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October 16, 2003

Via fax and UPS

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2003D-0412

International Conference on Harmonisation; Draft Guidance on E2D Postapproval Safety Data Management: Definitions and Standards for Expedited Reporting; Availability. [Federal Register Volume 68, Number 178, Page 53983, September 15, 2003]

Dear Sir/Madam:

Aventis appreciates the opportunity to comment on the above-referenced draft guidance entitled "*Postapproval Safety Data Management: Definitions and Standards for Expedited Reporting*".

The draft guidance was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The draft guidance provides definitions associated with postapproval product safety information and standards for collecting and expedited reporting of safety information to the regulatory authorities. The draft guidance is intended to harmonize internationally the collection and management of postapproval product safety data.

We offer the following comments/clarification for your consideration.

GENERAL COMMENTS:

For clarity and consistency, we suggest including a simplified numbering system for sections and subsections.

Please find the attached document, which includes Aventis' suggestions on the format and content of the guidance document. Aventis' suggestions are incorporated directly into the draft ICH E2D Word document.

2003D-0412

C1

SPECIFIC COMMENTS:

Line 239: 2.5.2. Solicited Sources

“ Solicited reports are those derived from organized data collection systems, which include clinical trials, post-approval named patient use programs, other patient support and disease management programs, surveys of patients or healthcare providers, or information gathering on efficacy or patient compliance. Adverse event reports obtained from any of these should not be considered spontaneous.

For the purposes of safety reporting, solicited reports should be handled as if they were study reports, and therefore should have an appropriate causality assessment...”

Recommendation: Aventis recommends that FDA clarify the following situation:

Receipt of a report emanating from a clinical trial of company C drug X, involving a company C drug Y (which is not a study drug): the investigator considers Y as "concomitant", ie. not suspect, while company C has a strong feeling that the reported reaction is associated with Y. However the investigator is not willing to consider Y as suspect. Therefore the report cannot be recorded as a suspected reaction to drug Y within this company-sponsored trial. Nevertheless, for company C, the report was collected in the setting of a scheme of solicited information; it should be recorded as such (and submitted), ie. assessed as associated = No for the investigator and associated = Yes for the company. Section 3.1.1. imply this way of doing so, but it should be further clarified in section 2.5.2.

Lines 262-264 (under 2.5.3. Licensor-Licensee Interaction): *“...The time frame for expedited regulatory reporting should normally be no longer than 15 calendar days from the first receipt of a case meeting minimum criteria by **any** of the partners, unless otherwise specified by local regulation...”*

Recommendation: Aventis recommends that the reporting clock starts upon receipt of the report by “either” partner instead of “any” of the partners (ie. reporting clock set on the date of their own receipt for each of the partners). This would be consistent with what is stated in section 3.2.2.

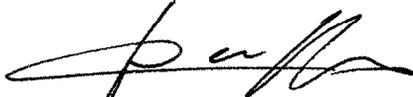
Lines 351-355: *“In the absence of qualifying descriptors, a report referring to a definite number of patients should not be regarded as a case until the minimum four criteria for case reporting are met. For example, “Two patients experienced...” or “ a few patients experienced” should be followed up for patient-identifiable information before regulatory reporting”*

Recommendation: This example describes two different situations: one where the number is definite and the other where the number is vague. When the number is definite, we suggest that the information should be reported in a single report until the minimum criteria are available for each patient, then the individual cases can be reported. When the number is not definite (e.g., a few patients...), then the information is too vague to be

reported as such; the minimum criteria should be available to make this information reportable.

On behalf of Aventis we appreciate the opportunity to comment on the "*Postapproval Safety Data Management: Definitions and Standards for Expedited Reporting*" and are much obliged for your consideration.

Sincerely,

A handwritten signature in black ink, appearing to read "Steve Caffé", written in a cursive style.

Steve Caffé, M.D.
Vice President, Head US Regulatory Affairs

Enclosure

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**POST-APPROVAL SAFETY DATA MANAGEMENT:
DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING**

ICH Harmonised Tripartite Guideline draft

**Recommended for Adoption
at Step 2 of the ICH Process
on July 18, 2003
by the ICH Steering Committee**

ICH E2D ver 3.8

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86 **1. INTRODUCTION**

87 It is important to establish an internationally standardized procedure in order to improve
88 the quality of post-approval safety information and to harmonise the way to gather and
89 report information. ICH E2A provides guidance on pre-approval safety data
90 management. Although many stakeholders have applied these E2A concepts to the
91 post-approval phase, there is a need to provide further guidance on the definitions and
92 standards for post-approval expedited reporting. This guideline is based on the content of
93 ICH E2A with consideration as to how the terms and definitions can be applied in the
94 post-approval phase of the product life cycle.

