

1 20 February 2012
2 EMA/827661/2011

3 **Guideline on good pharmacovigilance practices (GVP)**
4 **Module IX – Signal management**

Draft finalised by the Agency in collaboration with Member States and submitted to ERMS FG	19 January 2012
Draft agreed by ERMS FG	24 January 2012
Draft adopted by Executive Director	20 February 2012
Start of public consultation	21 February 2012
End of consultation (deadline for comments)	18 April 2012
Anticipated date for coming into effect after finalisation	July 2012

5 Comments should be provided using this [template](#). The completed comments form should be sent to
6 gvp@ema.europa.eu.

See websites for contact details

European Medicines Agency www.ema.europa.eu
Heads of Medicines Agencies www.hma.eu

The European Medicines Agency is
an agency of the European Union



7	Table of contents	
8	IX.A. Introduction	3
9	IX.B. Structures and processes	4
10	IX.B.1. Data sources for signal management	4
11	IX.B.2. Methodology for signal management	5
12	IX.B.3. The signal management process	5
13	IX.B.3.1. Introduction.....	5
14	IX.B.3.2. Signal detection	6
15	IX.B.3.2.1. Review of individual case safety reports	6
16	IX.B.3.2.2. Statistical analyses in large databases.....	6
17	IX.B.3.2.3. Combination of statistical methods and review of individual case safety reports..	7
18	IX.B.3.3. Signal validation.....	7
19	IX.B.3.4. Signal analysis and prioritisation	8
20	IX.B.3.5. Signal assessment.....	9
21	IX.B.3.6. Recommendation for action by competent authorities	10
22	IX.B.3.7. Exchange of information.....	10
23	IX.B.4. Quality requirements	11
24	IX.B.4.1. Tracking.....	11
25	IX.B.4.2. Quality systems and documentation	11
26	IX.B.4.3. Training	12
27	IX.C. Operation of the EU network	12
28	IX.C.1. Roles and responsibilities	12
29	IX.C.1.1. Roles and responsibilities of the Agency	13
30	IX.C.1.2. Roles and responsibilities of the lead/co-lead Member State	14
31	IX.C.1.3. Roles and responsibilities of the national competent authorities	14
32	IX.C.1.4. Roles and responsibilities of the Pharmacovigilance Risk Assessment Committee ..	15
33	IX.C.1.5. Roles and responsibilities of marketing authorisation holder.....	15
34	IX.C.2. Periodicity of data monitoring in EudraVigilance	16
35	IX.C.3. Signal analysis, prioritisation and assessment by the Pharmacovigilance Risk	
36	Assessment Committee (PRAC)	17
37	IX.C.4. Processes for EU-specific regulatory follow-up	17
38	IX.C.5. Record management in the EU regulatory network	18
39	IX.C.6. Transparency.....	18
40		
41		

42 IX.A. Introduction

43 The Report of CIOMS Working Group VIII on Practical Aspects of Signal Detection in Pharmacovigilance
44 (CIOMS, Geneva 2010) defines a signal as information that arises from one or multiple sources
45 (including observations and experiments), which suggests a new potentially causal association, or a
46 new aspect of a known association, between an intervention and an event or set of related events,
47 either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action [IM
48 Art 23(1)].

49 For the purpose of this Module, only new information related to an adverse reaction, and not to
50 potential beneficial effects, will be considered.

51 In order to suggest a new potentially causal association or a new aspect of a known association, any
52 signal should be validated taking into account other relevant sources of information.

53 The signal management process can be defined as the set of activities performed to determine
54 whether, based on an examination of individual case safety reports (ICSRs), aggregated data from
55 active surveillance systems or studies, literature information or other data sources, there are new risks
56 associated with an active substance or a medicinal product or whether risks have changed. The signal
57 management process shall cover all steps from detecting signals (signal detection), through their
58 validation and confirmation, analysis, prioritisation and assessment to recommending action, as well as
59 the tracking of the steps taken and of any recommendations made [IM Art 25(1)]. Whereas the
60 EudraVigilance database will be a major source of pharmacovigilance information, the signal
61 management process covers signals arising from outside the EudraVigilance database or not directly
62 supported by the EudraVigilance database. For the purpose of the EudraVigilance database, only
63 signals related to an adverse reaction shall be considered [IM Art 23(2)].

64 Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004, Directive 2010/84/EU
65 amending Directive 2001/83/EC and Commission Implementing Regulation on the Performance of
66 Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC
67 include provisions for signal management in the European Union (EU).

68 In this Module, all applicable legal requirements are referenced in the way explained in the GVP
69 Introductory Cover Note and are usually identifiable by the modal verb “shall”. Guidance for the
70 implementation of legal requirements is provided using the modal verb “should”.

71 In the EU, the main stakeholders in the signal management process include patients, healthcare
72 professionals, marketing authorisation holders, regulatory authorities, scientific committees and
73 decision-making bodies (such as competent authorities in the Member States and the European
74 Commission (EC)).

75 The objectives of this Module are:

- 76 • to provide general guidance and requirements on structures and processes involved in signal
77 management (section IX.B.);
- 78 • to describe how these structures and processes are applied in the setting of the EU
79 pharmacovigilance and regulatory network in order to detect whether there are new risks or
80 whether risks have changed (section IX.C.).

81 **IX.B. Structures and processes**

82 ***IX.B.1. Data sources for signal management***

83 The sources for identifying new signals are diverse. They potentially include all scientific information
84 concerning the use of authorised medicinal products including quality, non-clinical, clinical and
85 pharmacovigilance data. Sources for signals include spontaneous reporting systems, active surveillance
86 systems, non-interventional studies, clinical trials and other sources of information.

