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3 **Guideline on good pharmacovigilance practices (GVP)**
4 **Product- or Population-Specific Considerations I: Vaccines for prophylaxis**
5 **against infectious diseases**

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6

This track-change version identifies the majority of changes introduced to the public consultation version of this document as the Agency's response to the comments received from the public consultation. This track-change version is published for transparency purposes and must not be taken or quoted as the final version.

* For this reason, the timetable above, and in particular the date of coming into effect, apply only the clean version published as final.

For the final version of this module and any future updates, please see the GVP webpage of the Agency's website.



7	Table of Contents	
8	P.I.A.1. Terminology	4
9	P.I.A.2. Aspects specific to prophylactic vaccines	5
10	P.I.A.3. Changes of the benefit-risk balance	6
11	P.I.A.3.1. Efficacy and effectiveness	6
12	P.I.A.3.2. Biological variability	6
13	P.I.A.4. Aspects related to vaccination programmes	6
14	P.I.B. Structures and processes.....	7
15	P.I.B.1. Risk management system.....	7
16	P.I.B.1.1. RMP part I “Product overview”.....	7
17	P.I.B.1.2. RMP part II “Safety specification”	7
18	P.I.B.1.2.1. RMP module SI “Epidemiology of the indications and target population”.....	7
19	P.I.B.1.2.2. RMP module SII “Non-clinical part of the safety specification”.....	8
20	P.I.B.1.2.3. RMP module SIV “Populations not studied in clinical trials”	8
21	P.I.B.1.2.4. RMP module SVI “Additional EU requirements for the safety specification”	9
22	P.I.B.1.2.5. RMP module SVII “Identified and potential risks”	10
23	P.I.B.1.2.6. RMP module SVIII “Summary of the safety concerns”	10
24	P.I.B.1.3. RMP part III “Pharmacovigilance plan”	11
25	P.I.B.1.3.1. RMP section “Routine pharmacovigilance activities”	11
26	P.I.B.1.3.2. RMP section “Additional pharmacovigilance activities”	13
27	P.I.B.1.4. RMP part IV “Plans for post-authorisation efficacy studies”	15
28	P.I.B.1.5. RMP part V “Risk minimisation measures”	15
29	P.I.B.2. Periodic safety update report	15
30	P.I.B.2.1. Integrated benefit-risk analysis	16
31	P.I.B.3. Post-authorisation safety studies.....	16
32	P.I.B.4. Signal management.....	17
33	P.I.B.4.1. Standard case definitions.....	17
34	P.I.B.4.2. Single report of a serious adverse event.....	18
35	P.I.B.4.3. Signal detection in mass vaccination programmes	18
36	P.I.B.4.4. Disproportionality analyses	18
37	P.I.B.4.5. Observed to expected analyses	19
38	P.I.B.4.6. Signal evaluation.....	21
39	P.I.B.5. Batch recall and quarantine	22
40	P.I.B.5.1. Data requirements.....	22
41	P.I.B.5.2. Action based on clinical events in the absence of a known quality issue.....	23
42	P.I.B.5.3. Action due to identified quality deviations	24
43	P.I.B.6. Safety communication.....	24
44	P.I.C. Operation of the EU network.....	25
45	P.I.C.1. Roles and responsibilities	25
46	P.I.C.1.1. Vaccinated persons and parents/carers	25
47	P.I.C.1.2. Healthcare professionals.....	26
48	P.I.C.1.3. Marketing authorisation holders.....	26
49	P.I.C.1.4. Competent authorities in Member States	26
50	P.I.C.1.5. European Medicines Agency	27

51	P.I.C.2. Reporting of reactions and emerging safety issues.....	27
52	P.I.C.2.1.Reporting of vaccination failures.....	28
53	P.I.C.3. Risk Management System	28
54	P.I.C.4. Signal management.....	28
55	P.I.C.5. Safety communication about vaccines in the EU.....	29
56	P.I.C.6. Transparency of pharmacovigilance for vaccines in the EU.....	29
57	P.I.C.7. Vaccines intended for markets outside the EU.....	29

