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ICH E2D(R1) Guideline on post-approval safety data: definitions and standards for management and reporting of individual case safety reports

Step 2b

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*For more information please refer to Public consultation explanatory note: [Proposed E2B\(R3\) updates to align with ICH E2D\(R1\) guideline](#).

¹ Please note that the document reference number of the original Guideline is EMA/CPMP/ICH/3945/2003.





INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL
REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE
POST-APPROVAL SAFETY DATA:
DEFINITIONS AND STANDARDS FOR
MANAGEMENT AND REPORTING OF
INDIVIDUAL CASE SAFETY REPORTS

E2D(R1)

Draft version

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E2D(R1)
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POST-APPROVAL SAFETY DATA: DEFINITIONS AND STANDARDS FOR MANAGEMENT AND REPORTING OF INDIVIDUAL CASE SAFETY REPORTS

E2D(R1)

ICH Consensus Guideline

Table of Contents

1. INTRODUCTION	3
2. DEFINITIONS AND TERMINOLOGY	3
2.1 Basic Terms	3
2.1.1 Adverse Event (AE)	3
2.1.2 Adverse Drug Reaction (ADR)	3
2.1.3 Serious AE/ADR	4
2.1.4 Unexpected AE/ADR	5
2.1.5 Other Observations	5
2.1.6 Reporting Terminology	5
2.2 Individual Case Safety Report (ICSR) including Minimum Criteria for Reporting	6
2.3 Expedited Report	7
2.4 Primary Source	7
2.5 Healthcare Professional (HCP)	7
2.6 Consumer	7
2.7 Digital Platform	7
2.8 Organised Data Collection System (ODCS)	8
2.9 Patient Support Program (PSP)	8
2.10 Market Research Program (MRP)	9
3. TYPES OF INDIVIDUAL CASE SAFETY REPORTS	9
3.1 Spontaneous Reports	9
3.2 Solicited Reports	10
4. SOURCES OF INDIVIDUAL CASE SAFETY REPORTS	10
4.1 Communications by HCPs and Consumers	10
4.2 Literature	10
4.3 Digital Platforms	14
4.3.1 Digital platforms under the responsibility of the MAH	14

4.3.2	<i>Digital platforms not under the responsibility of the MAH</i>	14
4.4	Patient Support Programs (PSPs)	16
4.5	Market Research Programs (MRPs).....	17
4.6	Regulatory Authority Sources	18
4.7	Other Sources	18
5.	STANDARDS FOR REPORTING	18
5.1	What Should Be Reported?	18
5.1.1	<i>AEs/ADRs</i>	18
5.1.2	<i>Important Safety Findings</i>	19
5.1.3	<i>Other Observations</i>	19
5.1.3.1	Lack of Efficacy	20
5.1.3.2	Overdose, Abuse, Misuse, Medication Error and Occupational Exposure	20
5.1.3.3	Use of Medicinal Products in Pregnancy/Lactation	20
5.1.3.4	Off-label Use	21
5.2	Reporting Timeframes.....	21
6.	GOOD CASE MANAGEMENT PRACTICES	22
6.1	Assessing Patient and Reporter Identifiability	22
6.2	The Role of Narratives	23
6.3	Clinical Case Evaluation	24
6.4	Follow-up Information	25
6.4.1	<i>Other Observations</i>	26
6.5	Contractual Agreements	26
6.6	Duplicate Management	27
6.7	How to Report	28

1 **1. INTRODUCTION**

2 It is important to establish an internationally standardised procedure to ensure the quality of post-
3 approval safety information and to harmonise, where feasible, the way of gathering and reporting
4 information. The ICH E2D guideline provides guidance on definitions and standards for post-
5 approval individual case safety reporting, as well as good case management practices. This
6 guideline was originally based on the content of the ICH E2A guideline (which provides guidance
7 on pre-approval safety data management), with consideration as to how the terms and definitions
8 should be applied in the post-approval phase of the product life cycle. Detailed guidance on the
9 specific structure, format, standards, and data elements for transmitting Individual Case Safety
10 Reports (ICSRs) is provided in the ICH E2B guideline. Guidance on periodic reporting of
11 aggregated safety data is covered in the ICH E2C guideline.

12 This guideline provides recommendations that are harmonised to the extent possible given
13 differences in post-market safety reporting requirements among ICH regions. Where applicable,
14 this guideline notes where local and regional requirements may vary and, as such, marketing
15 authorisation holders (MAHs) should refer to the relevant local or regional regulatory authority's
16 requirements.

17 **2. DEFINITIONS AND TERMINOLOGY**

18 **2.1 Basic Terms**

19 ***2.1.1 Adverse Event (AE)***

20 An adverse event is any untoward medical occurrence in a patient administered a medicinal
21 product and which does not necessarily have to have a causal relationship with the medicinal
22 product. An adverse event can therefore be any unfavourable and unintended sign (for
23 example, an abnormal laboratory finding), symptom, or disease temporally associated with the
24 use of a medicinal product, whether or not considered related to this medicinal product.

25 ***2.1.2 Adverse Drug Reaction (ADR)***

26 Adverse drug reactions, as defined by local and regional requirements, concern noxious and
27 unintended responses to a medicinal product.

28 The phrase “responses to a medicinal product” means that a causal relationship between a
29 medicinal product and an adverse event is at least a reasonable possibility (refer to the ICH
30 E2A guideline). A reaction, in contrast to an event, is characterised by the fact that a causal
31 relationship between the medicinal product and the occurrence is suspected. For regulatory
32 reporting purposes, if an event is spontaneously reported, even if the relationship is unknown
33 or unstated, it meets the definition of an adverse drug reaction (see Section 5.1.1, AEs/ADRs).

34 **2.1.3 Serious AE/ADR**

35 In accordance with the ICH E2A guideline, a serious adverse event or reaction is any untoward
36 medical occurrence that at any dose:

- 37 • results in death;
- 38 • is life-threatening (NOTE: The term “life-threatening” in the definition of “serious” refers
39 to an event/reaction in which the patient was at risk of death at the time of the
40 event/reaction; it does not refer to an event/ reaction which hypothetically might have
41 caused death if it were more severe);
- 42 • requires inpatient hospitalisation or results in prolongation of existing hospitalisation;
- 43 • results in persistent or significant disability/incapacity;
- 44 • is a congenital anomaly/birth defect;
- 45 • is a medically important event or reaction.