87 Spontaneous reports of adverse reactions may be notified to pharmacovigilance systems, poison
88 centres, teratology information services, vaccine surveillance programmes, reporting systems
89 established by marketing authorisation holders, and any other structured and organised data collection
90 schemes allowing patients and healthcare professionals to report suspected adverse reactions related
91 to medicinal products. Competent authorities should ensure they are informed in a timely manner of
92 adverse reactions notified to reporting systems managed by other institutions or organisations. Due to
93 the increase in volume of spontaneous reports, the introduction of electronic safety reporting by
94 patients and healthcare professionals, and the mandatory electronic transmission of case reports from
95 marketing authorisation holders to competent authorities, the signal detection is now increasingly
96 based on periodic monitoring of large databases such as the EudraVigilance database. Spontaneous
97 reports contained in EudraVigilance are an essential data source supporting signal management in the
98 EU.

99 Signals from spontaneous reports may be detected from individual case safety reports (ICSRs),
100 included in adverse reaction databases, articles from the scientific literature, periodic safety update
101 reports (PSURs) or other information provided by marketing authorisation holders in the context of
102 regulatory procedures (e.g. variations, renewals, post-authorisation commitments) or the on-going
103 benefit-risk monitoring of medicinal products.

104 Active surveillance aims to stimulate the reporting of adverse reactions by healthcare professionals
105 through specially designed systems such as prescription event monitoring or sentinel networks based
106 on general practitioners or hospitals. They may be used to facilitate reporting of particular adverse
107 reactions or adverse events for specific drugs.

108 Signals may arise from a wide range of different study types, including quality, non-clinical,
109 interventional and non-interventional studies, systematic reviews and meta-analyses. Interventional
110 trials and observational studies may, by design, recruit and follow-up a defined population of subjects
111 who may experience adverse reactions. Aggregated data and statistical analyses may also point to an
112 elevated risk of an adverse event to be further investigated.

113 Results of registries or studies initiated or sponsored by the marketing authorisation holder should be
114 reported to the relevant national competent authority(ies) and/or the Agency according to their
115 obligations (see [Module VI](#)). Published results of relevant studies should be identified by marketing
116 authorisation holders by screening the scientific and medical literature for those journals/active
117 substances not included in the list screened by the Agency. For general guidance on performing
118 literature searches, refer to [Module VI](#).

119 National competent authorities should put in place a system encouraging the early reporting, as soon
120 as possible after the acceptance of the manuscript; of the results of post-authorisation safety studies
121 (PASS) conducted on their territory (see [Module VIII](#)).

122 Other sources of information include the internet, digital media (such as public websites, social
123 networks, blogs) or other systems through which patients and consumers may communicate adverse
124 experiences with medicinal products (see [Module VI](#)). Marketing authorisation holders and competent

125 authorities should try to gain further information related to reactions they become aware of from such
126 sources. If the available information is limited, suspected serious adverse reactions should be
127 confirmed if possible in other data sources such as EudraVigilance.

128 ***IX.B.2. Methodology for signal management***

129 As a general principle, signal detection should follow a structured and recognised methodology, which
130 may vary depending on the type of medicinal product it is intended to cover. Vaccines, which are
131 normally administered on a large scale to healthy individuals for anticipated benefits, may for example
132 require other methodological strategies than other medicinal products.

133 In order to determine the evidence supporting a signal, a structured and recognised methodology shall
134 be applied taking into account the clinical relevance, quantitative strength of the association,
135 consistency of the data, the exposure-response relationship, the biological plausibility, experimental
136 findings, possible analogies and the nature and quality of the data [IM Art 24(1)].

137 Different factors may be taken into account for the prioritisation of signals, namely the fact whether
138 the association or medicinal product is new, factors related to the strength of the association, factors
139 related to the seriousness of the reaction involved and factors related to the documentation of the
140 reports in the EudraVigilance database [IM Art 24(2)].

141 ***IX.B.3. The signal management process***

142 **IX.B.3.1. Introduction**

143 The signal management process covers all steps from detecting signals to recommending action(s). It
144 concerns all stakeholders involved in the safety monitoring of authorised medicinal products.

145 The signal management process includes the following steps:

- 146 • signal detection;
- 147 • signal validation;
- 148 • signal analysis and prioritisation;
- 149 • signal assessment;
- 150 • recommendation for action;
- 151 • exchange of information.

152 Although these steps generally follow a logical sequence, the wide range of sources of information
153 available for signal detection may require some flexibility in the conduct of signal management, for
154 example:

- 155 • when signal detection is primarily based on a review of individual case safety reports (ICSRs), this
156 activity may include validation and preliminary prioritisation of any detected signal;
- 157 • when a signal is detected from aggregated results of a study, it is generally not possible or
158 practical to assess each individual case, and validation may require collection of additional data;
- 159 • recommendation for action (followed by decision in accordance with the applicable legislation) and
160 exchange of information are components to be considered at every step of the process.

161 For the purpose of this guidance, signals originating from the monitoring of data from spontaneous
162 reporting systems are considered as the starting point of the signal management process. The same
163 principles should apply for data originating from other sources.

164 **IX.B.3.2. Signal detection**

165 Detailed guidance on methods of signal detection may be found in the Report of CIOMS Working Group
166 VIII on Practical Aspects of Signal Detection in Pharmacovigilance (CIOMS, Geneva 2010) and in the
167 Guideline on the Use of Statistical Signal Detection Methods in the EudraVigilance Data Analysis
168 System (EMA/106464/2006 rev. 1).

169 Whichever methods are employed for the detection of signals, the same principles should apply,
170 namely:

- 171 • the method used should be appropriate for the data set; for example, the use of complex statistical
172 tools may not be appropriate for small data sets;
- 173 • data from all appropriate sources should be considered;
- 174 • systems should be in place to ensure the quality of the signal detection activity;
- 175 • any outputs from a review of cumulative data should be assessed by an appropriately qualified
176 person in a timely manner;
- 177 • urgent and appropriate action should be taken whenever a potential safety issue with major public
178 health impact is detected;
- 179 • the process should be adequately documented, including the rationale for the method and
180 periodicity of the signal detection activity.

181 Detection of safety signals may be performed based on a review of ICSRs, from statistical analyses in
182 large databases, or from a combination of both.