58 P.I.A. Introduction

59 Vaccination is one of the most effective and widely used public health interventions, whose benefits for
60 individuals and the community have been abundantly demonstrated. Prominent examples are the
61 global eradication of smallpox and the elimination of poliomyelitis in most countries. As with any other
62 pharmaceutical product, however, no vaccine is without risks. Robust systems and procedures must be
63 in place to continuously monitor quality, safety and efficacy ~~of the product~~. ~~In this context,~~ vaccine
64 pharmacovigilance has been defined by the CIOMS/WHO Working Group on Vaccine Pharmacovigilance
65 as the science and activities related to the detection, assessment, understanding and communication
66 of adverse events following immunisation and other vaccine- or immunisation-related issues, and to
67 the prevention of untoward effects of the vaccine or immunisation.¹

68 The objective of this Module is to strengthen the conduct of pharmacovigilance for vaccines. It should
69 be noted that the overall objectives and processes of pharmacovigilance are ~~no different~~ similar
70 for vaccines and other types of medicinal products and this guidance does not replace the information
71 provided in the other modules of the Good Pharmacovigilance Practices (GVP). This Module focusses on
72 vaccine-specific aspects and unique challenges that should be borne in mind when designing and
73 implementing pharmacovigilance activities for vaccines.

74 This Module is relevant to vaccines used for pre- and post-exposure prophylaxis of infectious diseases
75 and does not cover therapeutic vaccines (e.g. viral-vector based gene therapy, tumour vaccines, anti-
76 idiotypic vaccines such as monoclonal antibodies used as immunogens). This guidance is addressed
77 primarily to marketing authorisation holders and competent authorities but may also be useful to other
78 stakeholders (e.g. sponsors of clinical studies, healthcare professionals, public health authorities).

79 P.I.B. provides guidance specific for vaccines in relation to the main pharmacovigilance processes
80 described in the Modules of the GVP. Where applicable, specific recommendations are provided for
81 situations where vaccines are administered in mass vaccination programmes and where a large
82 number of reports of suspected adverse reactions is expected in a short period of time.

83 P.I.C provides specific guidance related to the operation of the EU network.

84 The legal references for this guidance are Directive 2001/83/EC, as amended by Directive 2010/84/EU
85 (referenced as DIR), Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010
86 (referenced as REG), and the Commission Implementing Regulation (EU) No 520/2012 on the
87 Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive
88 2001/83/EC (referenced as IR).

89 Other relevant guidance include the CHMP Guideline on Clinical Development of Vaccines², guidance on
90 design and specific aspects of clinical trials to be conducted pre and post marketing authorisation, and
91 the CHMP Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-
92 Authorisation Data.³

93 P.I.A.1. Terminology

94 It is acknowledged that the term Adverse Event Following Immunisation (AEFI) is used at international
95 level. The term was defined as any untoward medical occurrence which follows immunisation and

¹ [Council for International Organizations of Medical Sciences \(CIOMS\). Definition and application of terms of vaccine pharmacovigilance \(report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance\). Genève: CIOMS; 2012. Definition and Application of Terms for Vaccine Pharmacovigilance. Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance, CIOMS 2012; available at \[http://whqlibdoc.who.int/publications/2012/9789290360834_eng.pdf\]\(http://whqlibdoc.who.int/publications/2012/9789290360834_eng.pdf\).](#)

² EMEA/CHMP/VWP/164653/2005, available on EMA website <http://www.emea.europa.eu>.

³ EMEA/CHMP/313666/2005, available on EMA website <http://www.emea.europa.eu>.