95

96 **2. DEFINITIONS AND TERMINOLOGY ASSOCIATED WITH**
97 **POST-APPROVAL DRUG SAFETY EXPERIENCE**

98

99 **2.1. Adverse Event Basic Terms**

100 **~~2.1.1. Adverse Event (or Adverse Experience)~~**

101 An adverse event (AE) is any untoward medical occurrence in a patient administered a
102 medicinal product and which does not necessarily have to have a causal relationship with
103 this treatment. An adverse event can therefore be any unfavorable and unintended sign
104 (for example, an abnormal laboratory finding), symptom, or disease temporally
105 associated with the use of a medicinal product, whether or not considered related to this
106 medicinal product.

107

108 **~~2.1.2. Adverse Drug Reaction (ADR)~~**

109 All noxious and unintended responses to a medicinal product related to any dose should
110 be considered adverse drug reactions.

111

112 The phrase “responses to a medicinal product” means that a causal relationship between a
113 medicinal product and an adverse event is at least a possibility (refer to ICH E2A).

114

115 A reaction, in contrast to an event, is characterized by the fact that a causal relationship
116 between the drug and the occurrence is suspected. If an event is spontaneously reported,
117 even if the relationship is unknown or unstated, it meets the definition of an adverse drug
118 reaction.

119

120 **2.32. Seriousness Criteria**

121 The most internationally agreed seriousness criteria appear in ICH guideline E2A. A
122 serious adverse event (~~experience~~) or reaction is any untoward medical occurrence that at
123 any dose:

124 * results in death

125 * is life-threatening

126 (NOTE: The term “life-threatening” in the definition of “serious” refers to an
127 event/a reaction in which the patient was at risk of death at the time of the
128 event/reaction; it does not refer to an event/a reaction which hypothetically might
129 have caused death if it were more severe),

130 * requires inpatient hospitalisation or results in prolongation of existing hospitalisation,

131 * results in persistent or significant disability/incapacity,

132 * is a congenital anomaly/birth defect,

133

134 * is a medically important event or reaction.

135 Medical and scientific judgment should be exercised in deciding whether other
136 situations should be considered as serious such as important medical events that
137 may not be immediately life-threatening or result in death or hospitalisation but
138 may jeopardise the patient or may require intervention to prevent one of the
139 other outcomes listed in the definition above. These should also be considered
140 serious.

141 Examples of such events are intensive treatment in an emergency room or at
142 home for allergic bronchospasm; blood dyscrasias or convulsions that do not
143 result in hospitalisation; or development of drug dependency or drug abuse.

144

145 **2.4.3. ~~Unexpected Adverse Drug Reactions~~ Expectedness**

146 An ADR whose nature, severity, specificity, or outcome is not consistent with the term or
147 description used in the official product information should be considered unexpected.

148

149 An ADR with a fatal outcome should be considered unexpected, unless the official
150 product information specifies a fatal outcome for the ADR. In the absence of special
151 circumstances, once the fatal outcome is itself expected, reports involving fatal outcomes
152 should be handled as for any other serious expected ADR in accord with appropriate
153 regulatory requirements.

154

155 Please note that the term “listedness” is not applicable for expedited reporting but is used
156 to characterize the event according to the Company Core Safety Information (refer to ICH
157 E2C for definitions).

158

159 *Additional considerations:*

160 “Class ADRs” should not automatically be considered to be expected for the subject drug.

161 “Class ADRs” should be considered to be expected only if described as specifically
162 occurring with the product in the official product information, as illustrated in the
163 following examples:

164 ● “As with other drugs of this class, the following undesirable effect occurs with Drug
165 X.”

166 ● Drugs of this class, including Drug X, can cause...”

167

168 If the ADR has not been documented with Drug X, statements such as the following are
169 likely to appear in the official product information:

170 ● “Other drugs of this class are reported to cause...”

171 ● “Drugs of this class are reported to cause..., but no reports have been received to date
172 with Drug X.”

