
Guidance for Industry and Investigators

Safety Reporting Requirements for INDs and BA/BE Studies

DRAFT GUIDANCE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)**

**September 2010
Drug Safety**

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**U.S. Department of Health and Human Services
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Guidance for Industry and Investigators¹

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I. INTRODUCTION

This document provides guidance to sponsors and investigators on safety reporting requirements for human drug and biological products² that are being investigated under an investigational new drug application (IND) and for drugs that are the subjects of bioavailability (BA) and bioequivalence (BE) studies that are exempt from the IND requirements. This guidance contains definitions used for safety reporting, makes recommendations on when and how to submit a safety report, and provides advice on other safety reporting issues that have generated questions from sponsors and investigators.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND AND OVERVIEW OF NEW REQUIREMENTS

On September 29, 2010, FDA published a final rule amending the IND safety reporting requirements under 21 CFR part 312 and adding safety reporting requirements for persons conducting BA and BE studies under 21 CFR part 320. The new requirements are designed to improve the overall quality of safety reporting, strengthen FDA's ability to review critical safety information, improve safety monitoring of human drug and biological products, and harmonize safety reporting internationally.

¹ This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) in conjunction with the Center for Biologics Evaluation and Research (CBER) at FDA.

² For the purposes of this document, unless otherwise specified, all references to "drugs" or "drug products" include human drug products and biological products that are also drugs.

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A. Overall Changes to IND Safety Reporting Requirements

Under former 21 CFR 312.32(c)(1)(i)(A) and (B), sponsors investigating a drug under an IND were required to notify FDA and all participating investigators, in a written IND safety report, of any adverse experience associated with the use of the drug that was both serious and unexpected, and any finding from tests in laboratory animals that suggested a significant risk for human subjects. The phrase *associated with the use of the drug* was defined to mean that “there is a reasonable possibility that the experience may have been caused by the drug” (former 21 CFR 312.32(a)). Notwithstanding this definition, sponsors frequently reported, as individual cases, serious adverse experiences for which there was little reason to believe that the drug caused the event. For example, sponsors often reported:

- Serious adverse experiences (e.g., mortality or major morbidity) that were likely to have been manifestations of the underlying disease
- Serious adverse experiences that commonly occurred in the study population independent of drug exposure (e.g., strokes or acute myocardial infarctions in an elderly population)
- Serious adverse experiences that were study endpoints (i.e., the study was evaluating whether the drug reduced the rate of these events).

These types of reports are generally uninformative when reported as single events, (i.e., without a comparison of the incidence of the event in treated and untreated subjects) and, therefore, do not meaningfully contribute to the developing safety profile of an investigational drug.

Attempting to review and evaluate these reports without the necessary context was also a drain on resources for FDA, investigators, and institutional review boards (IRBs),³ diverting them from other activities.

The tendency for sponsors to default to reporting an uninformative individual case seems to have been primarily related to misapplication of the *reasonable possibility* standard in the definition of *associated with the use of the drug*. For an individual case of the types of adverse events described above, there would generally not be enough evidence to suggest that there was a reasonable possibility that the drug caused the adverse event. Therefore, the event would not meet the definition of “associated with the use of the drug” and should not have been reported as an IND safety report.

The new requirements revise the definitions used for safety reporting and make clear when to submit expedited safety reports. The new requirements clearly distinguish circumstances in which it is appropriate to submit individual cases and circumstances in which cases should be aggregated and compared to a control group. These clarifications should increase the likelihood that submitted information will be interpretable and will meaningfully contribute to the

³ Investigators are required to promptly report “to the IRB...all unanticipated problems involving risk to human subjects or others,” including adverse events that should be considered unanticipated problems (21 CFR 312.53(c)(1)(vii), 312.66, and 21 CFR 56.108(b)(1)). Investigators often submit to the IRB every individual case that they receive from the sponsor. For more information on when an unanticipated risk should be reported to an IRB, see FDA’s *Guidance for Clinical Investigators, Sponsors, and IRBs, Adverse Event Reporting to IRBs – Improving Human Subject Protection*.
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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81 developing safety profile of the investigational drug and improve the overall quality of safety
82 reporting. In addition, reducing the number of uninformative individual reports will enhance the
83 ability of sponsors, FDA, investigators, and IRBs to focus on safety issues that affect public
84 health.

85
86 Because the new requirements specify reporting certain adverse events in the aggregate rather
87 than as individual cases, it is important for sponsors to have in place a systematic approach to
88 safety surveillance during product development that includes a process for evaluating
89 accumulating safety data (see section V.A.3.).

B. New Safety Reporting Requirements for BA and BE Studies (21 CFR 320.31(d)(3))

92
93 Under former 21 CFR 320.31(d), certain in vivo BA and BE studies in humans were exempted
94 from the IND requirements under part 312 if specific conditions were satisfied (i.e., samples of
95 any test article and reference standard were reserved by the persons conducting the study and
96 released to FDA upon request, studies were conducted in compliance with the requirements for
97 institutional review set forth in 21 CFR part 56 and informed consent set forth in 21 CFR part
98 50). Although these studies were not subject to the IND safety reporting requirements under 21
99 CFR 312.32, FDA has received safety information from these studies that has provided
100 important information about drugs under investigation. For this reason, the final rule contains
101 new safety reporting requirements under 21 CFR 320.31(d)(3) for persons conducting BA or BE
102 studies that are exempt from the IND requirements. These new requirements will help FDA
103 monitor the safety of these drugs and better protect human subjects enrolled in BA or BE studies.