96 which does not necessarily have a causal relationship with the usage of a vaccine. The adverse event
97 may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease. AEFIs
98 have been further classified [by the CIOMS/WHO Working Group on Vaccine Pharmacovigilance](#) into four
99 categories according to possible causes (apart from a coincidental event): vaccine product-related,
100 vaccine quality defect-related, immunisation error-related and immunisation anxiety-related.⁴ –The
101 term AEFI is not used in this guidance as the term “adverse event” (~~defined in see Annex I~~) already
102 designates any untoward medical occurrence in a patient administered a medicinal product and which
103 does not necessarily have a causal relationship with this medicinal product. In addition, EU regulatory
104 requirements concerning pharmacovigilance activities apply to adverse reactions, this term being
105 defined in the legislation (see [Annex I](#)).

106 The terms immunisation (the process of making a person immune ~~to an infection~~) and vaccination (the
107 administration of a vaccine with the aim to produce immune response) have slightly different meanings
108 and are not used interchangeably in this guidance. The term vaccination is generally used unless
109 ~~otherwise~~-justified [otherwise](#) by the context.

110 ***P.I.A.2. Aspects specific to prophylactic vaccines***

111 When conducting vaccine pharmacovigilance, the following aspects should be considered:

- 112 • vaccines are usually administered to otherwise healthy individuals, often very young or vulnerable;
113 they may be administered to a large fraction of the population and vaccination is mandatory in
114 some countries; there is therefore a high level of safety required for vaccines and tolerance to risk
115 is usually low;
- 116 • assessment of causality between adverse events and vaccines may be difficult: several vaccines
117 are often administered concomitantly, [it is inevitable that, with high vaccine uptake, incident cases
118 of many natural diseases in given population cohorts will occur in temporal association with
119 vaccination](#)~~vaccination may be given in children at the age where some diseases may emerge,~~
120 and considerations of dechallenge and rechallenge are not relevant to many vaccines which are
121 administered only once or have long-term immunological effects;
- 122 • vaccines are complex biological products which may include multiple antigens, live organisms,
123 adjuvants, preservatives and other excipients, and each of these components may have safety
124 implications; variability and ~~small~~ changes in the manufacturing process, new components and new
125 production and administration technologies may impact on safety, and this may require specific
126 pharmacovigilance systems;
- 127 • the benefit-risk balance for vaccines also depends on factors acting at the population level,
128 including the incidence, geographical distribution, seasonal characteristics and risk of transmission
129 of the infectious disease in the target population, the proportion of infected persons with a clinical
130 disease, ~~and~~ the severity of this disease, [vaccine coverage and herd immunity](#);
- 131 • concerns raised by the public may have ~~an~~ [negative](#) impact on the vaccination programme and
132 should be adequately addressed;
- 133 • effective communication about safety of vaccines and vaccination is difficult; ~~given the fact that~~
134 perceptions of harm may persist despite evidence that a serious adverse event is not related to the
135 vaccination, [and communicating about vaccine safety to multiple audiences \(e.g. healthcare
136 providers, patients and parents\) is complex.](#)

⁴ [Council for International Organizations of Medical Sciences \(CIOMS\). Definition and application of terms of vaccine pharmacovigilance \(report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance\). Genève: CIOMS; 2012. Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance, CIOMS 2012.](#)

137 ***P.I.A.3. Changes of the benefit-risk balance***

138 The benefit-risk balance of many vaccines is dynamic and may change over time, or may appear to
139 change over time, and this may impact on pharmacovigilance activities. Factors associated with these
140 changes include their efficacy and effectiveness in vaccination programmes and their biological
141 variability.

142 **P.I.A.3.1. Efficacy and effectiveness**

143 Unlike most medicinal products which are given to treat an illness, prophylactic vaccines offer the
144 potential to significantly reduce, or even eradicate, communicable diseases. This introduces a real
145 dynamic to the balance of risks and benefits, whereby the former may outweigh the latter over time
146 (e.g. live oral polio vaccine and vaccine-associated paralytic polio). This may decrease tolerance to the
147 risks of vaccines.