173 In these situations, the ADR should not be considered as expected for Drug X.

174

175 In the absence of sufficient documentation and in the face of uncertainty, a reaction
176 should be regarded as unexpected.

177

178 **2.4. ~~Other Definitions~~**

179 **2.4.1.5. ~~Healthcare Professionals~~**

180 Healthcare professionals are medically-qualified persons such as physicians, dentists,

181 pharmacists, nurses, coroners, or as otherwise specified by local regulations. Preferably,
182 information about the case should be collected from the healthcare professionals who are
183 directly involved in the patient's care. In some regions, the healthcare professional status
184 of the reporter is immaterial to reporting practices.

185

186 **2.4.26. Consumers**

187 For the purpose of these guidelines, Aa consumer is defined as a person who is not a
188 healthcare professional.

189

190 **2.75. Sources of Individual Case Safety Reports *(to be consistent with E2B)***

191 **2.75.1. Unsolicited Sources**

192 **2.75.1.1. Spontaneous Reports**

193 ~~2.5.1.1.1 Spontaneous Reports~~

194 A spontaneous report is an unsolicited communication by healthcare professionals or
195 consumers to a company, regulatory authority or other organization (e.g. WHO, Regional
196 Centers, Poison Control Center) that describes one or more adverse drug reactions in a
197 patient who was given one or more medicinal products and that does not derive from a
198 study or any organized data collection scheme.

199

200 Stimulated reporting may occur in certain situations, such as a notification by a “Dear
201 Healthcare Professional” letter, a publication in the press, or questioning of healthcare
202 professionals by company representatives. These reports should be considered
203 spontaneous.

204

205 ~~2.5.1.1.2. Consumer reports~~

206 Consumer adverse reaction reports should be handled as spontaneous reports irrespective
207 of any subsequent “medical confirmation”, a process required by some authorities for
208 reportability. Even if reports received from consumers do not qualify for regulatory
209 reporting, the cases should be retained. Emphasis should be placed on the quality of the
210 report and not on its source.

211

212 **2.75.1.2. Literature**

213 The Marketing Authorisation Holder (MAH) is expected to regularly screen the
214 worldwide scientific literature, by accessing widely used systematic literature reviews or
215 reference databases. Cases of ADRs from the scientific and medical literature, including
216 relevant published abstracts from meetings and draft manuscripts, might qualify for

217 expedited reporting. A regulatory reporting form with relevant medical information
218 should be provided for each identifiable patient. The publication reference(s) should be
219 given as the report source; additionally a copy of the article might be requested by the
220 local regulatory authority to accompany the report. All company offices are encouraged
221 to be aware of publications in their local journals and to bring them to the attention of the
222 company safety department as appropriate.

223

224 The regulatory reporting time clock starts once it is determined that the case meets
225 minimum criteria for reportability. MAHs should search the literature according to local
226 regulation or at least once a month. If the product source, brand, or trade name is not
227 specified, the MAH should assume that it was its product, although reports should
228 indicate that the specific brand was not identified.

229

230 **2.75.1.3 Internet**

231 MAHs are not expected to screen external websites for ADR information. However, if an
232 MAH becomes aware of an adverse reaction on a website that it does not manage, the
233 MAH should review the adverse reaction and determine whether it should be reported.
234 Unsolicited cases from the Internet should be handled as spontaneous reports.

235 MAHs should regularly screen their websites for potential ADR case reports. MAHs and
236 regulators should consider utilising their websites to facilitate ADR data collection, e.g.
237 by providing ADR forms for direct reporting or by providing appropriate contact details
238 for direct communication. For the determination of reportability the same criteria should
239 be applied as for cases provided via other ways.

240

241 **2.75.1.4 Other Sources**

242 If MAHs become aware of a case report from non-medical sources, it should be handled
243 as a spontaneous report.

244

245 **2.75.2. Solicited Sources**

246 Solicited reports are those derived from organized data collection systems, which include
247 clinical trials, post-approval named patient use programs, other patient support and
248 disease management programs, surveys of patients or healthcare providers, or
249 information gathering on efficacy or patient compliance. Adverse event reports obtained
250 from any of these should not be considered spontaneous.

251

252 For the purposes of safety reporting, solicited reports should be handled as if they were
253 study reports, and therefore should have an appropriate causality assessment. Further
254 guidance on study-related issues such as managing blinded therapy cases can be found in
255 ICH E2A.