III. DEFINITIONS (21 CFR 312.32(a))

106
107 The final IND safety reporting rule introduces new terms and definitions that are meant to be
108 clear, consistent, and in harmony with those used internationally. New definitions replace the
109 definition of the phrase *associated with the use of the drug* in former 21 CFR 312.32(a), which,
110 as discussed above, has been a source of confusion. The new definitions are provided below,
111 followed by further explanation or examples.

A. Adverse event (21 CFR 312.32(a))

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

114
115 An *adverse event* (also referred to as an adverse experience) can be any unfavorable and
116 unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally
117 associated with the use of a drug, without any judgment about causality. An adverse event can
118 arise from any use of the drug (e.g., off-label use, use in combination with another drug) and
119 from any route of administration, formulation, or dose, including an overdose.

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121 B. Adverse reaction⁴

122
123 An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset
124 of all suspected adverse reactions for which there is reason to conclude that the drug caused the
125 event.

127 C. Suspected adverse reaction (21 CFR 312.32(a))

128

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, ‘reasonable possibility’ means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

129

130 Within the reporting requirement under 21 CFR 312.32(c)(1)(i), FDA makes clear the meaning
131 of *reasonable possibility* by providing the following examples of types of evidence that would
132 suggest a causal relationship between the drug and the adverse event.

133

- 134 ■ A single occurrence of an event that is uncommon and known to be strongly associated
135 with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- 136 ■ One or more occurrences of an event that is not commonly associated with drug
137 exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon
138 rupture)
- 139 ■ An aggregate analysis of specific events observed in a clinical trial (such as known
140 consequences of the underlying disease or condition under investigation or other events
141 that commonly occur in the study population independent of drug therapy) that indicates
142 those events occur more frequently in the drug treatment group than in a concurrent or
143 historical control group

144

145 *Suspected adverse reactions* are the subset of all adverse events for which there is a reasonable
146 possibility that the drug caused the event. Inherent in this definition, and in the requirement to
147 report them is the need for the sponsor to evaluate the available evidence and make a judgment
148 about the likelihood that the drug actually caused the adverse event. We consider the definition
149 of *suspected adverse reaction* and the application of the *reasonable possibility* causality standard
150 to be consistent with the concepts and discussion about causality in the International Conference
151 on Harmonization (ICH) E2A guidance.⁵

⁴ For the purposes of prescription drug labeling, the term “adverse reaction” is defined to mean “an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event” (see 21 CFR 201.57(c)(7) and 201.80(g)).

⁵ *ICH E2A Guideline for Industry, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*, March 1995, pages 6-7.
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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D. Unexpected (21 CFR 312.32(a))

An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. “Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

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This definition relies entirely on a listing of the adverse events or suspected adverse reactions in the investigator brochure (or elsewhere in the general investigational plan if an investigator brochure is not required or available) as the basis for determining if newly acquired information generated from clinical trials or reported from other sources is *unexpected*. The suspected adverse reactions listed in the investigator brochure (i.e., “expected”) are those observed with the investigational drug and for which a causal relationship between the event and the drug is suspected or confirmed. Thus, adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

In addition, some adverse events are listed in the investigator brochure as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the ACE inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

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E. Serious (21 CFR 312.32(a))

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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This definition permits either the sponsor or the investigator to decide if an event is *serious*. Because serious adverse events are critically important for the identification of significant safety problems, FDA believes taking into account both the investigator’s and the sponsor’s assessment is important. For example, the investigator’s perspective may be informed by having actually observed the event, and the sponsor is likely to have broader knowledge of the drug and its effects to inform its evaluation of the significance of the event. If either the sponsor or investigator believes that the event is serious, the event must be considered serious and evaluated by the sponsor for expedited reporting (21 CFR 312.32(a)).

F. Life-threatening (21 CFR 312.32(a))

An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

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As with the definition of *serious*, the determination of whether an adverse event is life-threatening can be based on the opinion of either the investigator or sponsor. Thus, if either believes that it meets the definition of life-threatening, it must be considered life-threatening for reporting purposes (21 CFR 312.32(a)).

IV. REVIEW OF SAFETY INFORMATION (21 CFR 312.32(b))

During the course of drug development, a sponsor becomes aware of new safety information from a variety of sources. In general, adverse event information will be reported to a sponsor by investigators conducting ongoing clinical trials. Safety information may come from domestic or foreign sources. In addition, some types of information should be sought by the sponsor as part of its continuous pharmacovigilance on the safety of the drug. The sponsor is required to promptly review all information relevant to the safety of the drug (21 CFR 312.32(b)). This review should include examining data from all sources and deciding if an individual case of a

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206 serious and unexpected adverse event meets the criteria for reporting, as well as evaluating all
207 accumulating data at regular intervals to identify new safety signals.

208
209 The regulation includes some examples of sources, including information derived from any
210 clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific
211 literature, and unpublished scientific papers. (See 21 CFR 312.32(b)). Reports may also come
212 from foreign regulatory authorities and from foreign commercial marketing experience for drugs
213 that are not marketed in the United States (21 CFR 312.32(b)). The sponsor should conduct
214 literature searches at least annually, or at other appropriate intervals, to seek safety information
215 and report it if necessary. Safety information from any other source would also need to be
216 reviewed by the sponsor (e.g., safety information presented at a professional meeting) (21 CFR
217 312.32(b)).

218 219 **V. MONITORING THE SAFETY DATABASE AND SUBMITTING IND SAFETY** 220 **REPORTS**

221
222 Under 21 CFR 312.32(c), the sponsor is required to notify FDA and all participating
223 investigators in an IND safety report of potentially serious risks from clinical trials or any other
224 source, as soon as possible, but no later than 15 calendar days after the sponsor receives the
225 safety information and determines that the information qualifies for reporting. *Participating*
226 *investigators* include all investigators to whom the sponsor is providing drug under any of its
227 INDs or under any investigator's IND (21 CFR 312.32(c)(1)).