148 **P.I.A.3.2. Biological variability**

149 Unlike most medicines which are composed of relatively small molecules, vaccines are often highly
150 complex multi-component products manufactured from biological systems that are inherently variable
151 over time and between manufacturers (and sometimes between different production plants of the
152 same manufacturer). As with other biological products, the safety, quality and efficacy of vaccines are
153 as dependent on the product-specific manufacturing process as on the inherent profile of active
154 antigens and excipients.

155 Due to this biological variability, the safety profile of vaccines with well-established safety profiles
156 demonstrated by substantial use over many years may change over time. Such changes may be
157 unpredictable and may arise from slight modifications in the manufacturing process or unintended
158 quality deviations. Such changes can also be batch-specific. Furthermore, introduction of new or more
159 sensitive assays may reveal previously unknown impurities or adventitious agents which may warrant
160 a re-evaluation of quality and clinical safety.

161 This variability underlines the importance of brand-specific, and even batch-specific, pharmacovigilance
162 activities for vaccines, and for traceability and continuous surveillance even for ~~the most~~ 'well-
163 established' vaccines.

164 ***P.I.A.4. Aspects related to vaccination programmes***

165 Most vaccines are 'universal', i.e. they are offered routinely to everyone in a given population cohort
166 via a national public health programme. A typical new vaccine may achieve nearly 90% coverage in a
167 given age group over a relatively short time period. Vaccines may also be offered to population cohorts
168 via a targeted 'campaign' to tackle a specific infectious disease outbreak at a given point in time or
169 under special circumstances, such as in a national emergency, military or pandemic situation.

170 Such vaccination programmes are associated with a variety of challenges for pharmacovigilance. The
171 key ones include:

- 172 • a large number of suspected adverse reaction reports in a short time period may require resources
173 for processing, analysing, presenting and communicating data;
- 174 • it is inevitable that rare or serious incident illnesses will occur in temporal association with
175 vaccination; new suspected adverse reactions must be very rapidly investigated and distinguished
176 from coincidental illnesses;

- 177 • lack of a comparable unvaccinated concurrent cohort requires alternative statistical and
178 epidemiological methods to allow appropriate analysis of safety, e.g. case-only designs (see
179 [Appendix 1 of Module VIII and the ENCePP Guide on Methodological Standards in](#)
180 [Pharmacoepidemiology⁵](#));
- 181 • mass vaccination in a short time period may be associated with very unique business continuity
182 and infrastructure constraints; under such circumstances, specific consideration should be given to
183 adapting pharmacovigilance plans to meet these challenges and ensure that resource is prioritised
184 and necessary technical requirements are met (see [Module I](#) for public health emergency
185 planning);
- 186 • the vaccinated population may include immunocompromised individuals, including those infected
187 with human immunodeficiency virus (HIV), whose clinical status may not be known at the time of
188 vaccination and who may be at a higher risk of risk of occurrence of the infectious disease targeted
189 by the vaccine and of impaired immune response to vaccination, in particular when vaccinated with
190 live vaccines.

191 **P.I.B. Structures and processes**

192 ***P.I.B.1. Risk management system***

193 Most aspects of [Module V on risk management systems](#) are as applicable to vaccines as to other
194 medicinal products. ~~P.1.B.1. This section~~ supplements [that](#) ~~Module V~~ and presents vaccine-specific
195 aspects of the risk management plan ([RMP](#)).