183 ***IX.B.3.2.1. Review of individual case safety reports***

184 ICSRs may originate from a spontaneous reporting system, adverse event reports from active
185 surveillance or studies, or cases published in the literature. Even a single report of a serious or severe
186 adverse reaction (for example, one case of anaphylactic shock) may be sufficient for raising a signal
187 and taking further action. The information to be reviewed should include the number of cases (after
188 exclusion of duplicates and inadequately documented cases), the patient's demographics (e.g. age and
189 sex), the suspected medicinal product (e.g. dose administered) and adverse reaction (e.g. signs and
190 symptoms), the temporal association, the clinical outcome in relation to drug continuation or
191 discontinuation, the presence of potential alternative causes for the adverse event, the reporter's
192 evaluation of causality and the plausibility of a biological and pharmacological relationship. See Module
193 VI for guidance on ICSRs validation.

194 ***IX.B.3.2.2. Statistical analyses in large databases***

195 Signal detection is now increasingly based on a periodic monitoring of large databases of spontaneous
196 reports of adverse drug reactions. This has resulted from a number of factors, including an increase in
197 volume of spontaneous reports, the introduction of electronic safety reporting by patients and
198 healthcare professionals and the mandatory electronic transmission of case reports from marketing
199 authorisation holders to competent authorities. Such databases allow generation of statistical reports
200 presenting information on adverse reactions received over a defined time period for defined active
201 substances or medicinal products. Various statistical methods have been developed to automatically

202 identify signals of disproportionate reporting, i.e. higher reporting than expected of an suspected
203 adverse reaction for an active substance/medicinal product of interest compared to all other active
204 substances/medicinal products in the database, (expressed, for example, as a lower bound of the
205 proportionate reporting ratio ≥ 1). Given the limitations of these methods, a signal of disproportionate
206 reporting does not necessarily indicate that there is a signal to be further investigated or that a causal
207 association is present.

208 Use of statistical tools may not be appropriate in all situations. The size of the data set, the
209 completeness of the available information and the seriousness of the adverse events should be taken
210 into account when considering the use of statistical methods and the selection of criteria for the
211 identification of signals.

212 The periodicity at which statistical reports should be generated and reviewed may vary according to
213 the active substance/medicinal product, its indication and potential or identified risks. Some active
214 substances/medicinal products may also be subject to an increased frequency of data monitoring (see
215 IX.C.2.). The duration for this increased frequency of monitoring may also vary and be flexible with the
216 accumulation of data associated with the use of concerned active substance/medicinal product.

217 **IX.B.3.2.3. Combination of statistical methods and review of individual case safety reports**

218 Statistical reports may be designed to provide a tool for identifying suspected adverse reactions that
219 meet pre-defined criteria of frequency, severity, clinical importance, novelty or statistical reporting
220 association. Such filtering tools may facilitate the selection of the most important ICSRs to be reviewed
221 as a first step. The thresholds used in this filtering process (for example, at least 3 cases reported)
222 may vary according to the public health impact of reactions and the extent of usage of medicinal
223 products.

224 Where signal detection used an automated screening of a database, the corresponding ICSRs should
225 be individually reviewed (see IX.B.3.2.1.).

226 Irrespective of the statistical method used, the identification of signals should always involve clinical
227 judgment, considering its clinical relevance. The statistical method should be a supporting tool in the
228 whole process of signal detection and validation.

229 **IX.B.3.3. Signal validation**

230 When a signal has been detected, an evaluation of the data supporting the signal should be performed
231 to verify that the available documentation is strong enough to suggest a new potentially causal
232 association, or a new aspect of a known association, and therefore to justify further assessment of the
233 signal [IM Art 25(1)].

234 For this signal validation process, independently from the source of signals, the following should be
235 taken account:

- 236 • Clinical relevance including, for example:
 - 237 – strength of evidence for a causal effect (e.g. number of reports, taking into account exposure,
238 temporal association, plausible mechanism, de/re-challenge, alternative
239 explanation/confounders);
 - 240 – severity of the reaction and its outcome;
 - 241 – novelty of the reaction (e.g. new and serious adverse reactions);
 - 242 – clinical context (e.g. suspicion of a clinical syndrome including other reactions);

- 243 – possible drug-drug interactions and reactions occurring in special populations.
- 244 • Previous awareness:
- 245 – information is already included in the summary of product characteristics (SmPC) or patient
246 leaflet;
- 247 – the signal has already been assessed by a competent authority in the PSUR or risk
248 management plan (RMP), or was discussed at the level of a scientific committee or has been
249 subject to a regulatory procedure.

250 In principle only signals not falling under the above categories should be validated. However, an
251 already known signal may require validation if its apparent frequency of reporting, its temporal
252 persistence, its severity or a change in the previously reported outcome (such as fatality) suggests
253 new information as compared to the data included in the SmPC or previously assessed by the
254 competent authority.

- 255 • Availability of other relevant sources of information providing a richer set of data on the same
256 adverse reaction:
- 257 – literature findings regarding similar cases;
- 258 – experimental findings or biological mechanisms;
- 259 – screening of databases with larger datasets (e.g. EudraVigilance when the signal was sourced
260 initially by data from national or company-specific database).

261 Signal becomes a validated signal if the verification process of all relevant documentation is suggestive
262 of a new potentially causal association, or a new aspect of a known association, and therefore justifies
263 further assessment.

264 The magnitude and clinical significance of a signal may also be examined by descriptive analyses in
265 other available data sources or by analysis of the characteristics of exposed patients and their
266 medicinal product utilisation patterns (such analyses are also sometimes referred to as signal
267 refinement, signal strengthening or signal substantiation).

268 Signals for which the verification process is not suggestive of a new potentially causal association or a
269 new aspect of a known association are not-confirmed but may deserve special attention in subsequent
270 analyses. For example, there might be an inadequate case documentation or a suspicion of a causal
271 association only in a fraction of the ICSRs. In such scenarios, new cases of the same adverse reaction
272 or follow-up reports of previously received cases should be reviewed at adequate time intervals to
273 ensure that all relevant cases are considered.

