizes will be needed to collect information adequate to
324 characterize these risk factors.

325

326 **E. Types of Data That Should Typically Be Collected**

327

328 There are also certain types of data that should almost always be collected:

329

330 1. *Data in special populations*

331

332 Because there is often limited availability of data in special populations, generally all data
333 on use of a drug in special populations, including data on nonserious adverse events,
334 should be collected. For example, pediatric patients often respond to a drug differently
335 than adults. As a result, it is very important to collect all safety data in that population,
336 especially as it is difficult to enroll pediatric patients in studies. There also is generally
337 very limited information on exposure in pregnant and nursing women, so all safety data
338 should be collected in those populations as well. Finally, there are often limited data
339 available in the geriatric population, so these data should be collected as well.

340

341 2. *Certain adverse event data*

342

343 Data on all serious adverse events, deaths, and events that lead to dose modification or
344 discontinuation should be collected at all times. In addition, data on adverse events that
345 are troubling because of their potential seriousness, such as suicidality (suicidal ideation
346 or thoughts), should generally be collected, unless existing data mitigate such a concern.
347 Unscheduled visits, hospitalizations, and accidental injuries may also reflect adverse
348 events of the drug, so these occurrences should also be collected. In an oncology setting,

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349 data from all Grade 3 and 4 adverse events, as well as Grade 2 events that affect vital
350 organs (heart, liver) should always be collected.^{5,6,7}

351
352 3. *Data for all study subject withdrawals*

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354 It is critical to collect data about and explore the reasons why a subject leaves a study.
355 Designating withdrawals only as “withdrew consent” is uninformative and in most cases
356 probably reflects inadequate pursuit of the underlying reason for withdrawal. A sponsor
357 who discovers this designation in study data should take steps to educate investigators on
358 the need to probe more diligently the reasons for dropouts. Narratives that more fully
359 describe the circumstances for why subjects withdraw from treatment or declare that they
360 cannot follow the protocol or dosing strategies may be very informative and should be
361 collected along with adverse events occurring at those times. Such information may
362 inform the cause-specific reasons for why some subjects remain in a study or remain on
363 assigned treatment and others do not.

364
365 4. *Targeted adverse event data*

366
367 Data on adverse events that have been designated for reporting, based on the existing
368 safety profile, pharmacology of the drug, or patient population, are expected to be
369 collected, even if they are not serious, fatal, dose-modifying, or cause for discontinuation.
370 Events would presumably be so designated when they are important (e.g., are a cause of
371 discontinuation) and when the study may shed light on their occurrence (e.g., effects of
372 dose, blood levels, concomitant therapy, concomitant illness, or demographic factors).

373
374 5. *Long-term exposure to chronic usage treatments – characterizing the time course*
375 *of risk*

376
377 For chronically used treatments indicated for chronic diseases, it is often important to
378 know the time course of events and whether the event rate or risk changes over the
379 duration of exposure. Usually, it is important to have a sufficient denominator of patients
380 followed long enough to observe and estimate the time-dependent risk (e.g., every three
381 or six months of continued exposure). In such cases, it is important to fully collect
382 important serious event data as exposure progresses.

⁵ Using the grading system for adverse events in cancer trials described in the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE), U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. A Grade 4 adverse event results in need for life-saving urgent intervention; a Grade 3 adverse event results in severe or clinically significant but not immediately life-threatening consequences; hospitalization or prolonged hospitalization needed; disabling; results in limitations on ability to bathe, dress, undress, feed, use toilet, take medications; and a Grade 2 event results in need for moderate, minimal, or local or invasive intervention; results in limitations on age appropriate ability to prepare meals, grocery, and/or clothes shop, use the telephone, manage money.

⁶ Also see Section I of FDA guidance for industry, *Cancer Drug and Biological Products – Clinical Data in Marketing Applications*, 2001, for further discussion of collection of adverse event data in cancer trials.

⁷ Also see the FDA guidance for industry, *Gene Therapy Clinical Trials-Observing Subjects for Delayed Adverse Events*, 2006, for further discussion of collection of delayed adverse event data in long term follow-up studies for gene therapy trials.