228
229 In addition, the sponsor must identify in each IND safety report, all IND safety reports
230 previously submitted to FDA concerning a similar suspected adverse reaction and must analyze
231 the significance of the suspected adverse reaction in light of previous, similar reports or any
232 other relevant information (21 CFR 312.32(c)(1)). Sponsors should evaluate a suspected adverse
233 reaction in the context of other related reports or adverse events, including those that occurred in
234 pre- and postmarket studies. Sponsors should have processes in place to periodically review and
235 analyze their entire safety database, not only for IND safety reporting purposes, but also to
236 update investigator brochures with new safety information.

237
238 The sponsor must submit an IND safety report when any of the following criteria are met:

239 240 **A. Serious and unexpected suspected adverse reaction (21 CFR 312.32(c)(1)(i))**

241
242 The sponsor must report in an IND safety report any suspected adverse reaction that is both
243 serious and unexpected. Before submitting this report, the sponsor needs to ensure that the event
244 meets all three of the definitions contained in the requirement:

- 245
246
 - 247 ▪ Suspected adverse reaction
 - 248 ▪ Serious
 - 249 ▪ Unexpected

250 If the adverse event does not meet all three of the definitions, it should not be submitted as an
251 expedited IND safety report.

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252
253 Appropriately deciding whether the adverse event meets the definition of a *suspected adverse*
254 *reaction* is usually the most difficult determination, but it is critical to avoiding the submission of
255 uninformative IND safety reports. The sponsor should evaluate the available information and
256 decide if there is a reasonable possibility that the drug caused the adverse event and, therefore,
257 meets the definition of a *suspected adverse reaction*. The suspected adverse reaction must then
258 be reported expeditiously in an IND safety report if it also meets the definitions of *serious* and
259 *unexpected* (21 CFR 312.32(c)(1)(i)).

260
261 To assist sponsors with determining whether an adverse event meets the definition of suspected
262 adverse reaction, the requirement under 21 CFR 312.32(c)(1)(i) specifies that sponsors are to
263 report to FDA **only** if there is evidence to suggest a causal relationship between the drug and the
264 adverse event and provides examples of such evidence, described below.

265
266 1. *Individual occurrences (21 CFR 312.32(c)(1)(i)(A))*

267
268 Certain serious adverse events are informative as single cases because they are
269 uncommon and are known to be strongly associated with drug exposure. Some examples
270 include angioedema, blood dyscrasias, rhabdomyolysis, hepatic injury, anaphylaxis, and
271 Stevens-Johnson Syndrome. The occurrence of even one case of such adverse events
272 would meet the definition of *suspected adverse reaction* (i.e., that there is a reasonable
273 possibility that the drug caused the event).

274
275 2. *One or more occurrences (21 CFR 312.32(c)(1)(i)(B))*

276
277 A single occurrence, or a small number of occurrences, of a serious adverse event that is
278 uncommon in the study population, but not commonly associated with drug exposure
279 may also be informative. If the event occurs in association with other factors strongly
280 suggesting causation (e.g., strong temporal association, event recurs on rechallenge), a
281 single case may be sufficiently persuasive to report in an IND safety report. Often, more
282 than one occurrence from one or multiple studies would be needed before the sponsor
283 could determine that there is a *reasonable possibility* that the drug caused the event.
284 Examples include tendon rupture or heart valve lesions in young adults, or
285 intussusception in healthy infants.

286
287 3. *Aggregate analysis of specific events (21 CFR 312.32(c)(1)(i)(C))*

288
289 Certain serious adverse events can be anticipated to occur in the study population
290 independent of drug exposure. Such events include known consequences of the
291 underlying disease or condition under investigation (e.g., symptoms, disease progression)
292 and events unlikely to be related to the underlying disease or condition under
293 investigation, but common in the study population independent of drug therapy (e.g.,
294 cardiovascular events in an elderly population). An example of the former would be a
295 non-acute death observed in a trial in cancer patients. An example of the latter would be
296 an acute myocardial infarction observed in a long-duration trial in an elderly population

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297 with cancer. In some investigations, serious adverse events that are consequences of the
298 underlying disease may be study endpoints (e.g., mortality or major morbidity endpoints).
299

300 Because these serious adverse events meet the definition of *unexpected* at 21 CFR
301 312.32(a), as they are not listed in the investigator brochure (see sections III.D. and
302 VI.B.), sponsors have often reported them individually in IND safety reports. However,
303 these events do not warrant expedited reporting as individual cases because it is not
304 possible, based on a single case, to determine that there is a reasonable possibility that the
305 drug caused the event. The following recommendations are intended to assist sponsors
306 with protocol development and monitoring the safety database.
307

308 a) Reporting study endpoints (21 CFR 312.32(c)(5))
309

310 For trials that are designed to evaluate the effect of a drug on disease-related
311 mortality or major morbidity, endpoint information should be collected, tracked,
312 and monitored, usually by a Data Monitoring Committee (DMC), during the
313 course of the study. The protocol would pre-specify a monitoring plan for
314 determining if subjects receiving the drug treatment are at higher risk for the
315 outcome (e.g., all-cause mortality), and such results would be reported according
316 to the protocol. The study endpoints must be reported to FDA by the sponsor
317 according to the protocol, and not as IND safety reports, except in unusual cases
318 (21 CFR 312.32(c)(5)). For example, a death ordinarily would not be reported as
319 an individual case in an expedited report from a trial designed to compare all-
320 cause mortality in subjects receiving either drug treatment or a placebo. On the
321 other hand, in the same trial with an all-cause mortality endpoint, if the death
322 occurred as a result of an anaphylactic reaction that coincided with initial
323 exposure to the drug, or as a result of fatal hepatic necrosis, the death must be
324 reported as an individual case in an IND safety report because there would then be
325 evidence suggesting a causal relationship between the drug and the event (21 CFR
326 312.32(c)(5)).
327