256 Aventis recommends that FDA clarify the following situation:

257 - Receipt of a report emanating from a clinical trial of company C drug X, involving a
258 company C drug Y (which is not a study drug): the investigator considers Y as
259 "concomitant", ie. not suspect, while company C has a strong feeling that the reported
260 reaction is associated with Y. However the investigator is not willing to consider Y as
261 suspect. Therefore the report cannot be recorded as a suspected reaction to drug Y within
262 this company-sponsored trial. Nevertheless, for company C, the report was collected in
263 the setting of a scheme of solicited information; it should be recorded as such (and
264 submitted), ie. assessed as associated = No for the investigator and associated = Yes for
265 the company. Section 3.1.1. imply this way of doing so, but it should be further clarified
266 in section 2.5.2.

267

268

269

270 **2.75.3. Licensor-Licensee Interaction**

271 When companies co-develop, co-market, or co-promote products, it is considered very
272 important that explicit contractual agreements specify the processes for exchange of
273 safety information, including timelines and regulatory reporting responsibilities.
274 Whatever the contractual arrangement, the MAH is ultimately responsible for regulatory
275 reporting.

276

277 It is particularly important to ensure that processes are in place to avoid duplicate
278 reporting to the regulatory authority, e.g. assigning responsibility to one company for
279 literature screening. The time frame for expedited regulatory reporting should normally
280 be no longer than 15 calendar days from the first receipt of a case meeting minimum
281 criteria by any of the partners, unless otherwise specified by local regulation. Any
282 subsequent follow-up information sent to the regulators should be submitted by the same
283 MAH that reported the case originally.

284 Aventis recommends that the reporting clock starts upon receipt of the report by "either"
285 partner instead of "any" of the partners (ie. reporting clock set on the date of their own
286 receipt for each of the partners). This would be consistent with what is stated in section
287 3.2.2.

288

289 2.75.4. Regulatory Authority Sources

290 Individual serious unexpected adverse drug reaction reports originating from foreign
291 regulatory authorities are always subject to expedited reporting. Re-submission of
292 serious ADR cases without new information to the originating regulatory authority is not
293 usually required, unless otherwise specified by local regulation.

294

295 3. STANDARDS FOR EXPEDITED REPORTING**296 3.1. What Should Be Reported?****297 3.1.1. Minimum Criteria for Reporting**

298 Minimum required data elements for an ADR case are: an identifiable reporter, an
299 identifiable patient, an adverse reaction, and a suspect product. Lack of any of these four
300 elements means that the case is incomplete; however, MAHs are expected to exercise due
301 diligence to collect the missing data elements. It is recommended that as much
302 information as possible be collected at the time of the initial first report

303 3.1.21. Single-Individual Cases of Serious ADRs

304 Cases of adverse drug reactions from all sources that are both serious and unexpected are
305 subject to expedited reporting. The reporting of serious expected reactions in an
306 expedited manner varies among countries. Non-serious adverse reactions, whether
307 expected or not, would normally not be subject to expedited reporting.

308 For reports from studies and other solicited sources, all cases judged by either the
309 reporting healthcare professional or the MAH as having a possible causal relationship to
310 the medicinal product qualify as ADRs. For the purposes of reporting, spontaneous
311 reports associated with approved drugs imply a possible causality.

312

313 3.1.32. Reporting Guidelines for Other Observations

314 In addition to single case reports, any safety information from other observations that
315 could change the risk-benefit evaluation for the product should be promptly
316 communicated to the regulatory authorities.

317

318 3.1.32.1. Lack of Efficacy

319 Reports of lack of efficacy should not normally be expedited, but should be discussed in
320 the relevant periodic safety update report. However, in certain circumstances reports of
321 lack of efficacy should be treated as expedited cases for reporting purposes. Medicinal
322 products used for the treatment of life-threatening or serious diseases, vaccines, and
323 contraceptives are examples of classes of medicinal products where lack of efficacy

324 should be considered for expedited reporting. Clinical judgment should be used in
325 reporting, with consideration of the approved product labeling/prescribing information.

326

327 **3.1.32.2 Overdose**

328 Reports of overdose with no associated adverse outcome should not be reported as
329 adverse reactions. They should be routinely followed up to ensure that information is as
330 complete as possible with regard to symptoms, treatment, and outcome. The MAH
331 should collect any available information related to its products on overdose, and report
332 cases of these that lead to serious adverse reactions according to expedited reporting
333 criteria.