274 Marketing authorisation holders and competent authorities should establish tracking systems to
275 capture the outcome of the validation of signals including the reasons why signals did not suggest a
276 new potentially causal association, or a new aspect of a known association as well as information that
277 would facilitate further retrieval of the cases and assessment of the signal.

278 **IX.B.3.4. Signal analysis and prioritisation**

279 A key element of the signal management process is to promptly identify signals with important public
280 health impact or that may affect the benefit-risk balance of the medicinal product in treated patients.
281 These signals require urgent attention and need to be evaluated without delay. This prioritisation
282 process should consider:

- 283 • the strength and consistency of the evidence, e.g., biological plausibility, a high number of valid
284 cases reported in a short period of time, high values for the measure of reporting disproportionality
285 and rapid increase of that measure over time and identification of the signal in different settings
286 (e.g. general practice and hospital settings), data sources or countries;
- 287 • the impact on patients, depending on the severity, reversibility, potential for prevention and clinical
288 outcome of the safety issue, and the consequences of treatment discontinuation on the disease and
289 other therapeutic options;
- 290 • the public health impact, depending on the extent of utilisation of the product in the general
291 population and in a vulnerable population (e.g. medicinal products used in pregnant women,
292 children or the elderly) and the patterns of medicinal product utilisation (e.g. off-label use or
293 misuse); the public health impact may include an estimation of the number of patients that may be
294 affected by a serious adverse reaction, and this number could be considered in relation to the size
295 of the general population, the population with the target disease and the treated population;
- 296 • increased frequency or severity of a known adverse effect;
- 297 • novelty of the suspected adverse reaction, e.g. when an unknown suspected adverse reaction
298 occurs shortly after the marketing of a new medicinal product;
- 299 • if the marketing authorisation application for a new active substance is still under evaluation by a
300 national competent authority and a safety signal is reported from a third country where the
301 substance is already authorised, or a severe adverse reaction arising from that third country is
302 detected in EudraVigilance, this signal should also be prioritised.

303 In some circumstances, priority for evaluation can also be given to signals identified for medicinal
304 products or events with potential high media and pharmacovigilance stakeholder interest in order to
305 communicate the result of this evaluation to the public and healthcare professionals as early as
306 possible.

307 The outcome of signal prioritisation should include a recommendation of the time frame for the
308 evaluation of the signal.

309 The outcome of the signal prioritisation process should be entered in the tracking system, with the
310 justification for the level of prioritisation attributed to the signal.

311 **IX.B.3.5. Signal assessment**

312 The objective of signal assessment is to examine the evidence for a causal association between an
313 adverse reaction and a suspected medicinal product, to quantify this association (preferably in absolute
314 terms) and to identify the need for additional data collection or for any regulatory actions. It consists
315 of a thorough pharmacological, medical and epidemiological assessment of all the information available
316 on the signal of interest. This review should include pharmacological, non-clinical and clinical data
317 when available and be as complete as possible regarding the sources of information, including the
318 application dossier, literature articles, spontaneous reports and non-published information from
319 marketing authorisation holders and national competent authorities. Consultation with external experts
320 should also be considered. When information is drawn from a range of data sources, the strengths and
321 limitations of each of these should be considered in order to assess the contribution they can provide
322 to the evaluation of the safety issue. Summarising information from different data sources also
323 requires the choice of an internationally agreed definition of the medical issue. If no such definition
324 exists, an operational definition should be developed.

325 Signals sometimes need to be assessed at the therapeutic or system organ class level or at the level of
326 a standardised MedDRA query and the search for information may need to be extended to other
327 products of the class and to other adverse reactions, such as to other terms linked to a complex
328 disease (e.g. optic neuritis as a possible early sign of multiple sclerosis), to a prior stage of the
329 reaction (e.g. QT prolongation and torsades de pointes) or to clinical complications of the adverse
330 reaction of interest (e.g. dehydration and acute renal failure).

331 Gathering information from various sources may take time. A staged approach for signal assessment
332 should therefore be considered, for example. For a new signal of a severe adverse reaction, temporary
333 measures could be taken if the first stage of the assessment based on information already available
334 concludes that there is a potential risk that needs to be prevented.

335 **IX.B.3.6. Recommendation for action by competent authorities**

336 The range of recommendations that may be taken as a result of the assessment may vary according to
337 the applicable legislation and the conclusion of the signal assessment.

338 Although the recommendation for action normally takes place in a logical sequence after signal
339 assessment based on the totality of the information, the need for action should be considered
340 throughout the signal management process. For example, the first case of an adverse reaction
341 indicating a manufacturing defect may require immediate recall of a product batch. The review of
342 available information at the signal validation or signal prioritisation stages may similarly conclude that
343 the evidence is sufficiently strong to inform healthcare professionals and patients. In such situations, it
344 is still necessary to proceed with a formal assessment of the signal in order to confirm or not the safety
345 issue in order to extend or lift the temporary action.

346 The assessment may request active monitoring of the signal or for additional information to be
347 provided by the marketing authorisation holder in order to confirm that this conclusion is valid for all
348 indications and patient groups. It may also conclude that the issue needs to be reviewed periodically,
349 for example through the PSURs.

350 Actions may include additional investigations or risk minimisation activities if the mechanisms of
351 occurrence of the suspected adverse reaction highlight the possibility of preventing or mitigating the
352 adverse reaction. If the conclusion was based on limited evidence, it may be necessary to conduct a
353 post-authorisation safety study (PASS) to investigate the potential safety issue (see **Module VIII**).

354 Whenever additional activities are requested by a competent authority to the marketing authorisation
355 holder, the request should specify a timeframe by which they should be completed, including progress
356 reports and interim results, proportionate to the severity and public health impact of the issue.
357 Marketing authorisation holders and competent authorities should consider the feasibility of conducting
358 a study within the set timelines taking into account the characteristics of the safety issue of interest,
359 such as its incidence and the need for a prospective study design. Temporary measures to ensure the
360 safe and effective use of the medicinal product or to eliminate the risk should be considered, including
361 the possibility of temporarily suspending the marketing authorisation of the medicinal product.