328 b) Serious adverse events that are not study endpoints
329

330 Other serious adverse events that are not study endpoints, such as known
331 consequences of the underlying disease or condition under investigation or
332 events common in the study population, are also anticipated to occur with some
333 frequency during the course of the trial, regardless of drug exposure. In general,
334 a limited number of occurrences of an adverse event in a study population in
335 which occurrences of the event are anticipated independent of drug exposure is
336 not an adequate basis to conclude that the event is a suspected adverse reaction
337 (i.e., that there is a reasonable possibility that the drug caused the event). Such
338 events should not be reported individually as they occur because they are
339 uninformative as single cases. At appropriate intervals, the numbers of such
340 events in each arm of a controlled study should be compared and reported to
341 FDA expeditiously as an IND safety report if there is an imbalance between arms
342 suggesting there is a reasonable possibility that the drug caused the adverse

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343 event. If an imbalance is noted in a study and the study is part of a larger drug
344 development program, it will be important to evaluate the entire clinical trial
345 database.

346
347 *i. Identifying and monitoring protocol-specified serious adverse*
348 *events*

350 At the time of protocol development, the sponsor should identify in the
351 protocol the serious adverse events that it does not plan to report
352 individually in an expedited manner because they are anticipated to occur
353 in the study population at some frequency independent of drug exposure.
354 It is not possible or desirable to list in the protocol every adverse event
355 that may be common in the study population. Factors to consider when
356 deciding which adverse events to identify include, for example,
357 characteristics of the study population, natural progression of the disease,
358 background event rates, co-morbid conditions, and past experience with
359 similar populations. The sponsor should limit the list to those events that
360 are common even in the absence of drug exposure. For example, in a
361 long-term osteoporosis trial in an elderly population, it would be
362 reasonable to list myocardial infarction, but unreasonable to list acute
363 narrow angle glaucoma, an event that can occur in this elderly population,
364 but is relatively rare. The protocol should also describe how the protocol-
365 specified serious adverse events will be monitored. The sponsor or an
366 independent group should monitor the identified events during the course
367 of the trial and submit an IND safety report if an aggregate analysis
368 indicates that the events are occurring more frequently in the drug
369 treatment group (see section V.A.3.c.).

370
371 *ii. Reporting serious adverse events that are not protocol-specified*

372
373 The fact that an event is not identified in the protocol does not mean that
374 the sponsor should report a single occurrence of the event expeditiously.
375 The sponsor should use judgment in determining whether there is a
376 reasonable possibility that the drug caused the event. Often, a single case
377 will be unpersuasive. For example, in the osteoporosis trial described
378 above, a single case of acute narrow angle glaucoma would generally not
379 be reported in an expedited IND safety report because such cases are seen
380 in an untreated elderly population, but if monitoring for subsequent cases
381 revealed additional cases in the drug-treatment group, the sponsor would
382 consider the events to meet the definition of suspected adverse reactions at
383 21 CFR 312.32(a) and would report them expeditiously.
384

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385 c) Safety surveillance for ongoing clinical trials⁶
386

387 Because it is critical that a drug product's risks be adequately assessed during
388 development, sponsors should ensure that they have in place a systematic
389 approach for safety surveillance. Such an approach should include a process for
390 reviewing, evaluating and managing accumulating safety data from the entire
391 clinical trial database at appropriate intervals. In some cases, a specific
392 committee, preferably independent with substantial external representation, could
393 be created to perform this function. In others, the sponsor may choose to create a
394 safety team within the sponsor's organization that would oversee the evolving
395 safety profile of the investigational drug and evaluate, at appropriate intervals, the
396 accumulating data from individual and multiple clinical trials, as well as other
397 available information.
398

399 **B. Findings from other sources (21 CFR 312.32(c)(1)(ii) and (iii))**
400

401 The sponsor must also report expeditiously any findings from clinical, epidemiological, or
402 pooled analysis of multiple studies or any findings from animal or in vitro testing that suggest a
403 significant risk in humans exposed to the drug (21 CFR 312.32(c)(1)(ii) and (iii)). These reports
404 are required for studies from any source, regardless of whether they are conducted under the IND
405 or by the sponsor (21 CFR 312.32(c)(1)(ii) and (iii)). A finding that suggests a *significant risk*
406 would ordinarily result in a safety-related change in the protocol, informed consent, investigator
407 brochure (excluding routine updates of these documents), or other aspects of the overall conduct
408 of the clinical investigation. For example, actions often taken in response to a significant risk
409 finding include immediate revision of the informed consent, intensification of subject
410 monitoring, revised eligibility criteria or screening procedures, enrollment hold, or consideration
411 of discontinuation of the trial. The sponsor is also required to submit a protocol amendment that
412 describes the change to the protocol or other documents (21 CFR 312.30(b)) in addition to the
413 IND safety report.
414

415 1. *Findings from other studies (21 CFR 312.32(c)(1)(ii))*
416

417 Findings that suggest a significant risk generally arise from ongoing or completed clinical
418 studies, pooled data from multiple studies, epidemiological studies, and published and
419 unpublished scientific papers. Findings from clinical studies that are subject to this
420 requirement are those that have not already been reported under 21 CFR 312.32(c)(1)(i).
421 For example, any clinically important finding from a drug interaction study or from a
422 study evaluating QT interval would be reported under this provision.
423

⁶ For more discussion of this subject, see the *Report of the Council for International Organizations of Medical Sciences (CIOMS) Working Group VI's* discussion of a "multidisciplinary safety management team" (Management of Safety Information from Clinical Trials. Report of CIOMS Working Group VI (2005), pp. 55-67) and FDA's guidances, *Establishment and Operation of Clinical Trial Data Monitoring Committees and Premarketing Risk Assessment*. FDA's guidances are available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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2. Findings from animal or in vitro testing (21 CFR 312.32(c)(1)(iii))

Findings from animal studies, such as carcinogenicity, mutagenicity, teratogenicity, or reports of significant organ toxicity at or near the expected human exposure are examples of the types of findings that could suggest a significant risk. Before reporting a finding to FDA, the sponsor should use judgment to determine whether the finding suggests a significant risk in humans or is too preliminary to interpret without replication or further investigation.