334

335 **3.2. Reporting Time Frames**

336 In general, expedited reporting of serious and unexpected ADRs refers to 15 calendar
337 days. Time frames for other types of reports vary among countries.

338

339 **3.2.1. Minimum Criteria for Reporting**

340 ~~Minimum required data elements for an ADR case are: an identifiable reporter, an~~
341 ~~identifiable patient, an adverse reaction, and a suspect product. Lack of any of these four~~
342 ~~elements means that the case is incomplete; however, MAHs are expected to exercise due~~
343 ~~diligence to collect the missing data elements. It is recommended that as much~~
344 ~~information as possible be collected at the time of the initial first report.~~

345

346 **3.2.12. Time Clock Start Point**

347 The regulatory reporting time clock (in calendar days) starts on the date when any
348 personnel of the MAH first receive a case report that fulfills minimum criteria as well as
349 the criteria for expedited reporting. In general, this date should be considered as day 0.
350 When additional medically significant information is received for a previously reported
351 case, the regulatory reporting time clock begins again for submission of the follow-up
352 report.

353

354 **3.2.23 Non-serious ADRs**

355 Cases of non-serious ADRs are not normally reportable on an expedited basis. The
356 spontaneous reports of non-serious ADRs should be reported in the periodic safety update
357 report.

358

359 **4. GOOD CASE MANAGEMENT PRACTICE**

360 Accurate, complete and bona fide information is very important for MAHs and regulatory
361 agencies identifying and assessing ADR reports. Both are faced with the task of
362 acquiring sufficient information to help ensure that the reports are authentic, accurate, as
363 complete as possible, and non-duplicative.

364

365 **4.1. Assessing Patient and Reporter Identifiability**

366 Patient and reporter identifiability is necessary to avoid case duplication, detect fraud,
367 and facilitate follow-up of appropriate cases. The term identifiable in this context refers
368 to the verification of the existence of a patient and a reporter.

369

370 One or more of the following automatically qualifies a patient as identifiable: age (or age
371 category, e.g., adolescent, adult, elderly), gender, initials, date of birth, name, or patient
372 identification number. Additionally, in the event of second-hand reports, every effort
373 should be made to verify the report source. All parties supplying case information (or
374 approached for case information) ~~are subject to the notion of identifiability~~ should be
375 identifiable: not only the initial reporter (the initial contact for the case), but also others
376 supplying information.

377

378 In the absence of qualifying descriptors, a report referring to a definite number of patients
379 should not be regarded as a case until the minimum four criteria for case reporting are
380 met. For example, “Two patients experienced...” or “a few patients experienced” should
381 be followed up for patient-identifiable information before regulatory reporting. (Don’t
382 you think that this example describes two different situations: one where the number is
383 definite and the other when the number is vague. When the number is definite the
384 information should be reported in a single report until the minimum criteria are available
385 for each patient, then the individual cases can be reported. When the number is not
386 definite (e.g., a few patients...), then the information is too vague to be reported as such;
387 the minimum criteria should be available to make this information reportable).

388

389 **4.2. The Role of the Narratives**

390 The objective of the narrative is to summarize all relevant clinical and related information,
391 including patient characteristics, therapy details, medical history, clinical course of the
392 event(s), diagnosis, and ADR(s) (including the outcome, laboratory evidence and any
393 other information that supports or refutes an ADR). The narrative should serve as a
394 comprehensive, stand-alone “medical story”. The information should be presented in a
395 logical time sequence; ideally this should be presented in the chronology of the patient’s

396 experience, rather than in the chronology in which the information was received. In
397 follow-up reports, new information should be clearly identified.

398

399 Abbreviations and acronyms should be avoided, with the possible exception of laboratory
400 parameters and units. Key information from supplementary records should be included in
401 the report, and their availability should be mentioned in the narrative and supplied on
402 request. Any autopsy or other post-mortem findings (including a coroner's report) should
403 also be provided when available if allowed by local privacy protection laws. Terms in the
404 narrative should be accurately reflected by appropriate coding.

405

406 **4.3. Single-Clinical Case Evaluation**

407 The purpose of careful medical review is to ensure correct interpretation of medical
408 information. Regardless of the source of an ADR report, the recipient should carefully
409 review the report for the quality and completeness of the medical information. This
410 should include, but is not limited to, consideration of the following:

- 411 • Is a diagnosis possible?
- 412 • Have the relevant diagnostic procedures been performed?
- 413 • Were alternative causes of the reaction(s) considered?
- 414 • What additional information is needed?