362 If there is no evidence of a risk for patients, the competent authority may decide that no further
363 assessment or action is required.

364 **IX.B.3.7. Exchange of information**

365 Exchange of information between competent authorities, marketing authorisation holders and other
366 concerned parties may be needed to share information on signals, collect additional data, further
367 evaluate the safety issue and take decisions to protect patients' health. The timing of the

368 communication may vary according to the safety issue, but information on signals should be
369 communicated only if they have been validated.

370 Marketing authorisation holders should communicate any relevant information regarding signals to
371 competent authorities as part of their pharmacovigilance obligations and ongoing monitoring of the
372 benefit-risk of the medicinal products. Validated signals that may have implications for public health
373 and the benefit-risk profile of the product in treated patients should be immediately communicated to
374 the competent authorities, and when appropriate this should include proposals for action.

375 Competent authorities should communicate results of signal assessments to marketing authorisation
376 holders.

377 ***IX.B.4. Quality requirements***

378 **IX.B.4.1. Tracking**

379 All validation, prioritisation, assessment, timelines, decisions, actions, plans, reporting as well as all
380 other key steps need to be recorded and tracked systematically. Tracking systems need to be
381 documented and should include also signals, for which the verification process conducted was not
382 suggestive of a new potentially causal association, or a new aspect of a known association, as they
383 may merit special attention in case of subsequent analysis. All records need to be archived [IM Art
384 25(5), Art 28] (see **Module I**).

385 **IX.B.4.2. Quality systems and documentation**

386 An essential feature of a signal management system is that it is clearly documented to ensure that the
387 system functions properly and effectively, that the roles, responsibilities and required tasks are
388 standardised, that these tasks are conducted by people with appropriate expertise and are clear to all
389 parties involved and that there is provision for appropriate control and, when needed, improvement of
390 the system. Therefore, a system of quality assurance and quality control consistent with the quality
391 system standards should be in place and applied to all signal management processes (see **Module I**).
392 Detailed procedures for this quality system should be devised, documented and implemented. The
393 organisational roles and responsibilities for the activities and maintenance of documentation, quality
394 control and review, and for ensuring corrective and preventive action need to be assigned and
395 recorded. This should include the responsibilities for quality assurance auditing of the signal
396 management system, including auditing of sub-contractors. Data and document confidentiality (per the
397 applicable regulations), security and validity (including integrity when transferred) should be
398 guaranteed.

399 Through the tracking system, all parties should keep an audit trail of their signal management
400 activities and of the relevant queries and their outcomes. Information received, searches, search
401 outputs, assessments and decisions (both positive and negative) regarding potential signals should be
402 archived. This should include the outcome of the signal validations.

403 Audit trail should also allow traceability of how validated signals have been investigated.

404 Documentation by the marketing authorisation holder demonstrating compliance with these provisions
405 may be requested and reviewed before and after authorisation, for purposes such as assessment or
406 inspection.

407 **IX.B.4.3. Training**

408 Staff should be specifically trained in signal management activities in accordance with their roles and
409 responsibilities. This concerns not only staff within the safety departments but also staff who may
410 become aware of potential signals or support signal management, such as staff within regulatory, non-
411 clinical research, medical, pharmacoepidemiology and market research departments. The training
412 should include MedDRA and available signal source databases, as applicable. The training system and
413 location of the training records need to be documented, and curricula vitae and job descriptions need
414 to be archived.

415 **IX.C. Operation of the EU network**

416 ***IX.C.1. Roles and responsibilities***

417 Within the context of the operation of the EU regulatory network, the Agency and national competent
418 authorities shall collaborate to monitor the data available in the EudraVigilance database for medicinal
419 products authorised in the Union used within the terms of the marketing authorisation as well as
420 outside the terms of the marketing authorisation, and for medicinal products authorised in the Union
421 that may induce adverse reactions as a result of an occupational exposure [IM Art 22(1)].

422 Signal management in the EU regulatory network should be a shared responsibility of the Agency,
423 national competent authorities, the Pharmacovigilance Risk Assessment Committee (PRAC) and the
424 marketing authorisation holders. The detection of signals shall be based on a multidisciplinary
425 approach and shall be supported by statistical analysis within EudraVigilance [IM Art 23(3)]. The
426 identification of signals based on statistical analysis should be a matter of clinical judgment and subject
427 to validation as detailed in [IX.B.3.3](#).

428 Regarding medicinal products authorised in accordance with Regulation (EC) No 726/2004, the
429 monitoring of data in EudraVigilance, signal detection and signal validation shall be performed by the
430 Agency [REG Art 28a(1)]. The Agency shall be supported, as appropriate by the rapporteur appointed
431 by the PRAC [IM Art 26(5)]. The Agency should also take the lead for active substances contained in
432 several medicinal products, where at least one marketing authorisation has been granted in
433 accordance with Regulation (EC) No 726/2004.

434 For medicinal products authorised in accordance with Directive 2001/83/EC, the monitoring of data in
435 EudraVigilance, signal detection and signal validation shall be performed by the national competent
436 authorities. For active substances and medicinal products authorised in the EU not monitored by the
437 Agency, a work sharing may be introduced. For medicinal products authorised in accordance with
438 Directive 2001/83/EC in more than one Member State and for active substances contained in several
439 medicinal products where at least one marketing authorisation has been granted in accordance with
440 Directive 2001/83/EC, Member States may agree within the Coordination Group for Mutual Recognition
441 and Decentralised Procedures - Human (CMDh), in collaboration with the PRAC, to appoint a lead
442 Member State for the monitoring of data in the EudraVigilance database and for validation and
443 confirmation of signals. The lead Member State may be supported by a co-leader. Any such
444 appointment shall be reviewed at least every four years. When appointing a lead Member State and as
445 appropriate a co-leader, the CMDh in collaboration with the PRAC, may take into account whether any
446 Member State is acting as reference Member State, in accordance with Article 28(1) of Directive
447 2001/83/EC, or as lead Member State for the assessment of periodic safety update reports in
448 accordance with Article 107(e) of Directive 2001/83/EC [IM Art 26(1) and 26(2)].