196 **P.I.B.1.1. RMP part I “Product overview”**

197 This section should describe the intended purpose and impact of the vaccine, e.g. whether it is
198 intended to prevent a disease or serious outcomes of the disease. It should provide information
199 relevant to the safety of the vaccine and describe:

- 200 • the type of vaccine, e.g. whether it is a live attenuated viral or bacterial vaccine, an inactivated
201 vaccine, a vaccine based on proteins, polysaccharides or protein-conjugated polysaccharides, a
202 genetically engineered vaccine or a novel concept (e.g. temperature selected mutants);
- 203 • details of combined vaccines, where two or more vaccine antigens are combined in one
204 pharmaceutical preparation in order to prevent multiple diseases or one disease caused by
205 different serotypes;
- 206 • any new technology or novel delivery systems such as viral and bacterial vectors or patches, or
207 alternative route of administration such as nasal administration;
- 208 • any immunogenic adjuvants, stabilisers, preservatives, excipients and residual material from the
209 manufacturing process, including the immunological mode of action of any novel adjuvant.

210 **P.I.B.1.2. RMP part II “Safety specification”**

211 ***P.I.B.1.2.1. RMP module SI “Epidemiology of the indications and target population”***

212 This section should focus on the natural history of the target disease, highlighting any difference
213 between countries as appropriate. It should discuss any relevant examples of the impact of previous

⁵ See http://www.encepp.eu/standards_and_guidances/index.shtml

214 and similar vaccines on the disease. For vaccines already included into a vaccination programme, the
215 impact of the vaccine on the epidemiology of the vaccine-preventable condition should be considered.

216 ***P.I.B.1.2.2. RMP module SII “Non-clinical part of the safety specification”***

217 This section should present findings of pre-clinical testing related to the antigen, the adjuvant,
218 impurities ~~and~~, contaminants and the vaccine as a whole, and to interactions of the vaccine
219 components, as well as any impact these findings have on the clinical testing and post-authorisation
220 surveillance.

221 Cells from human, animal (including insects), bacterial or yeast origin may be used in an early step of
222 the manufacturing process. As a consequence, residual proteins of the host cells may be present in the
223 final product. As these impurities may consist of proteins that have structural homology with human
224 proteins, potential harm caused by these residuals should be discussed, including any need for clinical
225 testing.

226 Preservatives and stabilisers may not be immunologically inert (e.g. polygeline). Removal of a
227 preservative and/or stabiliser from a well-established vaccine, or change of the source of any vaccine
228 component, may have an impact on the safety profile of the vaccine and may require amendment of
229 the RMP to include non-clinical data on the modified vaccines.

230 Vaccine-related quality aspects should be discussed in this section if relevant to safety. Manufacturing
231 of medicines in biological systems, such as fermentation of bacteria, growth of virus in cell culture or
232 expression of proteins by recombinant technology, may introduce variability within certain limits of the
233 composition of the final product. In principle, contamination with unwanted infectious agents and other
234 risks linked to any aberrant material cannot be totally excluded. These potential risks should be
235 considered as they may result in adverse reactions.

236 ***P.I.B.1.2.3. RMP module SIV “Populations not studied in clinical trials”***

237 Sample size and duration of clinical trials should be discussed in terms of power to detect common and
238 uncommon adverse reactions and to address long-term risks. Limitations of the clinical trials should
239 also be presented in terms of the relevance of inclusion and exclusion criteria in relation to the target
240 population for vaccination.

241 Populations to be considered for discussion should include:

242 • Special age groups

243 Immunological responses to vaccines depend on the independent and coordinated function of
244 innate and adaptive immune responses which evolve with age. Differences of the immune
245 response in different age categories may not only translate to different efficacy/effectiveness of
246 vaccines, but also to differences in the safety profile. Adverse reactions may occur solely in
247 certain age categories, e.g. hypotonic-hyporesponsive episodes in young children.
248 Furthermore, the frequency of adverse reactions may change in relation to age. Targeted
249 surveillance of adverse reactions in different age groups may be warranted.

250 • Pregnancy

251 Although most live attenuated vaccines are contraindicated in pregnant women due to the
252 known or suspected risk of transplacental infection of the foetus, inadvertent exposure during
253 pregnancy cannot be totally excluded. Risk to the developing foetus from vaccination of the
254 mother with an inactivated vaccine during pregnancy is considered theoretical but should be
255 discussed, including data collected in the post-authorisation phase if available.