415 ADR terms should be used consistently and in accord with recommended standards for
416 diagnosis. The report should include the verbatim term, which quotes the reporter. Staff
417 receiving reports should provide an unbiased and unfiltered report of the information
418 from the reporter. While the report recipient is encouraged to actively query the reporter
419 to elicit the most complete account possible, inferences and imputations should be
420 avoided in report submission. However, clearly identified evaluations by the MAH are
421 considered acceptable and, for some authorities, required.

422 Encouraging good communication on medical information with the reporter will serve to
423 improve the quality of case documentation.

424 When a case is reported by a consumer, his/her description of the event should be retained,
425 although confirmatory or additional information from any relevant healthcare
426 professionals should also be sought and included. Ideally, supplemental information
427 should be obtained from the healthcare professional directly involved in the care of the
428 patient.

429

430 **4.4. Follow-up Information**

431 The information from ADR cases when first received is generally incomplete. Ideally,

432 comprehensive information would be available on all cases, but in practice efforts should
433 be made to seek additional information on selected reports (see Attachment). In any
434 scheme to optimize the value of follow-up, the first consideration should be prioritization
435 of case reports by importance.

436 The priority for follow-up should be as follows: cases which are 1) both serious and
437 unexpected, 2) serious and expected, and 3) non-serious and unexpected. In addition to
438 seriousness and expectedness as criteria, cases “of special interest” also deserve extra
439 attention as a high priority (e.g., ADRs under active surveillance at the request of the
440 regulators), as well as any cases that might lead to a labeling change decision.

441 Follow-up information should be obtained, via a telephone call and/or site visit and/or via
442 a written request. The company should provide specific questions it would like to have
443 answered. Efforts should be tailored toward optimising the chances to obtain the new
444 information. Written confirmation of details given verbally should be obtained whenever
445 possible. In exceptional circumstances, a regulatory authority might be able to assist an
446 MAH to obtain follow-up data if requests for information have been refused by the
447 reporter. ~~The company should provide specific questions it would like to have answered.~~

448
449 In order to facilitate the capture of clinically relevant and complete information, use of a
450 targeted questionnaire/specific form is encouraged, preferably at the time of the initial
451 report. Ideally, healthcare professionals with thorough pharmacovigilance training and
452 therapeutic expertise should be involved in the collection and the direct follow up of
453 reported cases (particularly those of medical significance). For serious ADRs, it is
454 important to continue follow-up and report new information until the outcome has been
455 established or the condition is stabilized. How long to follow-up such cases will require
456 judgment.

457
458 MAHs should collaborate on follow-up if more than one MAH’s drug is suspected as a
459 causal agent in a case.

460
461 It is important that, at the time of the original report, sufficient details about the patient
462 and reporter be collected and retained to enable future investigations, within the
463 constraints imposed by local data privacy legislation.

464

465 **4.4.1. Follow-up Related to Pregnancy Exposure**

466 MAHs are expected to follow up all reports, from healthcare professionals or consumers,
467 of pregnancies where the embryo/foetus could have been exposed to one of its medicinal

468 products. When an active substance, or one of its metabolites, has a long half-life, this
469 should be taken into account when considering whether a foetus could have been exposed
470 (i.e. medicinal products taken before the gestational period need to be considered). If a
471 pregnancy results in an abnormal outcome that the reporter considers might be due to the
472 drug, this should be treated as an expedited report if the minimum criteria for expedited
473 reporting are met.

474

475 **4.5. How to Report**

476 The CIOMS I (Council of International Organisations for Medical Sciences) form has
477 been a widely accepted standard for expedited adverse event reporting. However, no
478 matter what the form or format used, it is important that certain basic information/data
479 elements, when available, be included with any expedited report, whether in a tabular or
480 narrative presentation. It is recommended that the Medical Dictionary for Regulatory
481 Activities (MedDRA) be used for coding medical information. The standards for
482 electronic submission of Individual Case Safety Reports (ICSR), according to ICH
483 E2B/M2, should be implemented.

484 The listing in the Attachment addresses those data elements regarded as desirable; if all
485 are not available at the time of expedited reporting, efforts should be made to obtain them.