C. Increased occurrence of serious suspected adverse reactions (21 CFR 312.32(c)(1)(iv))

The sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure (21 CFR 312.32(c)(1)(iv)). A baseline incidence rate may not always be available, but when one is available, a clinically important increase from that rate must be reported (21 CFR 312.32(c)(1)(iv)). The decision about when to report is a matter of judgment based on a variety of factors including the study population, the nature and seriousness of the reaction, and the magnitude of the observed increase in the rate. For example, rhabdomyolysis is a recognized, infrequent adverse reaction that is known to occur in the HMG-CoA reductase inhibitor class of drugs (i.e., statins). A higher rate with one member of the class in a high-dose study would merit reporting.

VI. OTHER SAFETY REPORTING ISSUES

A. Alternative reporting arrangements (21 CFR 312.32(c)(3))

Title 21 of the CFR, §§ 312.32(c)(1) and 312.32(c)(1)(v) specify the format and timeframe for reporting suspected adverse reactions in an IND safety report (see section VII). Sponsors may request and adopt different reporting formats or frequencies if agreed to in advance by the director of the FDA review division that has responsibility for review of the IND (21 CFR 312.32(c)(3)). In addition, FDA may require a sponsor to submit IND safety reports in a different format or at a different frequency than required under 21 CFR 312.32(c)(1) and 312.32(c)(1)(v). (See 21 CFR 312.32(c)(3)). FDA may require a sponsor to continue to report expeditiously a medically significant suspected adverse reaction that is listed in the investigator brochure as observed with the drug (i.e., expected) so that its rate can be carefully monitored. For example, if an occurrence of Stevens-Johnson Syndrome was observed in a subject receiving the investigational drug, FDA may require expedited reporting of additional cases of rash of a lesser severity. FDA may also require an alternative format or frequency for reporting suspected adverse reactions from clinical trials once a study or design has been identified as posing a potential or previously unforeseen risk to participants.

B. Investigator brochure

The purpose of the investigator brochure is to provide the investigator with information (clinical and nonclinical) about the investigational drug that is relevant to the study of the drug in human

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470 subjects. The investigator brochure should include the information that is important for the
471 investigator who is administering the drug to human subjects to know and understand. The
472 investigator brochure is required to include information about (see 21 CFR 312.23(a)(5)):

473

- 474 ▪ Drug substance and formulation
- 475 ▪ Pharmacological and toxicological effects of the drug in animals (and in humans, if known)
- 476 ▪ Pharmacokinetics and biological disposition of the drug in animals (and in humans, if
477 known)
- 478 ▪ Information relating to safety and effectiveness in humans obtained from prior clinical
479 studies
- 480 ▪ Information about possible risks and side effects to be anticipated on the basis of prior
481 experience with the drug under investigation or with related drugs
- 482 ▪ Precautions or special monitoring to be done as part of the investigational use of the drug

483

484 Although the most important purpose of the investigator brochure is to provide the investigator
485 with information about the investigational product, the investigator brochure is also used by the
486 sponsor as the basis for determining if a suspected adverse reaction is *unexpected* for purposes of
487 IND safety reporting (see section III.D.).

488

489 1. *Clinical risk information*

490

491 With respect to clinical risk information, the investigator brochure should list those
492 adverse events that have been observed with an investigational drug and for which a
493 causal relationship with the drug is suspected or confirmed. In addition, the investigator
494 brochure should list adverse events that commonly occur with the class of drugs or may
495 be predicted to occur based on the pharmacological properties of the drug, even if not yet
496 observed with the drug under investigation, to alert the investigator to the possibility of
497 their occurrence. The investigator brochure should not list adverse events that are
498 unlikely to have been caused by the drug because such lists could dilute the importance
499 of clinically meaningful risk information and as a result, may put subjects at risk.

500

501 2. *Updating the investigator brochure*

502

503 During the course of the clinical trial, the sponsor must update the investigator brochure
504 on an ongoing basis with new important safety information (21 CFR 312.55). Some
505 updates to the investigator brochure should be made as soon as possible while others can
506 be made on a routine basis. For example, a new safety finding that represents a
507 significant risk to study subjects (e.g., a finding that renally impaired subjects are likely
508 to experience a serious adverse reaction) should be communicated to the investigator
509 immediately, along with an update to the investigator brochure and possibly to the
510 protocol (e.g., a change in screening procedures and eligibility criteria). On the other
511 hand, an update to reflect a minor change in a suspected adverse reaction rate could be
512 done on an annual basis.

513

514 Until the investigator brochure is updated to include a new serious, suspected adverse
515 reaction, subsequent occurrences of similar serious, suspected adverse reactions must be

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516 submitted expeditiously in IND safety reports (21 CFR 312.32(c)(1)(i)). The sponsor
517 should exercise judgment when deciding if the threshold has been reached for adding a
518 newly observed adverse event to the investigator brochure. Criteria to consider usually
519 include the strength of the evidence from individual or multiple cases and previous
520 knowledge about the drug or drug class. In some cases, the threshold for including an
521 adverse event may be lower if it could result in a significant adverse outcome for trial
522 participants.