46 Medical and scientific judgment should be exercised in deciding whether other situations
47 should be considered serious such as important medical events that might not be immediately
48 life-threatening or result in death or hospitalisation but might jeopardise the patient or might
49 require intervention to prevent one of the other outcomes listed in the definition above.
50 Examples of such events which may occur following the use of a medicinal product are
51 intensive treatment in an emergency room or at home for allergic bronchospasm, blood
52 dyscrasias or convulsions that do not result in hospitalisation, or development of dependency
53 or substance use disorder.
54

55 **2.1.4 Unexpected AE/ADR**

56 MAHs should treat AEs/ADRs in ICSRs as unexpected if the reported AE/ADR is not included
57 in any section of the local/regional product labelling (e.g., Prescribing Information or
58 Summary of Product Characteristics). In addition, an AE/ADR in an ICSR whose nature,
59 severity, or specificity is not consistent with the term or description used in the local/regional
60 product labelling should be considered unexpected. When an MAH is uncertain whether an
61 AE/ADR in an ICSR for a country or region should be treated as expected or unexpected, the
62 AE/ADR should be treated as unexpected for that local country or region.

63 An ADR included in the local/regional product labelling should be considered unexpected
64 when it is reported with a fatal outcome in an ICSR unless the labelling specifically states that
65 the ADR might be associated with a fatal outcome.

66 Product labelling may include information related to ADRs for the pharmaceutical class to
67 which the medicinal product belongs. This situation is often referred to as “Class ADRs”, and
68 such class ADRs should not automatically be considered “expected” when reported in an ICSR
69 for one of the medicinal products. In this instance, MAHs should refer to the relevant local or
70 regional requirements.

71 NOTE: In contrast to the term “unexpected”, the term “unlisted” is not applicable to individual
72 case safety reporting but is used to characterise the ADR according to the Company Core
73 Safety Information (refer to the ICH E2C guideline for definitions).

74 **2.1.5 Other Observations**

75 “Other observations” refers to certain occurrences associated with use of a medicinal product,
76 including: use in pregnancy/lactation; lack of efficacy; overdose, abuse, misuse, medication
77 error, occupational exposure; and off-label use. In some cases, “other observations” can occur
78 without any associated AEs/ADRs, while in other cases “other observations” can occur with
79 an associated AE/ADR.

80 **2.1.6 Reporting Terminology**

81 Throughout this guideline, the term “reporting”, unless specifically indicated otherwise, refers

82 to MAHs submitting ICSRs to a regulatory authority (i.e., regulatory reporting), as opposed to
83 MAHs receiving or collecting information about a case from a primary source.

84 For the purpose of reporting, requirements in some regions refer only to ADRs, whereas other
85 regions refer to AEs. For simplicity, the term AE(s)/ADR(s) is used throughout this guideline.
86 Refer to local and regional requirements for specifications and requirements on the reporting
87 of AEs or ADRs to each Regulatory Authority. The term “AE(s)/ADR(s)” includes
88 AE(s)/ADR(s) or other observations, unless specifically stated otherwise.

89 **2.2 Individual Case Safety Report (ICSR) including Minimum Criteria for Reporting**

90 An ICSR is a description of an AE/ADR or other observation in an individual patient at a specific
91 point of time.

92 The minimum criteria for reporting ICSRs are:

- 93 • At least one AE/ADR – see Section 5.1.1, or other observation – see Section 5.1.3;
- 94 • At least one suspect or interacting¹ medicinal product;
- 95 • An identifiable patient – see Section 6.1;
- 96 • At least one identifiable reporter – see Section 6.1;

97 A case is the information received by an MAH or regulatory authority about an AE/ADR or other
98 observation. Cases missing any of the above criteria do not qualify for reporting; due diligence
99 should be exercised to collect the missing criteria.

100 While these criteria are the minimum needed for a case to be eligible for reporting, regulatory
101 authorities may have additional criteria, as specified by local and regional requirements, for
102 reporting of a case to be required. See Section 5, Standards for Reporting, for more information
103 on what should be reported.

¹ The term suspect medicinal product includes interacting medicinal products. “Interacting” medicinal products are products for which the reporter indicates a suspected interaction with other medicinal products. All interacting medicinal products are considered to be suspect medicinal products (See ICH E2B).

104 An ICSR can be a description of at least one AE/ADR, or other observation (see Section 5.1.3,
105 Other Observations), or both.

106 **2.3 Expedited Report**

107 An expedited report is an individual case safety report that meets the requirements for reporting as
108 soon as possible, but no later than 15 calendar days after day zero (see Section 5.2, Reporting
109 Timeframes).

110 **2.4 Primary Source**

111 A primary source(s) is a person who provides facts about a case. Primary sources, often referred
112 to as “reporters”, include healthcare professionals and consumers who provide facts about a case
113 to the MAH or regulatory authority. Primary sources should be distinguished from senders who
114 gather information on a case from primary sources and transmit it (e.g., MAH to regulatory
115 authority). Several sources, such as healthcare professionals and/or consumers, may provide
116 information on the same case. The ‘primary source for regulatory purposes is the person who first
117 provided facts on the case (see ICH E2B). In the case of a literature article, the author(s) is/are a
118 primary source.

119 **2.5 Healthcare Professional (HCP)**

120 Healthcare professional is defined as a primary source who is medically-qualified such as a
121 physician, dentist, pharmacist, nurse, coroner (if medically trained), or as otherwise specified by
122 local or regional requirements.

123 **2.6 Consumer**

124 Consumer is defined as a primary source who is not a healthcare professional. Examples include
125 a patient, patient representative (including a legal representative), caregiver, friend, or relative of
126 a patient.

127 **2.7 Digital Platform**

128 A digital platform is the software and technology used to enable transmission of information
129 between users (see Section 4.3, Digital Platforms).

130 **2.8 Organised Data Collection System (ODCS)**

131 An organised data collection system (ODCS) is an activity that gathers data in a planned manner,
132 thereby enabling review to be performed.

133 Local or regional regulatory authorities may require a protocol for certain types of ODCS (i.e.,
134 clinical trials and non-interventional studies). In this context a protocol means a document that
135 describes the objectives, design, methodology, statistical considerations and organisation of a
136 clinical trial or study.