256 • Immunocompromised individuals

257 Immunocompromised individuals, including those infected with human immunodeficiency virus
258 (HIV), may have a higher risk of occurrence of the infectious disease targeted by the vaccine
259 and of ~~an~~-impaired immune response to vaccination, in particular when vaccinated with live
260 vaccines. Therefore, the benefit-risk balance in this patient group may need specific
261 consideration.

262 • [Patients with other relevant underlying conditions or comorbidities \(e.g. contraindications\).](#)

263 **P.I.B.1.2.4. RMP module SVI “Additional EU requirements for the safety specification”**

264 The following aspects should be addressed in this section:

265 • Potential for transmission of infectious agents

266 For live attenuated vaccines, this section should address aspects such as shedding (including
267 shedding from vaccinated individuals to unvaccinated close contacts), transmission of the
268 attenuated agents to close contacts, risk for pregnant women and the foetus, and reversion to
269 virulence.

270 As for all biological products, the potential for infections caused by residuals of biological
271 material used in the manufacturing process as well as contaminations introduced by the
272 manufacturing process should be evaluated and addressed.

273 • Potential for medication errors

274 This section should address potential for vaccination errors and mechanisms put in place to
275 adequately follow-up and investigate the root cause of any errors. Causes of vaccination errors
276 to be considered include:

- 277 - inappropriate handling or breakdown in the cold chain, which may lead to adverse
278 reactions such as infection due to bacterial contamination of the vaccine, transmission
279 of blood-borne infection, abscess formation at the site of injection or loss of
280 efficacy/effectiveness; these issues apply particularly to multi-dose container vaccines
281 without preservatives;
- 282 - the method of administration (wrong or suboptimal route, inadequate dose, incorrect
283 diluent), which may be associated with adverse reactions or vaccination failure;
- 284 - non-compliance with recommended vaccination schedule, which may lead to
285 vaccination failure;
- 286 - product packaging and branding, which may lead to administration errors, especially if
287 other types of vaccines are used concurrently in the vaccination programme, in which
288 case similar packaging and branding should be avoided;
- 289 - circumstances of a mass vaccination (e.g. in a pandemic) with use of multi-dose vials
290 or with the need for dilution;
- 291 - situations where several vaccines are marketed in a same country for the same
292 indication, which may lead to patients receiving a vaccination series with different
293 products or too many doses of a vaccine.

294 **P.I.B.1.2.5. RMP module SVII “Identified and potential risks”**

295 This section should provide information on the important identified and important potential risks
296 associated with use of the vaccine pre- and post-authorisation.

297 The following important potential risks should be considered:

- 298 • waning immunity, requiring a continuous evaluation of the need for a booster dose;
- 299 • potential risks anticipated from experience with similar vaccines and vaccine ingredients
300 (considering the biological plausibility); what constitutes “similar” will be a case-by-case decision,
301 based on the disease, the disease target population, the vaccine type, the carrier protein or other
302 criteria, as scientifically appropriate;
- 303 • potential risks associated with concomitant administration of several vaccines, such as for
304 paediatric vaccines or vaccines used in travel medicine;
- 305 • potential interactions with medicinal products usually given to the target population or
306 administered as a prophylactic treatment (e.g. antipyretics in order to minimise adverse
307 reactions);
- 308 • syndromes closely resembling wild-type disease, caused on rare occasions by some live attenuated
309 vaccines (e.g. vaccine-induced measles meningitis or encephalitis, yellow fever vaccine and
310 viscerotropic disease); in these cases, host risk factors such as age, gender and immune status
311 should be described and the need for further investigations should be addressed, including clinical,
312 serological and immunochemical analyses, and antigen detection, quantification and sequence
313 analysis; certain strains may also be associated with adverse events usually seen with the wild-
314 type disease;
- 315 • adverse events proposed to be reported and assessed with high priority, because, based on
316 experience with the vaccine concerned or similar vaccines in terms of manufacturing process,
317 composition (e.g. adjuvants), immunogenicity and novelty, they represent potential risks that
318 would need immediate investigation or regulatory action, they could lead to a change in the
319 benefit-risk balance of the vaccine, or they would require prompt communication to the public by
320 regulatory or public health authorities; proposal for such adverse events of special interests
321 (AESIs) may be particularly useful in situations of a mass vaccination programme where it is
322 expected that a large number of adverse reactions may be reported and their processing may need
323 to be prioritised.