523

C. Unblinding

524

525
526 The blind should ordinarily be broken for serious and unexpected adverse events that would meet
527 the criteria for reporting as single occurrences or one or more occurrences (see sections V.A.1.
528 and V.A.2). Knowledge of the treatment received is necessary for interpreting the event, may be
529 essential for the medical management of the subject, and may provide critical safety information
530 about a drug that could have implications for the ongoing conduct of the trial (e.g., monitoring,
531 informed consent). In general, if the blind is broken and the subject was receiving placebo, the
532 event should not be reported in an IND safety report because there is not a reasonable possibility
533 that the drug caused the adverse event. If the blind is broken and the subject was receiving drug
534 treatment (test drug or active comparator), the suspected adverse reaction must be reported in an
535 IND safety report (21 CFR 312.32(c)(1)(i)). Any similar occurrences in the placebo group
536 would be described in the IND safety report as part of the analysis of the significance of the
537 suspected adverse reaction in light of other relevant information, and subsequent occurrences
538 submitted as followup information to the IND safety report. For those adverse events that would
539 not be reported unless an aggregate analysis indicated that they are occurring more frequently in
540 the drug-treatment group than in the placebo group, a determination that the adverse event is a
541 suspected adverse reaction would require analysis and reporting of the event rates in both the
542 drug-treatment and placebo groups.

543

544 As described in section V.A.3.a. above, there should generally be no need to report unblinded
545 study endpoints in an IND safety report. In many cases, an independent DMC would monitor the
546 serious events that are study endpoints. If a sponsor has concerns that unblinding will
547 compromise the integrity of the study, the sponsor can propose, in advance, an alternative
548 reporting format or frequency to maintain the blind that must be agreed to by the director of the
549 review division in FDA that has responsibility for review of the IND (21 CFR 312.32(c)(3)).
550 Any alternative arrangements would need to identify the serious adverse events in the protocol
551 that will not be reported on an individual basis, and include the plan for monitoring and reporting
552 results to FDA.

553

D. Investigator Reporting (21 CFR 312.64(b))

554

555
556 Most of the information about the safety of a drug prior to marketing comes from clinical trials.
557 Therefore, adverse event reports from investigators are critically important, as they are
558 monitoring the study subjects and making observations about the safety of the investigational
559 drug. Except for study endpoints, the investigator must immediately report to the sponsor all
560 serious adverse events, regardless of whether the investigator believes that they are drug related,
561 including those events listed in the protocol as anticipated to occur in the study population

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562 independent of drug exposure or in the investigator brochure as predicted to occur with the drug
563 (21 CFR 312.64(b)) unless an alternative reporting arrangement has been made under 21 CFR
564 312.32(c)(3). Study endpoints that are also serious adverse events are reported to the sponsor in
565 accordance with the protocol.

566

567 *1. Assessment of causality*

568

569 Although the investigator's view of the causal relationship between an adverse event and
570 the investigational drug is important, FDA believes that the sponsor is better positioned
571 than the individual investigator to assess the overall safety of the investigational drug
572 because the sponsor has access to serious adverse event reports from multiple study sites
573 and is able to aggregate and analyze these reports. For this reason, investigators must
574 immediately report any serious adverse event to the sponsor, without regard to causality
575 (21 CFR 312.64(b)). However, it is also important for the sponsor to consider the
576 investigator's view when assessing the safety of the drug and determining whether to
577 report expeditiously to FDA because the investigator is knowledgeable about the human
578 subject (e.g., medical history, concomitant medications), administers the investigational
579 drug, monitors the subject's response to the drug, is aware of the subject's clinical state
580 and thus may be sensitive to distinctions between events due to the underlying disease
581 process versus events that may be drug-related, and may have observed the event.
582 Therefore, the investigator must include an assessment of causality (i.e., whether there is
583 a reasonable possibility that the drug caused the event) in the report to the sponsor (21
584 CFR 312.64(b)). The sponsor should decide how to capture the investigator's causality
585 assessment (e.g., rating scale, yes/no response to a question such as, "Was there a
586 reasonable possibility that the drug caused the adverse event?").

587

588 *2. Study endpoints*

589

590 The investigator must report study endpoints that are serious adverse events in
591 accordance with the protocol (21 CFR 312.64(b)). Because endpoints are specifically
592 defined in the protocol, they are often not collected on the adverse event pages of the case
593 report form. The exception to this reporting requirement is when there is evidence
594 suggesting a causal relationship between a drug and an event (e.g., death from
595 anaphylaxis). In this case, the investigator must immediately report the event to the
596 sponsor, even if the event is a component of the endpoint (e.g., all-cause mortality) (21
597 CFR 312.64(b)).

598

599 *3. Nonserious adverse events*

600

601 The investigator must record nonserious adverse events and report them to the sponsor
602 according to the timetable for reporting specified in the protocol (21 CFR 312.64(b)).
603 Generally, nonserious events are recorded on the case report forms, and are retrieved by
604 the sponsor, or submitted to the sponsor, at regular intervals during the course of the
605 investigation. The investigator's assessment of causality is not required for nonserious
606 adverse events.