137 For MAH ODCS activities that are not conducted according to a protocol (e.g., a market research
138 program, a patient support program), the MAH should have documentation that describes the:

- 139 1. Objectives of the ODCS activity;
- 140 2. Source(s) of the data;
- 141 3. Dataset that the MAH will collect or receive and review in order to meet the objectives of the
142 activity detailed under item 1, including the time period that will be represented by the data;
- 143 4. Method the MAH will use to review the dataset to meet the objective of the activity;
- 144 5. Process for collection and management of any AEs/ADRs that may be identified.

145 For the purposes of this Guideline, ODCS excludes the MAHs' standard procedures for the
146 surveillance, receipt, evaluation, and reporting of spontaneous postmarketing AEs/ADRs and other
147 postmarketing AEs/ADRs managed as spontaneous reports (i.e., the MAH's routine
148 pharmacovigilance operations for spontaneous reports), see Section 4.

149 Specific examples of ODCS in the context of this Guideline include clinical trials, non-
150 interventional studies (e.g., pharmacoepidemiologic, drug utilisation studies, registries), patient
151 support programs, and market research programs. Other examples include: an MAH activity using
152 a patient forum on a digital platform to assess patient perceptions of the safety of disease
153 treatments; and a product-specific analysis of consumer positivity or negativity about the product
154 (i.e., a sentiment analysis) conducted by an MAH using posts on social media networking sites.

155 **2.9 Patient Support Program (PSP)**

156 PSPs are ODCSs initiated by an MAH, in which patients enrol for the purpose of supporting their
157 use of the MAH's medicinal product, or the management of their medical condition, and which
158 include a mechanism for two-way communication between the MAH (or third party acting on the
159 MAH's behalf) and patients or healthcare professionals. Examples of PSPs include adherence
160 support, disease management, and certain reimbursement, and educational programs. See Section
161 4.4, Sources of ICSRs, PSPs, for further details.

162 Programs meet the definition of a PSP if 1) they solicit medical information about the patient's
163 use of a medicinal product and/or 2) the design of the program is such that the MAH (or a third
164 party acting on the MAH's behalf) would foreseeably receive medical information about the
165 patient's use of a medicinal product (e.g., when a program involves HCP interaction with a patient
166 to administer medication or provide medical advice).

167 MAH-initiated programs that do not meet the criteria above (e.g., delivery of a product to a
168 patient's home, provision of vouchers or coupons) are not considered to be PSPs, as long as the
169 MAH does not request medical information about the patient's use of a medicinal product. PSPs
170 exclude: clinical trials; non-interventional studies, such as post-authorisation safety studies which
171 have a scientific intent or are testing a hypothesis; all forms of compassionate use; and named
172 patient supply.

173 **2.10 Market Research Program (MRP)**

174 MRPs are ODCSs which are used for planned collections of healthcare professional and/or
175 consumer insights by an MAH, on medicinal products and/or a disease area, for the purpose of
176 marketing and business development.

177 **3. TYPES OF INDIVIDUAL CASE SAFETY REPORTS**

178 **3.1 Spontaneous Reports**

179 A spontaneous report is a direct communication by an HCP or consumer to an MAH, regulatory
180 authority or other organisation (e.g., World Health Organisation Uppsala Monitoring Center,
181 Regional Pharmacovigilance Center) that describes one or more AEs/ADRs in a patient who was
182 exposed to one or more medicinal products and that was not gathered as part of an ODCS.

183 In certain situations, public communication about an AE/ADR (e.g., a “Dear Healthcare
184 Professional” communication, litigation, or publication or reporting in the media) results in
185 stimulated reporting (i.e., increased reporting by primary sources regarding the AE/ADR).
186 Stimulated reports should be considered spontaneous reports.

187 Local or regional requirements may require HCPs to report AEs/ADRs not gathered as part of an
188 ODCS to regulatory authorities; these reports should also be managed as spontaneous reports.

189 **3.2 Solicited Reports**

190 Solicited reports are those derived from ODCSs (see Section 2.8, ODCS). For the purposes of
191 reporting, solicited ICSRs should be classified as “report from study” in ICH E2B format and
192 should have a causality assessment (see Section 5.1.1, AEs/ADRs).

193 **4. SOURCES OF INDIVIDUAL CASE SAFETY REPORTS**

194 **4.1 Communications by HCPs and Consumers**

195 Communications by HCPs and consumers are reports from an HCP or consumer to an MAH,
196 regulatory authority, or other organisation (e.g., World Health Organisation Uppsala Monitoring
197 Center, Regional Pharmacovigilance Center) that describes one or more AEs/ADRs. These reports
198 may be spontaneous or they may have been gathered as part of an ODCS. For the purposes of
199 ICSR reporting, if spontaneous, then the “Type of Report” in ICH E2B format should be classified
200 as “spontaneous report”. If gathered as part of an ODCS (i.e., solicited), then the “Type of Report”
201 in ICH E2B format should be classified as “report from study”.

202 **4.2 Literature**

203 Each MAH is encouraged, and in some regions required, to regularly monitor the worldwide
204 scientific literature for safety information concerning their products by conducting a search and
205 literature review using large reference databases with broad coverage. MAHs should follow local
206 and regional requirements regarding their obligations to perform literature screening and the
207 frequency of such screening.

208 MAHs should assess whether AEs/ADRs from scientific literature, including relevant published

209 abstracts from meetings and draft manuscripts, qualify for reporting. Whether or not AEs/ADRs
210 from literature are required to be reported as ICSRs depends on local and regional requirements.
211 Once a determination is made to submit a literature ICSR, follow the ICH E2B Guideline for
212 instructions on designating the “Type of Report”: if a case in the literature arises from spontaneous
213 observations, “Type of Report” in ICH E2B format should be classified as “spontaneous report”
214 if a case in the literature arises from a study, “Type of Report” in ICH E2B format should be
215 classified as “report from study”. In this context, spontaneous observations are descriptions of
216 AEs/ADRs in a patient or group of patients (i.e., individual case report or case series) which the
217 author(s) identified in their clinical experience. In contrast, literature cases arising from a study
218 are AEs/ADRs identified from publications where the author(s) gathered the cases only as part of
219 an ODCS (for example, an author who plans and conducts a search of a dataset for cases meeting
220 pre-specified criteria). See Section 2.8, ODCS. If it is unclear from the literature report whether
221 or not the case(s) cited are spontaneous observations or whether they arise from a study, then this
222 item should be classified as “other”.