449 All Member States retain however, their responsibility pursuant to Article 107h(1)(c) and (3) of
450 Directive 2001/83/EC [IM Art 26(4)].

451 The national competent authorities and the Agency should validate any signal that has been detected
452 by them in the course of their continuous monitoring of the data in EudraVigilance [IM Art 25(6)].
453 Signal communication to the PRAC should always be preceded by its validation.

454 In this context, roles and responsibilities for signal management in the EU regulatory network are as
455 follows:

456 **IX.C.1.1. Roles and responsibilities of the Agency**

457 The Agency:

- 458 • shall make public a list of active substances/medicinal products and the authority (lead Member
459 State, co-lead Member State or the Agency) responsible for their monitoring in EudraVigilance [IM
460 Art 26(3)];
- 461 • shall take the lead for EudraVigilance data monitoring, signal detection and signal validation for
462 centrally authorised products and for active substances contained in several medicinal products,
463 where at least one marketing authorisation has been granted in accordance with Regulation (EC)
464 No 726/2004;
- 465 • following consultation with the PRAC may publish a list of medical events that have to be taken into
466 account for the detection of a signal [IM Art 23(3)];
- 467 • shall support the monitoring of the data in the EudraVigilance database by providing access to:
 - 468 – data outputs and statistical reports allowing a review of new adverse reactions and of all
469 adverse reactions reported to EudraVigilance in relation with an active substance or a medicinal
470 product;
 - 471 – customised queries supporting the evaluation of individual case safety reports and case series;
 - 472 – customised grouping and stratification of data enabling the identification of patient groups with
473 a higher risk of occurrence of adverse reactions or with a risk of a more severe adverse
474 reaction;
 - 475 – statistical signal detection methods [IM Art 27(1)];
- 476 • should prepare a technical document establishing common triggers for signal detection and
477 describing EudraVigilance data outputs and statistical reports;
- 478 • shall administer a tracking system (see IX.C.5.) for validated signals that require further
479 assessment [IM Art 25(7)];
- 480 • shall enter validated signals in the tracking system and shall transmit signals it has validated to the
481 PRAC with a proposal for analysis and prioritisation [IM Art 25(7)];
- 482 • shall confirm in collaboration with the Member States within 15 days (including, if appropriate, in
483 the EudraVigilance database and taking into account other information available) any validated
484 signal communicated by marketing authorisation holders involving a centrally authorised product
485 or an active substance for which the EudraVigilance data monitoring is performed by the Agency;
486 in this context, where the validity of the signal is not confirmed within 15 days, no further action
487 shall be required [IM Art 25(5)];
- 488 • should confirm (including, if appropriate, in the EudraVigilance database) any other signal
489 communicated by a third party (e.g. regulatory authority from outside the EU), involving a
490 centrally authorised products or an active substance for which the EudraVigilance data monitoring
491 is performed by the Agency;

- 492 • shall forthwith communicate to the concerned marketing authorisation holder(s) the conclusions of
493 the assessment of the signal by the PRAC¹ [IM Art 25(9)];
- 494 • should collaborate to the signal validation performed by a national competent authority that
495 detected a signal involving a centrally authorised products or an active substance for which the
496 EudraVigilance data monitoring is performed by the Agency;
- 497 • shall keep an audit trail of its signal detection activities [IM Art 28].

498 **IX.C.1.2. Roles and responsibilities of the lead/co-lead Member State**

499 The lead/co-lead Member State:

- 500 • shall take the lead for EudraVigilance data monitoring, signal detection and signal validation for
501 active substances/medicinal products, for which it has been appointed the lead or co-lead Member
502 State;
- 503 • shall enter validated signals in the tracking system and shall transmit validated signals for active
504 substances/medicinal products for which it has been appointed the lead Member State, to the PRAC
505 with a proposal for prioritisation [IM Art 25(7)];
- 506 • shall confirm within 15 days (including, as appropriate, in the EudraVigilance database and taking
507 into account other information available) any validated signal communicated by marketing
508 authorisation holder involving an active substance/medicinal product for which it has been
509 appointed the lead or a co-lead Member State; in this context, where the validity of the signal is
510 not confirmed within 15 days, no further action shall be required [IM Art 25(5)];
- 511 • should validate (including, if appropriate, in the EudraVigilance database) any other signal
512 communicated by a third party (e.g. regulatory authority from outside the EU) involving an active
513 substance/medicinal product for which it has been appointed the lead or a co-lead Member State;
- 514 • should collaborate to the signal validation performed by a national competent authority that
515 detected a signal involving an active substances/medicinal products for which it has been
516 appointed the lead or a co-lead Member State;
- 517 • shall keep an audit trail of their signal detection activities [IM Art 28].