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608 For certain trials, such as a postmarket outcome trial for a drug that has a well-established
609 safety profile, recording most nonserious adverse events may not be necessary. Under 21
610 CFR 312.32(c)(3), the sponsor can arrange that only specific types of adverse events be
611 reported to the sponsor (e.g., those that resulted in withdrawal from the study or cessation
612 of therapy, modification of dose, or addition of another drug). Other nonserious adverse
613 events would then not need to be recorded by the investigator on the case report form.
614

615 E. Investigations of Marketed Drugs (21 CFR 312.32(c)(4))

616
617 According to 21 CFR 312.32(c)(4), the only reports that must be submitted as IND safety reports
618 for a drug marketed or approved in the United States are those arising from a study conducted
619 under the IND (at domestic or foreign sites). The sponsor must also submit safety information
620 from the clinical study as prescribed by the postmarketing safety reporting requirements (e.g.,
621 under 21 CFR 310.305, 314.80, 600.80, 606.170 or under the Dietary Supplement and
622 Nonprescription Drug Consumer Protection Act (Public Law 109-462)). All other reports (e.g.,
623 marketing experience, studies not under an IND) would be reported in accordance with the
624 relevant postmarket safety reporting requirements.
625

626 The table below⁷ summarizes the reporting requirements for submitting safety reports from a
627 clinical study.
628

Drug marketed or approved* in U.S.?	Under U.S. IND?	Trial site location	Must report to IND?	Must report per postmarket requirements?
Yes	Yes	U.S. or Foreign	Yes	Yes
Yes	No	U.S. or Foreign	No	Yes
No	Yes	U.S. or Foreign	Yes	
No	No	Foreign		

629 *If a drug is approved in the United States, but is not currently being marketed in the United
630 States, the postmarket requirements would still apply.
631

632 VII. SUBMITTING AN IND SAFETY REPORT (21 CFR 312.32(c)(1)(v))

633 A. Format

634
635
636 The format for IND safety reports is based on the type of expedited report. For reports of
637 individual cases, a sponsor would ordinarily use FDA Form 3500A. FDA will accept foreign
638 suspected adverse reaction reports on a CIOMS I Form instead of FDA Form 3500A (21 CFR
639 312.32(c)(1)(v)). These forms should be completed with all available information, including a
640 brief narrative describing the suspected adverse reaction and any other relevant information. If
641 applicable, the narrative must also include identification of similar reports and an analysis of the
642 significance of the suspected adverse reaction (21 CFR 312.32(c)(1)).

⁷ Reporting requirements for BA and BE studies that are not conducted under an IND and subject to the requirements under 21 CFR part 320 are not addressed in the table, but are addressed in section IX of this document. Areas in the table are left blank when an IND or marketing application would not exist.

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643
644 For reports of overall findings or pooled analyses from published and unpublished in vitro,
645 animal, epidemiological, or clinical studies, a narrative format must be used (21 CFR
646 312.32(c)(1)(v)). If the findings are published, the sponsor should include a copy of the
647 publication. FDA will typically also request information on the individual cases from aggregated
648 data from a clinical study.

649
650 Each report must prominently identify its contents (21 CFR 312.32(c)(1)(v)). For example, an
651 IND safety report would be identified in box A5 of FDA Form 3500A as an “IND Safety
652 Report,” and submission of follow-up information would be identified as a “Followup IND
653 Safety Report.” Currently, FDA is not able to accept electronic submission of these reports.
654

B. Where to submit

655
656
657 The report must be transmitted to the review division in CDER or CBER that has responsibility
658 for review of the IND (21 CFR 312.32(c)(1)(v)). If there are INDs in different review divisions,
659 the report should cross-reference all open INDs.
660

C. Reporting timeframe

661
662
663 The timeframe for submitting an IND safety report to FDA and all participating investigators is
664 no later than 15 calendar days after the sponsor determines that the suspected adverse reaction or
665 other information qualifies for reporting (21 CFR 312.32(c)(1)). If FDA requests any additional
666 data or information, the sponsor must submit it to FDA as soon as possible, but no later than 15
667 calendar days after receiving the request (21 CFR 312.32(c)(1)(v)).
668

669 Unexpected fatal or life-threatening suspected adverse reactions represent especially important
670 safety information and, therefore, must be reported more rapidly to FDA (21 CFR 312.32(c)(2)).
671 Any unexpected fatal or life-threatening suspected adverse reaction must be reported to FDA no
672 later than 7 calendar days after the sponsor’s initial receipt of the information (21 CFR
673 312.32(c)(2)). We recommend that sponsors notify FDA by telephone or facsimile transmission.
674 Other means of rapid communication (e.g., email) may also be used, if prior to transmission, the
675 sponsor contacts the Project Manager in the FDA review division that has responsibility for
676 review of the IND and ascertains that other means of rapid transmission are acceptable.
677

VIII. FOLLOW-UP INFORMATION (21 CFR 312.32(d))

678
679
680 Most IND safety reports are derived from observations from clinical trials. In the setting of a
681 clinical trial, information is collected in a controlled environment so that the information needed
682 to evaluate the suspected adverse reaction (e.g., information that would be contained in a
683 narrative report or on FDA Form 3500A) is generally readily available. If any information
684 necessary to evaluate the suspected adverse reaction is missing or unknown, the sponsor should
685 actively seek such information from the source of the report. Any relevant additional
686 information that the sponsor obtains that pertains to a previously submitted IND safety report
687 must be submitted to FDA as a *Followup IND Safety Report* without delay, as soon as the

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688 information is available (21 CFR 312.32(d)(2)). The sponsor should maintain records of its
689 efforts to obtain additional information.

690
691 For example, if information on concomitant medications is obtained after the initial IND safety
692 report is submitted, and such information is relevant to evaluating the suspected adverse reaction,
693 a sponsor should submit a *Followup IND Safety Report* immediately. However, if the sponsor
694 obtains other information that is not relevant to evaluating the suspected adverse reaction,
695 records of such information should be maintained by the sponsor, and if applicable, submitted in
696 an information amendment (21 CFR 312.31) or in an IND annual report (21 CFR 312.33).