223 When submitting ICSRs from literature, an ICSR with relevant medical information should be
224 provided for each identifiable patient (see Section 6.1, Assessing Patient and Reporter
225 Identifiability). The literature reference should be included in the ICSR², and the first listed author
226 (or the corresponding author, if one is specified) should be given as the primary source;
227 information about co-authors does not need to be documented. Additionally, regulatory authorities
228 may request, and in some regions require, a copy of the article to accompany the ICSR. MAHs are
229 encouraged, and in some regions required, to include in their literature screening scientific journals
230 or other publications available in their local region or language.

231 MAHs may conduct literature searches themselves or use external services (i.e., third parties acting
232 on behalf of the MAH) to conduct literature searches. MAHs and/or the third parties acting on

² See ICH E2B for the standard format to be used for literature citations: citations should be provided in the style specified by the Vancouver Convention, known as “Vancouver style”, which has been developed by the International Committee of Medical Journal Editors. The conventional styles, including styles for special situations, can be found in the following reference: International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med 1997; 336:309-15.

233 their behalf should review the literature search results without undue delay to identify AEs/ADRs.
234 When required, follow-up activities should be initiated in a timely manner to collect missing data
235 on the minimum criteria for reporting and/or to obtain additional medically relevant information
236 (see Sections 2.2, ICSR, and 6.4, Follow-up Information). The regulatory time clock for the
237 reporting of ICSRs from the scientific literature starts (day zero) as soon as the MAH or third party
238 acting on their behalf identifies sufficient information to determine that the criteria for ICSR
239 reporting (i.e., the minimum criteria for reporting (refer to Section 2.2, ICSR, and 5.2, Reporting
240 Timeframes)) are met, and not necessarily on the date of the search. If follow-up is required to
241 determine that the criteria for ICSR reporting are met, then day zero is the date the MAH receives
242 sufficient follow-up information to determine that these criteria are met.

243 In some literature articles, a suspect product is identified by its active substance, and the product
244 source, brand, or trade name is not specified. Unless otherwise specified by regional requirements,
245 the MAH is not required to collect or submit ICSRs from literature if the MAH can determine,
246 based on the country, product name, active substance name, pharmaceutical form, batch number,
247 marketing status, or other characteristics, that the product is not the MAH's product. If unable to
248 make this determination, then the MAH should presume that the product is the MAH's product
249 and therefore should collect and report ICSRs as appropriate. The MAH should indicate in their
250 ICSRs that the specific brand was not identified.

251 Literature cases may differ from information from other sources, particularly concerning causality,
252 as authors may reference many events and many medicinal products, and the author may not
253 necessarily suspect the products to be causally related to the events described in the article; MAHs
254 should consider the relationship between products and events in this context. If an author explicitly
255 states in an article that an event is not associated with a medicinal product, or the event occurred
256 before the patient was exposed to the product, the MAHs should not submit it as an ICSR.

257 If multiple products are mentioned in an article, an ICSR should be submitted by the MAH(s)
258 whose product(s) is/are suspected, by the article's author, to be associated with one or more
259 AEs/ADRs. (Note that more than one MAH may have suspect products, and thus each MAH

260 should submit ICSR(s), for a single article).

261 For regions where translations of a literature article are required to be submitted with the ICSR,
262 translation of the abstract or only pertinent sections of the article should be acceptable if it captures
263 all the relevant information for an ICSR, including at least the four minimum criteria for reporting
264 (see Section 2.2, ICSR), especially for long articles whose subject matter may be largely outside
265 the scope of the case(s) in question. The full translation of a publication should be provided upon
266 request by a regulatory authority. Unless specifically otherwise required, translation into English
267 is the accepted standard.

268 A publication may duplicate or provide follow-up to a report previously received by an MAH or
269 regulatory authority via other means (e.g., spontaneously). Duplicate detection and management
270 should be performed when articles are identified in scientific literature, to establish whether the
271 AE/ADR has previously been reported. The literature reference² should be adequately recorded in
272 the ICSR; this will help recipients of the ICSRs to detect possible duplicate reports when ICSRs
273 of the same case are reported by multiple MAHs (see Section 6.6, Duplicate Management). If the
274 article is referring to information that is in a pre-existing case, then the MAH should add the
275 publication's citation to the pre-existing case, along with additional relevant medical details, if
276 available, and report as a follow-up ICSR as appropriate. For reporting purposes, new information
277 from a literature source should be managed as with any other follow-up report.

278 See Section 4.6, Regulatory Authority Sources, regarding publications containing cases that the
279 authors obtained from a regulatory authority's publicly available National or Regional AE/ADR
280 database.

281 Literature which presents the results from non-interventional studies, meta-analyses, or systematic
282 literature reviews may be excluded from reporting as ICSRs depending on local and regional
283 requirements. For literature where the cases do not qualify for ICSR reporting, but which represent
284 new or significant safety findings, the MAH should consider including the findings in the literature
285 section of their next relevant periodic report, where applicable. MAHs should also follow the
286 advice in Section 5.1.2, Important Safety Findings, about communicating safety findings to

287 regulatory authorities.

288 **4.3 Digital Platforms**

289 A digital platform is the software and technology used to enable transmission of information
290 between users. Digital platforms include but are not limited to social media, web sites, internet
291 forums, chat rooms, and software applications (apps).

292 A general distinction should be made between those digital platforms that are under the
293 responsibility of the MAH, and those that are not under the responsibility of the MAH.

294 ***4.3.1 Digital Platforms Under the Responsibility of the MAH***

295 The MAH is responsible for the content of, and communications made available via digital
296 platforms, that are owned, controlled, or operated by, or on behalf of, the MAH. A donation
297 (financial or other) by an MAH to an organisation that owns the digital platform does not
298 necessarily mean that the MAH is responsible for the content of and communications made
299 available via that digital platform, provided that the MAH does not control any content or
300 communications made available via the digital platform.