518 **IX.C.1.3. Roles and responsibilities of the national competent authorities**

519 The national competent authorities:

- 520 • shall specifically monitor data originated in their territory [IM Art 25(3)], including data arising
521 from sources mentioned in IX.B.1.;
- 522 • if a lead/co-lead Member State or the Agency has been appointed for the monitoring of an active
523 substance/medicinal product, the national competent authorities:
- 524 – should validate in collaboration with the lead/co-lead Member State or the Agency any signal
525 detected from all available sources;
- 526 – should enter validated signals in the tracking system and shall transmit validated signals to the
527 PRAC with a proposal for analysis and prioritisation;

¹ until pharmacovigilance contact points for all European marketing authorisation holders are established following implementation of Art 57 of Regulation (EU) No 1235/2010, the communication should be via a dedicated mailbox

- 528 • if no lead/co-lead Member State or the Agency has been appointed for the monitoring of an active
529 substance/medicinal product authorised in their territory, the national competent authorities:
- 530 – shall monitor the data of the EudraVigilance database for these medicinal products to
531 determine whether there are new risks or whether risks have changed;
- 532 – shall confirm within 15 days (including, as appropriate, in the EudraVigilance database and
533 taking into account other information available) any validated signal communicated by
534 marketing authorisation holder involving an active substance/medicinal product marketed in
535 their territory; in this context, where the validity of the signal is not confirmed within 15 days,
536 no further action shall be required [IM Art 25(5)];
- 537 – shall validate any signal detected from EudraVigilance for these medicinal products;
- 538 – shall enter validated signals in the tracking system and shall transmit validated signals to the
539 PRAC with a proposal for prioritisation;
- 540 • shall keep an audit trail of their signal detection activities [IM Art 28].

541 **IX.C.1.4. Roles and responsibilities of the Pharmacovigilance Risk**
542 **Assessment Committee**

543 The Pharmacovigilance Risk Assessment Committee (PRAC):

- 544 • shall prioritise validated signals for further assessment [IM Art 25(7)] [REG Art 28a];
- 545 • should nominate a rapporteur for the assessment of the validated signals with a time frame for the
546 assessment;
- 547 • shall transmit to the Committee for Medicinal Products for Human Use (CHMP) or to the CMDh, as
548 appropriate, any recommendations following the signal assessment;
- 549 • shall perform a regular review of the signal management methodology to be used and publish
550 recommendations, as appropriate [IM Art 24(3)];
- 551 • should review the list of medical events that have to be taken into account for the detection of a
552 signal before their publication by the Agency [IM Art 23(3)].

553 **IX.C.1.5. Roles and responsibilities of marketing authorisation holder**

554 The marketing authorisation holder:

- 555 • shall monitor all available data and information for signals;
- 556 • shall monitor the data in EudraVigilance to the extent of their accessibility [IM Art 22(2)]. See also
557 EudraVigilance access rights for stakeholder group III in the [EudraVigilance Access Policy for](#)
558 [Medicines for Human Use](#)². The frequency of the monitoring should be at least once monthly and
559 shall be proportionate to the identified risk, the potential risk and the need for additional
560 information [IM Art 25(2)];
- 561 • shall monitor all emerging data and perform worldwide signal detection activities [IM Art 22(2)];
562 signal detection should include the validation of signals taking into account elements of information
563 presented in [IX.B.3.3](#);

² EudraVigilance access policy for medicines for human use published on 8 July 2011
<http://eudravigilance.ema.europa.eu/human/docs/EV%20Access%20Policy%20for%20human%20use%20doc.pdf>

- 564 • shall validate any detected signal and shall forthwith inform the responsible competent authority in
565 line with the list as published by the Agency (referred to in lines 463-464) [IM Art 25(4)];
- 566 • should notify as an Emergency Safety Issue (see **Module VI**) any safety issue arising from its signal
567 detection activity;
- 568 • should collaborate with the PRAC for the assessment of the signals by providing additional
569 information upon request;
- 570 • should keep an audit trail of their signal detection activities.

571 ***IX.C.2. Periodicity of data monitoring in EudraVigilance***

572 National competent authorities and the Agency shall ensure the monitoring of data in the
573 EudraVigilance database with a frequency proportionate to the identified risk, the potential risk and the
574 need for additional information [IM Art 25(2)]. The monitoring should be based on a periodic review of
575 statistical outputs (e.g. reaction monitoring reports) to determine whether there are new or changed
576 risks in the safety profile of an active substance/medicinal product. The statistical outputs contain
577 adverse drug reactions in a structured hierarchy (e.g. MedDRA hierarchy) per active
578 substance(s)/medicinal product(s) and allow filters and thresholds to be applied on several fields as
579 appropriate.

580 The baseline frequency for reviewing the statistical outputs from EudraVigilance should be once-
581 monthly. An increase to the baseline frequency of data monitoring in EudraVigilance may be decided
582 by the lead Member State, the national competent authority or the Agency if justified by the identified
583 or potential risks of the product, or by the need for additional information. The PRAC should be
584 informed of the decision and its justification.

585 For products subject to additional monitoring (see **Module X**), the frequency for reviewing the
586 statistical outputs should be every 2 weeks until the end of additional monitoring, or its extension. A 2-
587 week frequency for reviewing the statistical outputs may also be applied for any other product taking
588 into account the following criteria:

- 589 • any product considered to have an identified or potential risk that could impact significantly on the
590 risk-benefit balance or have implications for public health. This may include risks associated with
591 an important misuse, abuse or off-label use. The product may be moved back to baseline
592 frequency of monitoring if risks are not confirmed;
- 593 • any product for which the safety information is limited due to low patient exposure during drug
594 development, including products authorised under conditional approval or under exceptional
595 circumstances, or for which there are vulnerable or poorly studied patient populations or important
596 missing information (e.g. children, pregnant women, renally impaired patients) while post-
597 marketing exposure is likely to be significant;
- 598 • any product that contains active substances already authorised in the Union but is indicated for use
599 in a new patient population or with a new route of administration;
- 600 • any product for which the existing marketing authorisation has been significantly varied (e.g.
601 changes to indication, posology, pharmaceutical form or route of administration), thereby
602 modifying the exposed patient population or the safety profile.

603 A signal arising from the EudraVigilance data monitoring activities does not necessarily imply that the
604 product has to be more frequently monitored.

605 More frequent monitoring than every 2 weeks should be based on a proposal from the lead Member
606 State, national competent authority or the Agency. It should be targeted to a safety concern of interest
607 especially during public health emergencies (e.g. pandemics) and may be applied in the context of
608 customised queries or near real time alerts³ conducted in the EudraVigilance Data Analysis System
609 (EVDAS).