486

487 **References Sources**

- 488 1. Current Challenges in Pharmacovigilance: Pragmatic Approaches (Report of CIOMS
489 Working Group V), Geneva 2001
- 490 2. Rules Governing Medicinal Products in the European Union, Volume 9,
491 PHARMACOVIGILANCE: Medicinal Products for Human Use
492 <http://pharmacos.eudra.org/F2/eudralex/vol-9/home.htm>
- 493 3. Guidance for Industry: Postmarketing Safety Reporting for Human Drug and
494 Biological Products Including Vaccines, Food and Drug Administration, March 2001
495 (draft) <http://www.fda.gov/cder/guidance/4153dft.pdf>
- 496 4. Safety Reporting Requirements for Human Drug and Biological Products, Proposed
497 Rule, Food and Drug Administration, March 2003
- 498 5. Notifications #421 on the Enforcement of Revised Pharmaceutical Affairs Law, the
499 Director General, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare,
500 March, 1997

501

Attachment

502

RECOMMENDED KEY DATA ELEMENTS FOR INCLUSION

503

**IN EXPEDITED REPORTS
OF SERIOUS ADVERSE DRUG REACTIONS**

504
505
506
507
508

509 The following list of items has its foundation in several established precedents, including
510 those of CIOMS Ia; the WHO Collaborating Centre for International Drug Monitoring,
511 Uppsala; and various regulatory authority forms and guidelines. Some items might not be
512 relevant depending on the circumstances. Attempts should be made to obtain follow-up
513 information on as many other listed items as are pertinent to the case.

514

515 **1. Patient Details**

- 516 • Initials
- 517 • Other relevant identifier (patient number, for example)
- 518 • Gender
- 519 • Age, age category (e.g., adolescent, adult, elderly) or date of birth
- 520 • Concomitant conditions
- 521 • Medical history
- 522 • Relevant family history

523

524 **2. Suspected Medicinal Product(s)**

- 525 • Brand name as reported
- 526 • International Non-Proprietary Name (INN)
- 527 • Batch number
- 528 • Indication(s) for which suspect medicinal product was prescribed or tested
- 529 • Dosage form and strength
- 530 • Daily dose (specify units - e.g., mg, ml, mg/kg) and regimen
- 531 • Route of administration
- 532 • Starting date and time
- 533 • Stopping date and time, or duration of treatment

534

535 **3. Other Treatment(s)**

536 The same information as in item 2 should be provided for the following:

- 537 • Concomitant medicinal products
538 (including non-prescription, over-the-counter medicinal products, herbal
539 remedies, dietary supplements, complementary and alternative therapies, etc.) .

- 540 • Relevant medical devices

541

542 **4. Details (all available) of Adverse Drug Reaction(s)**

- 543 • Full description of reaction(s), including body site and severity
- 544 • The criterion (or criteria) for regarding the report as serious
- 545 • Description of the reported signs and symptoms
- 546 • Specific diagnosis for the reaction
- 547 • Onset date (and time) of reaction
- 548 • Stop date (and time) or duration of reaction
- 549 • Dechallenge and rechallenge information
- 550 • Relevant diagnostic test results and laboratory data
- 551 • Setting (e.g., hospital, out-patient clinic, home, nursing home)
- 552 • Outcome (recovery and any sequelae)
- 553 • For a fatal outcome, stated cause of death
- 554 • Any autopsy or other post-mortem findings (including a coroner's report)

555

556

557 **5. Details on Reporter of an ADR**

- 558 • Name
- 559 • Mailing address
- 560 • Electronic mail address
- 561 • Telephone and/or facsimile number
- 562 • Reporter type (consumer, healthcare professional, etc.)
- 563 • Profession (specialty)

564

565 **6. Administrative and MAH Details**

- 566 • Source of report (spontaneous, epidemiological study, patient survey, literature,
567 etc.)
- 568 • Date the event report was first received by manufacturer/company
- 569 • Country in which the event occurred
- 570 • Type (initial or follow-up) and sequence (first, second, etc.) of case information
571 reported to authorities
- 572 • Name and address of MAH
- 573 • Name, address, electronic mail address, telephone number, and facsimile number
574 of contact person of MAH
- 575 • Identifying regulatory code or number for marketing authorisation dossier

- 576 • Company/manufacturer's identification number for the case (this number must be
577 the same for the initial and follow-up reports on the same case).