301 MAHs should regularly screen digital platforms under their responsibility for AEs/ADRs.
302 The frequency of the screening should allow for the MAH to identify and report AEs/ADRs
303 within the required reporting timeline (see Section 5.2, Reporting Timeframes). AEs/ADRs
304 should be managed as spontaneous or solicited depending on the context in which the MAH
305 received the report: for example, AEs/ADRs spontaneously reported by patients on any
306 part of an MAH's product website should be managed as spontaneous reports (see Section
307 3.1 Spontaneous Reports); and AEs/ADRs identified from an ODCS conducted on a digital
308 platform under the MAH's responsibility should be considered solicited reports (see
309 Section 3.2, Solicited Reports) and managed according to the documentation describing
310 the ODCS activity (see Section 2.8, ODCS).

311 ***4.3.2 Digital Platforms Not Under the Responsibility of the MAH***

312 MAHs are not expected to screen or review digital platforms not under their responsibility

313 for AE(s)/ADR(s).

314 However, if an MAH screens or accesses data from a digital platform not under its
315 responsibility, and the MAH's activity is conducted in a planned manner consistent with
316 an organised data collection, the MAH should consider the activity to be an ODCS (see
317 Section 2.8, ODCS).

318 If accessing data on a digital platform in the context of an ODCS, the MAH should have
319 documentation in place as detailed in Section 2.8, ODCS. The source of the data described
320 in the ODCS documentation should specify the digital platform(s) being accessed. The
321 timeframe that the MAH will conduct the activity (including review of the dataset) should
322 also be specified in the documentation.

323 When accessing data from a digital platform not under its responsibility in the context of
324 an ODCS, an MAH is not expected to search for AEs/ADRs beyond conducting its planned
325 review of the dataset collected for the activity as detailed in its documentation. If the MAH
326 identifies AEs/ADRs during the course of the review, the AEs/ADRs should be recorded,
327 managed, assessed for causality and reported in accordance with the requirements
328 applicable for solicited reports (see Section 5.1.1, AEs/ADRs), or as otherwise required by
329 local or regional requirements.

330 The regulatory time clock for reporting starts (day zero) as soon as the MAH (or third party
331 acting on their behalf), when reviewing the accessed data, identifies an AE/ADR and has
332 sufficient information to determine that the criteria for reporting (i.e., the minimum criteria
333 as defined in Section 2.2, ICSR) are met; day zero is not necessarily the date the digital
334 platform data was accessed. If follow-up is conducted, then day zero is the date of receipt
335 of follow-up information sufficient to determine that criteria for ICSR reporting are met.
336 See Section 5.2, Reporting Timeframes, for additional guidance on the time clock for
337 reporting.

338 If an AE/ADR collected from a digital platform in the context of an ODCS meets reporting

339 requirements to a regulatory authority, the “Study Type” data element in ICH E2B should
340 be used to reflect the origin of the report as “Digital Platform”. This designation enables
341 these ICSRs to be distinguished from ICSRs originating from studies and other ODCS.
342 Note: if the AE/ADR was collected in the context of a PSP or MRP, then the “Study Type”
343 data element in ICH E2B should be used to reflect the origin of the report as PSP or MRP,
344 as appropriate, instead of digital platform (see Sections 4.4, PSP, and 4.5, MRP).

345 If an MAH becomes aware of AEs/ADRs on a digital platform not under the MAH’s
346 responsibility, and the MAH received the information outside of the context of an ODCS
347 (e.g., an MAH employee is viewing a website to identify possible answers/solutions to a
348 business question and sees an AE/ADR mentioned), the MAH is expected to review the
349 safety information and collect AEs/ADRs; although these cases are not direct
350 communications to the MAH, they should be managed as spontaneous reports unless local
351 or regional requirements indicate otherwise (see Section 5, Standards for Reporting, for
352 information on standards and timeline for reporting).

353
354 Note: see Section 4.6, Regulatory Authority Sources, regarding cases from regulatory authorities’
355 National or Regional AE/ADR databases available to MAHs via the regulatory authorities’ digital
356 platforms.

357 **4.4 Patient Support Programs (PSPs)**

358 MAHs should review all information received in a PSP for AEs/ADRs. AEs/ADRs that the MAH
359 becomes aware of in the context of a PSP should be managed as solicited reports which includes
360 an appropriate causality assessment (see Section 5.1.1, AEs/ADRs), or as otherwise required by
361 local or regional requirements.

362 For the setup and conduct of PSPs, MAHs should have documentation in place as detailed in
363 Section 2.8, ODCS.

364 PSPs vary in their nature and design. A single PSP may include a combination of activities such

365 as nurse support, chatrooms, and delivery services. Each of the individual activities in the
366 combined program may or may not meet the criteria of a PSP (see Section 2.9, PSP) on its own.
367 For example, a stand-alone service delivering product to a patient’s home would not meet the
368 criteria for a PSP (see Section 2.9, PSP). However, if a program includes delivery service
369 combined with another activity that does meet criteria of a PSP (such as a nurse helping to
370 administer a drug), then the combined program is considered a PSP. If any one or more of the
371 individual activities in the combined program do meet the PSP criteria, then AEs/ADRs received
372 from any part of the program should be managed as coming from a PSP (i.e., as solicited reports).

373 If an AE/ADR from a PSP meets reporting requirements, the “Study Type” data element in ICH
374 E2B should be used to reflect the origin of the report as “PSP”. This enables ICSRs from PSPs to
375 be distinguished from those originating from studies and other ODCS. MAHs may conduct a PSP
376 using a digital platform; in this situation the ICH E2B data element value for “PSP” should be
377 selected.

378 AEs/ADRs arising from MAH activities that only allow one-way interactions (e.g., delivery
379 services, provision of vouchers or coupons) which are not part of an ODCS should be managed as
380 spontaneous reports. Such standalone activities, which are not part of a combined multi-activity
381 PSP, do not meet criteria for a PSP (i.e., do not have a mechanism for two-way interactions). When
382 MAHs use third-party service providers to conduct part of or all of a PSP, the MAH should have
383 contractual arrangements in place to ensure that those third-party service providers report
384 AEs/ADRs to the MAH.