697

IX. SAFETY REPORTING REQUIREMENTS FOR BA AND BE STUDIES

699

700 The IND safety reporting requirements under 21 CFR 312.32 apply to BA and BE studies that
701 are conducted under an IND. However, BA and BE studies that meet the conditions for
702 exemption under 21 CFR 320.31 are not conducted under an IND and are not subject to the IND
703 safety reporting requirements. The final rule contains new safety reporting requirements under
704 21 CFR 320.31(d)(3) that apply to persons conducting BA or BE studies that are exempt from
705 the IND requirements. The following information addresses these new requirements.

706

707 FDA believes that BA and BE studies that meet the requirements for exemption are generally
708 safe. The occurrence of a serious adverse event is very unusual because the number of subjects
709 enrolled in such a study is small, subjects are usually healthy volunteers, and drug exposure is
710 typically brief. However, FDA occasionally receives safety-related information associated with
711 these types of studies, which could reflect either a problem with the drug product being evaluated
712 or with the study design being used. For these reasons, the occurrence of any serious adverse
713 event, whether or not it is considered drug-related, is of interest. Timely review of this safety
714 information is critical to ensuring the safety of study subjects.

715

A. New BA/BE Study Safety Reporting Requirements (21 CFR 320.31(d)(3))

717

718 The person conducting a BA or BE study, including any contract research organization, must
719 notify FDA and all participating investigators of any serious adverse event, regardless of whether
720 the event is considered drug-related, observed during conduct of the study, as soon as possible
721 but in no case later than 15 calendar days after becoming aware of its occurrence (21 CFR
722 320.31(d)(3)). Serious adverse events observed in the investigational drug group and in the
723 approved drug group (e.g., reference listed drug) must be reported (21 CFR 320.31(d)(3)).

724

725 If any information necessary to evaluate the serious adverse event is missing or unknown, the
726 person conducting the study should actively seek such information and maintain records of
727 efforts made to obtain additional information. Any relevant additional information that is
728 obtained that pertains to a previously submitted safety report must be submitted to FDA as a
729 *Followup Bioavailability/Bioequivalence Safety Report* as soon as the information is available
730 (21 CFR 320.31(d)(3)). In addition, upon request from FDA, the person conducting the study
731 must submit to FDA any additional data or information that FDA deems necessary, as soon as
732 possible, but in no case later than 15 calendar days after receiving the request (21 CFR
733 320.31(d)(3)).

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734

735 If the adverse event is fatal or life-threatening, the person conducting the study must also notify
736 the Office of Generic Drugs within CDER as soon as possible but in no case later than 7 calendar
737 days after becoming aware of its occurrence (21 CFR 320.31(d)(3)). We recommend that these
738 notifications be made by telephone or facsimile transmission.

739

B. BA/BE Studies Conducted at Non-U.S. Sites

740

741 Under 21 CFR 320.31(d)(3), persons conducting human BA and BE studies in the United States
742 that are exempt from the IND requirements under part 312 must report any serious adverse
743 events from the study to FDA and to all participating investigators. The requirements under 21
744 CFR 320.31(d)(3) do not apply to human BA and BE studies that are exempt from the IND
745 requirements and conducted outside of the United States. However, as part of the information
746 required to establish that the proposed drug product can be expected to have the same therapeutic
747 effect as the reference listed product, adverse event information from foreign clinical studies
748 must be included in the abbreviated new drug application (ANDA) submission (see 21 CFR
749 314.94(a)(7)).

750

C. How and Where to Submit a Report (21 CFR 320.31(d)(3))

751

752 Each report must be submitted on FDA Form 3500A (21 CFR 320.31(d)(3)). The form should
753 be completed with all the available information, including a brief narrative describing the serious
754 adverse event, an assessment of causality, and any other relevant information. If applicable, the
755 narrative should also include identification of other similar reports and an analysis of the
756 significance of the serious adverse event. A summary of the study protocol should be submitted
757 with the report.

758

759 Each report must bear prominent identification of its contents (21 CFR 320.31(d)(3)). For
760 example, a report would be identified in box A5 of FDA Form 3500A as a
761 *Bioavailability/Bioequivalence Safety Report* or a *Followup Bioavailability/Bioequivalence*
762 *Safety Report*, as applicable. The drug product should be listed in box C1 of FDA Form 3500A,
763 and if the serious adverse event occurs in a subject receiving the investigational drug product, the
764 established name of the reference listed drug should be listed and identified as investigational.

765

766 Because FDA is not currently able to accept email or electronic submission of these reports, send
767 them in paper form to the Director, Office of Generic Drugs in the Center for Drug Evaluation
768 and Research at FDA.⁸

769

X. IMPLEMENTATION

770

771 The effective date for the final rule is March 28, 2011. Many of the requirements in the final
772 rule are not new, but have been clarified to promote submission of meaningful safety
773 information. Because many sponsors already have processes in place for ongoing surveillance of
774 information. Because many sponsors already have processes in place for ongoing surveillance of

775

⁸ The address for the Office of Generic Drugs is available at <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm119100.htm>. The phone and fax numbers (for fatal or life-threatening adverse event reports) are also available at this site.

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777 accumulating safety information, FDA does not anticipate that implementation of these new
778 requirements will require sponsors to make major changes to their current practices or ongoing
779 clinical trials. However, sponsors should review their ongoing clinical trials and if a sponsor has
780 any questions about whether changes are necessary to meet the new requirements (e.g.,
781 aggregating certain serious adverse events, not reporting study endpoints as IND safety reports),
782 the sponsor should contact the FDA review division responsible for the IND.
783