610 ***IX.C.3. Signal analysis, prioritisation and assessment by the*** 611 ***Pharmacovigilance Risk Assessment Committee (PRAC)***

612 Any signal that has been detected and validated by the Agency or a national competent authority
613 should be sent to the PRAC for consideration. The PRAC should agree on a prioritisation based on the
614 individual patient and public health impact of the potential change to the risk-benefit-balance.

615 Depending on the level of the prioritisation, an analysis of the need for further assessment or for
616 immediate action should be made, taking into account the time frame proposed by the Agency or the
617 national competent authority that detected the signal.

618 When it considers that immediate action is needed, the PRAC should make a recommendation on the
619 action(s) required and appropriate procedure(s) should be initiated by the Agency and/or national
620 competent authorities in conjunction with the marketing authorisation holder.

621 When it considers that further assessment is needed, the PRAC should nominate a rapporteur for the
622 evaluation and should define a timeframe for this evaluation taking into account the prioritisation of
623 the signal. The rapporteur for the signal assessment should transmit to the PRAC a report stating
624 whether there may be new risks, whether risks have changed or whether there is a change in the risk-
625 benefit balance in relation with the concerned active substance or medicinal product. The report should
626 also include proposal for actions, if appropriate.

627 Following the circulation of the rapporteur's assessment report, the PRAC should make a
628 recommendation, stating the reasons on which it is based. The recommendation should include an
629 implementation timetable for completion of any actions requested of the marketing authorisation
630 holder. The Agency should inform the marketing authorisation holder(s) of the recommendation made
631 by the PRAC in the event of new risks or risks that have changed or when changes to the risk-benefit
632 balance have been detected.

633 ***IX.C.4. Processes for EU-specific regulatory follow-up***

634 Where the PRAC considers that follow-up action may be necessary, the signal shall be assessed and
635 any subsequent action concerning the marketing authorisation shall be agreed within a timescale
636 commensurate with the extent and seriousness of the matter in accordance with Article 107h(2) of
637 Directive 2001/83/EC and Article 28a(2) of Regulation (EC) No 726/2004 [IM Art 25(8)] The
638 recommendation of the PRAC should be sent to the CHMP in the case of an active substance that is
639 centrally-authorized and to the CMDh in the case of an active substance that is nationally authorised
640 including authorisation through the mutual recognition or decentralised procedure. The PRAC might
641 consider any or a combination of the following conclusions:

- 642 • no further evaluation or action is required at EU level;
- 643 • the marketing authorisation holder should conduct further evaluation of data and provide the
644 results of that evaluation according to a defined timeline;
- 645 • the marketing authorisation holder should submit an *ad-hoc* PSUR;

³ EVDAS automated data processing and network transmission takes usually 1 day

- 646 • the marketing authorisation holder should sponsor a post-authorisation study according to an
647 agreed protocol and submit the final results of that study;
- 648 • the marketing authorisation holder should be requested to submit a RMP or an updated RMP;
- 649 • the marketing authorisation holder should take any measures that are required for ensuring the
650 safe and effective use of the medicinal product;
- 651 • the marketing authorisation should be varied, suspended, revoked or not renewed;
- 652 • the Member States or the Commission should initiate as appropriate, the procedure provided for in
653 Article 31 or in Section 4, Urgent Union Procedure or in Article 31 where appropriate, of Directive
654 2001/83/EC;
- 655 • urgent safety restrictions in accordance with Article 22 of Regulation (EC) No 1234/2008;
- 656 • need for an inspection in order to verify that the marketing authorisation holder for the medicinal
657 product satisfies the pharmacovigilance requirements laid down in Titles IX and XI of Directive
658 2001/83/EC;
- 659 • inclusion in the list of medicinal products that are subject to additional monitoring where falling
660 within the scope defined in Article 23 of Regulation (EC) No 726/2004.

661 Where recommended by the PRAC and agreed by the CHMP or the CMDh as appropriate, a procedure
662 should be initiated with a timetable in which the marketing authorisation should be varied, suspended,
663 revoked or not renewed where applicable.

664 ***IX.C.5. Record management in the EU regulatory network***

665 The Agency and the national competent authorities shall keep an audit trail of all their signal
666 management activities relating to EudraVigilance and of the relevant queries and their outcomes.

667 Any signal that has been detected and validated by the Agency or a national competent authority in
668 line with the processes described in IX.B. and that requires further analysis by the PRAC should be
669 entered into the web-based European Pharmacovigilance Issues Tracking Tool (EPITT) administered by
670 the Agency. All subsequent evaluations, timelines, decisions, actions, plans, reporting and all other key
671 steps need to be recorded and tracked systematically in EPITT by the Agency or the national
672 competent authority in line with the guidance document Exchange of Information Relating to Signals
673 through EPITT by the EU Regulatory Network (EMA/383041/2011).

674 ***IX.C.6. Transparency***

675 Article 26(1) of Regulation (EC) No 726/2004 states that the Agency shall, in collaboration with the
676 Member States and the Commission, set up and maintain a European medicines web-portal for the
677 dissemination of information on medicinal products authorised in the EU. Article 102(d) of Directive
678 2001/83/EC states the Member States shall ensure that the public is given important information on
679 pharmacovigilance concerns relating to the use of a medicinal product in a timely manner through
680 publication on the web-portal and through other means of publicly available information as necessary;
681 Article 26(j) of Regulation (EC) No 726/2004 states that by means of that portal, the Agency shall
682 make public at least the following: conclusions of assessments, recommendations, opinions, approvals
683 and decisions taken by the Committees referred to in points (a) and (aa) of Article 56(1) of this
684 Regulation and by the CMDh, the national competent authorities and the EC in the framework of the
685 procedures of Articles 28, 28a and 28b of this Regulation and of sections 2 and 3 of Chapter 3 and
686 Chapter 4 of Title IX of Directive 2001/83/EC.

687 In this context, several key documents will be made publicly available through the Agency's web-
688 portal. These documents will include the conclusions of the PRAC assessments and recommendations
689 following the evaluation of signals.