385 **4.5 Market Research Programs (MRPs)**

386 MAHs should review all information received in an MRP for AEs/ADRs. Any AEs/ADRs that the
387 MAH becomes aware of in the context of an MRP should be managed as solicited reports, which
388 includes an appropriate causality assessment (see Section 5.1.1, AEs/ADRs), or as otherwise
389 required by local or regional requirements.

390 For the setup and conduct of MRPs, MAHs should have documentation in place as detailed in
391 Section 2.8, ODCS.

392 If an AE/ADR meets reporting requirements, the “Study Type” data element in ICH E2B should
393 be used to reflect the origin of the report as “MRP”. This enables ICSRs from MRPs to be
394 distinguished from those originating from studies and other ODCS. MAHs may conduct an MRP
395 using a digital platform; in this situation the ICH E2B data element value for “MRP” should be
396 selected.

397 **4.6 Regulatory Authority Sources**

398 Cases originating from a regulatory authority are subject to reporting to other regulatory authorities
399 (according to local and regional requirements) by each MAH.

400 Cases from available National or Regional AE/ADR databases owned or operated by a regulator
401 may be obtained by the MAH (either directly or via literature articles). MAHs should cross-
402 reference to the source reports by including the regulator’s case ID number, if available to the
403 MAH, in the appropriate ICH E2B data element.

404 Re-submission of ICSRs to the originating regulatory authority is not required unless otherwise
405 specified by local or regional requirements, or unless the MAH has obtained or received new
406 information about the case from a primary source.

407 **4.7 Other Sources**

408 If an MAH becomes aware of an AE/ADR from non-medical sources, e.g., the lay press or other
409 media, although not a direct communication to the MAH, it should be managed as a spontaneous
410 report unless local or regional requirements indicate otherwise. Reports received by the MAH as
411 a result of litigation should also be managed as spontaneous reports.

412 **5. STANDARDS FOR REPORTING**

413 **5.1 What Should Be Reported?**

414 **5.1.1 AEs/ADRs**

415 Cases of AEs/ADRs that are both serious and unexpected are subject to expedited reporting.
416 The reporting of serious expected AEs/ADRs in an expedited manner varies according to local
417 or regional requirements. Non-serious AEs/ADRs, whether expected or not, would normally

418 not be subject to *expedited* reporting but may be reportable as ICSRs per local or regional
419 requirements and timelines.

420 For purposes of reporting, spontaneous reports imply a suspected causal relationship (see
421 Section 2.1.2, ADR).

422 For purposes of reporting, solicited reports are classified as “report from study” in ICH E2B
423 and should have a causality assessment; solicited reports should only be submitted if a causal
424 relationship between a medicinal product and an adverse event is at least a reasonable
425 possibility, as assessed by either the reporter or the MAH.

426 Cases that contain only an outcome (e.g., death/hospitalisation) may be subject to reporting
427 per local or regional requirements.

428 ***5.1.2 Important Safety Findings***

429 Safety findings which do not qualify for ICSR reporting and which may lead to changes in
430 the known risk-benefit balance of a medicinal product and/or impact on public health should
431 be communicated as soon as possible to the regulatory authorities in accordance with local or
432 regional requirements. Examples include any significant unanticipated safety findings from
433 an in vitro, animal, epidemiological, or clinical study that suggest a significant human risk,
434 such as evidence of mutagenicity, teratogenicity, carcinogenicity, or immunogenicity or
435 increased mortality.

436 ***5.1.3 Other Observations***

437 It is recognized that an MAH may become aware of certain observations as detailed below
438 related to the use of a product that may or may not be associated with an AE/ADR. These
439 cases should be recorded by the MAH and followed up to obtain information needed for
440 evaluation of the case.

441 Such observations in the absence of an AE/ADR should only be reported as an ICSR if
442 required by local or regional regulations, guidelines, or other regulatory authority conditions
443 and should be discussed in the periodic report according to the ICH E2C guidelines where

444 applicable.

445 **5.1.3.1 Lack of Efficacy**

446 Reports of lack of efficacy occurring independently (i.e., with no associated AE/ADR) should
447 only be reported as ICSRs if required by local or regional regulations, guidelines, or other
448 regulatory authority conditions. Note that in some countries lack of efficacy may be
449 considered an AE/ADR itself, depending on local or regional requirements. Products used in
450 critical conditions or for the treatment of life-threatening diseases, vaccines, and
451 contraceptives are examples of classes of medicinal products where lack of efficacy with no
452 AE/ADR may be subject to ICSR reporting according to local or regional requirements.
453 MAHs should apply judgement when determining if a case report represents a lack of efficacy
454 with consideration of the local product labelling. Reports associated with AEs/ADRs are
455 subject to ICSR reporting requirements.

456 **5.1.3.2 Overdose, Abuse, Misuse, Medication Error and Occupational Exposure**

457 Reports associated with overdose, abuse, misuse, medication error, or occupational exposure,
458 with no associated AE/ADR should only be reported as ICSRs if required by local or regional
459 regulations, guidelines, or other regulatory authority conditions. MAHs should apply
460 judgement when determining if a case represents overdose, abuse, misuse, medication error
461 or occupational exposure with consideration of the local product labelling and indication.
462 Reports associated with AEs/ADRs *are* subject to ICSR reporting requirements.

463 **5.1.3.3 Use of Medicinal Products in Pregnancy/Lactation**

464 Reports of exposure through a parent, such as the use of medicinal products in pregnancy or
465 breastfeeding, with no associated AE/ADR in either the parent or the child should only be
466 reported as ICSRs if required by local or regional regulations, guidelines, or other regulatory
467 authority conditions. AEs/ADRs, such as abnormal outcome following parental exposure,
468 including congenital anomalies, potential epigenetic responses, developmental disorders in
469 the foetus or child, foetal death/spontaneous abortion, or AEs/ADRs in the mother or new-
470 born, are subject to ICSR reporting requirements.

471 **5.1.3.4 Off-label Use**

472 Reports of intentional use of a product not in accordance with the terms of the marketing
473 authorisation with no associated AE/ADR should only be reported as ICSRs if required by local
474 or regional regulations, guidelines, or other regulatory authority conditions. MAH should apply
475 judgement when determining if a case report represents off-label use with consideration of the
476 local product labelling. Reports associated with AEs/ADRs are subject to ICSR reporting
477 requirements.

478 **5.2 Reporting Timeframes**

479 In general, ICSRs that fulfil local or regional criteria for expedited reporting (see Section 5.1, What
480 Should Be Reported?) should be submitted as soon as possible, but not later than 15 calendar days
481 after day zero (see below). Timeframes for reporting AEs/ADRs that are reportable as ICSRs, but
482 which do not meet local criteria for expedited reporting, including non-serious AEs/ADRs, may
483 vary according to local or regional requirements and may be subject to non-expedited (greater than
484 15 calendar days) timelines.

485 The regulatory reporting time clock is considered to start on the date when any personnel of the
486 MAH (including third parties, such as service providers and contractual partners, acting on behalf
487 of the MAH) obtains sufficient information to determine that a case report fulfils the minimum
488 criteria for reporting (see Section 2.2, ICSR). This date should be considered day zero unless
489 otherwise specified by local or regional requirements. Refer to Sections 4.2 and 4.3 for specific
490 information regarding day zero for case reports from literature and digital platforms.

491 When additional medically relevant information is received for a previously reported case, the
492 reporting time clock is considered to begin again for submission of the follow-up report, as such
493 day zero for follow-up information is the date the MAH receives the additional information. In
494 addition, a case initially classified as a non-expedited report, would qualify for expedited reporting
495 upon receipt of follow-up information that indicates the case should be re-classified (e.g., from
496 non-serious to serious), and day zero is the date of receipt of the follow-up information.

497 When submitting an amendment to a previously submitted report (i.e., a correction based on MAH

498 internal quality review) with no receipt of additional information, a new clock start date (day zero)
499 should not be assigned.

500 **6. GOOD CASE MANAGEMENT PRACTICES**

501 Accurate, complete, and authentic information is important for MAHs and regulatory agencies
502 identifying and assessing AE/ADR reports. Both are faced with the task of acquiring sufficient
503 information to help ensure that the reports are authentic, accurate, as complete as possible, and
504 non-duplicative.

505 MAHs should follow local and regional requirements for the protection of personal data privacy
506 including patients, reporters, HCPs, and others, when transmitting or re-transmitting information
507 in ICSRs.

508 The ICSR should include the verbatim terms as used by the reporter, or an accurate translation.
509 Any MAH personnel receiving information about a case should provide an unbiased and unfiltered
510 report of the information from the reporter. While the recipient of the information is encouraged
511 to actively query the reporter to elicit the most complete account possible, inferences and
512 imputations should be avoided in report submission. However, clearly identified evaluations by
513 the MAH are considered appropriate and are required by some regulatory authorities, and they
514 should be recorded in the relevant ICH E2B data elements.

515 When information is received from a consumer, their description of the event should be retained.
516 The MAH should request and include follow-up information from the consumer or relevant HCPs
517 as needed, seeking consent where necessary.

518 **6.1 Assessing Patient and Reporter Identifiability**

519 Patient and reporter identifiability is important to avoid case duplication, ensure authenticity, and
520 facilitate follow-up of appropriate cases. The term identifiable in this context refers to the
521 verification of the existence of a patient and a reporter (i.e., a primary source; see Section 2.4,
522 Primary Source). Second-hand reports (i.e., situations where an individual notifies the MAH of an
523 AE/ADR but does not have first-hand knowledge about the event), are considered incomplete and,

524 where permissible and feasible, attempts should be made to verify the existence of an identifiable
525 patient and reporter.

526 One or more of the following should automatically qualify a patient as identifiable: age (or age
527 category, e.g., adolescent, adult, elderly), gestational age, gender, initials, date of birth, name, or
528 patient identification number.

529 Examples of characteristics that qualify a reporter as identifiable include but are not limited to:
530 name, initials, or address (e.g., reporter’s organisation, department, street, city, state or province,
531 postcode, country, email, phone number), qualification (e.g., healthcare professional, lawyer,
532 consumer or other non-healthcare professional). For cases where the reporter wishes to remain
533 anonymous, the ICSR should still be reported, as long as the existence of an individual as the
534 reporter is known.

535 In the absence of qualifying descriptors, a report referring to a definite number of patients should
536 not be regarded as a case until the four minimum criteria for reporting are met. For example,
537 “Twenty patients experienced...” or “a few patients experienced” should be followed up for
538 patient-identifiable information before creating an ICSR. To qualify for ICSR reporting it should
539 be possible to associate an AE/ADR or AEs/ADRs with a specific identifiable patient.

540 In relation to cases from digital platforms, the identifiability of the reporter/patient refers to the
541 existence of a real person (i.e., where permissible and feasible, attempts can be made to verify that
542 the patient and the reporter exist). The presence of a digital platform username or identifier (i.e.,
543 “handle”) in the absence of qualifying identifiers is insufficient to confirm that there is a real
544 patient and/or reporter. In addition, MAHs should only consider the person providing the
545 information to qualify as a reporter if the person experienced the event or has first-hand
546 information about it. Where follow-up is feasible, MAHs should attempt to obtain evidence of the
547 existence of a real patient and reporter (e.g., via requesting at least one identifiable characteristic
548 such as gender, age, or age category).

549 **6.2 The Role of Narratives**

550 The objective of the narrative is to summarise all relevant clinical and related information,
551 including patient characteristics, therapy details, medical history, concurrent conditions, clinical
552 course of the event(s), AE(s)/ADR(s) including the outcome, diagnosis, laboratory evidence
553 (including normal ranges), and any other information that supports or refutes an AE/ADR. The
554 narrative should serve as a comprehensive, stand-alone “medical story”. The information should
555 be presented in a logical time sequence; ideally this should be presented in the chronology of the
556 patient’s experience, rather than in the chronology in which the information was received. In
557 follow-up reports, new information should be clearly identified.

558 Abbreviations and acronyms should be avoided, with the possible exception of laboratory
559 parameters and units. Key information from supplementary records should be included in the
560 report, and its availability should be mentioned in the narrative and appropriate ICH E2B data
561 element and supplied on request. Any relevant autopsy or pathologic findings should also be
562 summarised in the narrative and related documents should be provided according to local or
563 regional requirements and where permitted by local data privacy laws.

564 Terms (e.g., AEs/ADRs, indication, and medical conditions) in the narrative should be accurately
565 reflected in appropriate ICH E2B data elements.

566 **6.3 Clinical Case Evaluation**

567 The purpose of careful medical review is to ensure correct interpretation of medical information.
568 If possible, information about the case should be collected from the HCPs who are directly
569 involved in the patient’s care. Regardless of the source of an AE/ADR report, the initial recipient
570 should carefully review the report for the accuracy and completeness of the medical information.
571 The review should include, but is not limited to, the following considerations:

- 572 • Are the AE(s)/ADR(s) serious (according to the criteria in Section 2.1.3, Serious
573 AE/ADR)?
- 574 • Is a diagnosis possible from the AE(s)/ADR(s) and is it supported by evidence?
- 575 • Have the relevant diagnostic procedures been performed?

- 576 • Were alternative causes and/or confounding factors for the AE(s)/ADR(s) considered?
- 577 • Is there information regarding a temporal association between the medicinal product and
- 578 the AE(s)/ADR(s), and information on the outcome?
- 579 • What additional information is needed?

580 **6.4 Follow-up Information**

581 Initial AE/ADR reports may not have sufficient information for clinical case evaluation, and
582 efforts should be made to seek additional information on reports, including AE(s)/ADR(s) that
583 were reported second-hand (i.e., cases where the reporter is aware of an AE/ADR, but does not
584 have first-hand knowledge of relevant information about the event).

585 To optimise the value of follow-up, the first consideration should be prioritisation of case reports
586 by importance. Highest priority for follow-up are cases which are both serious and unexpected.
587 At a slightly lower priority are serious, expected and non-serious, unexpected cases. However,
588 in addition to seriousness and expectedness as criteria, cases “of special interest” (e.g.,
589 AEs/ADRs under enhanced monitoring at the request of regulatory authorities) also deserve extra
590 attention.

591 All requests/attempts for follow-up information should be documented. The MAH should provide
592 specific questions it would like to have answered. Follow-up methods should be tailored towards
593 optimising the collection of missing information.

594 To facilitate the capture of clinically relevant and complete information, use of a targeted
595 questionnaire/specific form is encouraged, preferably at the time of the initial report. Individuals
596 with the appropriate level of pharmacovigilance training and therapeutic expertise should be
597 involved in the follow-up of received cases. For serious AEs/ADRs, it is important to continue
598 follow-up and report new information until the outcome has been established or the patient’s
599 condition is stabilised.

600 It is important that at the time of the original report, sufficient details about the patient and reporter
601 be collected and retained to enable follow-up, within the constraints imposed by local data privacy

602 laws. In relation to cases from digital platform not under the responsibility of the MAH, MAHs
603 should exercise caution prior to conducting follow-up of any message marked as private, as this
604 may constitute a breach of consent depending on local and regional privacy regulations.

605 **6.4.1 Other Observations**

606 As per Section 5.1.3, Other Observations, reports of other observations (without an AE),
607 should also be followed up to obtain complete information, and to ascertain if an AE/ADR has
608 occurred.

609 **6.4.1.1 Overdose, Abuse, Misuse, Medication Error and Occupational Exposure**

610 Reports should be followed up to ensure that the information is as complete as possible with
611 regard to suspected drug(s) and the context of occurrence.

612 **6.4.1.2 Use of Medicinal Products in Pregnancy/Lactation**

613 MAHs are expected to follow up all pregnancy reports from HCPs or consumers where the
614 embryo/foetus could have been exposed (through maternal or paternal exposure) to one of its
615 medicinal products. When an active substance, or one of its metabolites, has a long half-life,
616 this should be taken into account when considering whether a foetus could have been exposed
617 (e.g., if medicinal products taken before the gestational period commenced should be
618 considered). MAHs should collect information on the outcome of the pregnancy, health of the
619 new-born, and, where appropriate (for example, per a regulatory authority condition),
620 development of the child. Consideration should be given as to whether the product is
621 specifically indicated for use during pregnancy.

622 **6.5 Contractual Agreements**

623 The marketing of many medicines takes place through contractual agreements between two or
624 more companies, which may market one or more products with the same active substance name in
625 the same or different countries/regions. Pharmacovigilance arrangements vary considerably with
626 respect to inter-company information exchange and regulatory responsibilities.

627 It is important that agreements specify the management and reporting of ICSRs (i.e., processes for

628 exchange of safety information, including timelines and regulatory reporting responsibilities) in
629 accordance with local and regional requirements. Processes should be in place to identify
630 responsibilities, as applicable, and avoid duplicate reporting to regulatory authorities (e.g., clearly
631 assigning responsibility for literature monitoring and ICSR reporting (including from regulatory
632 authority sources)).

633 Whatever the nature of the arrangement, the MAH is ultimately responsible for reporting within
634 the required timelines; therefore the contractual partners should minimise the data exchange period
635 to enable compliance with MAH responsibilities (see Section 5.2, Reporting Timeframes).

636 **6.6 Duplicate Management**

637 Detection and handling of duplicate reports is an important element of good case management.
638 Regulatory Authorities and MAHs should consider and manage duplicates when reviewing
639 pharmacovigilance data, as duplicates negatively impact signal detection.

640 Examples of common causes of duplicate reports are:

- 641 • A consumer and HCP reporting the same AE/ADR or other observation;
- 642 • Multiple HCPs treating the same patient reporting the same AE/ADR or other observation;
- 643 • An AE/ADR or other observation being reported by the original reporter to both the MAH
644 and the regulator;
- 645 • Literature reporting of the same AE/ADR or other observations by multiple MAHs.

646
647 MAHs may utilise duplicate management strategies that are most suitable for their individual
648 situation. ICH E2B supports specific actions to be taken upon detection of duplicates (i.e.,
649 population of ICH E2B data elements with other case identification numbers by which the case is
650 known and submission of nullification/amendment reports as applicable).

651 Duplicate detection relies on good quality data and is generally based on similarities but should
652 take into account that information in ICSRs may differ between reporters.

653 **6.7 How to Report**

654 ICSRs should be transmitted electronically using the ICH E2B format, according to the ICH E2B
655 guidelines. In countries/regions where ICH E2B has yet to be implemented, other formats (e.g.,
656 CIOMS I) may be utilised. ICH E2B uses the Medical Dictionary for Regulatory Activities
657 (MedDRA, ICH M1) for coding medical information.