324 The information on potential mechanisms for each identified or potential risk should include available
325 data on association of the risk with the antigen itself, any other ingredient of the vaccine, including
326 adjuvants, stabilisers, preservatives or residuals of the manufacturing process, the target population,
327 interactions with other vaccines or medicinal products or the vaccination schedule. If some of these
328 factors are clearly associated with some identified or potential risks, it may be appropriate to present
329 these risks in different categories.

330 **P.I.B.1.2.6. RMP module SVIII “Summary of the safety concerns”**

331 This section should include a summary of the safety concerns (important identified risks, important
332 potential risks and important missing information).

333 Important missing information to be considered includes long-term duration of protection, waning
334 immunity and need for (a) booster dose(s) (in absence of information justifying their classification as
335 potential risks) and the [possible clinical impact of different policies concerning vaccination schedules](#)
336 and target population [which differ from those studied pre-authorisation](#).

337 **P.I.B.1.3. RMP part III “Pharmacovigilance plan”**

338 What constitute routine and additional pharmacovigilance activities is described in Module V.

339 The methodology for data collection ~~from~~in both routine and additional pharmacovigilance activities for
340 vaccines should allow data retrieval and analysis by age groups (including premature infants,
341 neonates, infants and the elderly), number of doses, different vaccination schedules and defined risk
342 factors or underlying diseases. ~~Clusters of reported adverse events/reactions should be identified. Full~~
343 ~~traceability of all manufacturing changes and links to safety data should be ensured.~~

344

345

346 ***P.I.B.1.3.1. RMP section “Routine pharmacovigilance activities”***

347 Where routine pharmacovigilance activities normally used by the marketing authorisation holder for
348 medicinal products have been adapted to vaccines, these amendments should be described in this
349 section, for examples alternative methods to perform signal detection or alternative algorithms to
350 evaluate individual case safety reports.

351 Where appropriate, this section should ~~also~~ describe routine pharmacovigilance activities ~~carried out~~
352 in place for the surveillance of the following events and reactions:

- 353 • serious but rare adverse reactions (even if the sole aim is to provide reassurance on safety);
- 354 • batch-related adverse reactions, including the measures taken to clearly identify the name of the
355 product and the batch numbers involved in suspected adverse reactions (see ~~Module VI-B-3-~~ and a
356 description of how traceability of manufacturing changes will allow identify any related adverse
357 reactions;⁶
- 358 ~~• including autoimmune disorders;~~
- 359 • identified and potential interactions with co-administration of other vaccines, including the
360 increased risk for adverse reactions and clinically relevant immunological interference;
- 361 • possible safety concerns reported with combined vaccines such as increased frequency or severity
362 of known adverse reactions (local or systemic), as small differences of local or systemic adverse
363 reactions between the combined vaccine and the precursor (combined or individual) vaccine(s) are
364 usually not detected in pre-authorisation studies;
- 365 • any adverse events of special interest (AESIs) identified as an important potential risk in the safety
366 specification; standard case definitions should be provided (e.g. Brighton Collaboration case
367 definitions⁶) and age-stratified data on incidence rates in the population targeted by the
368 vaccination programme should be compiled ~~and presented~~; if such data do not exist, they should
369 be included in the pharmacovigilance plan as data to be collected in the post-authorisation phase
370 (see P.I.B.1.3.2.);
- 371 • inappropriate use of vaccines and patterns of error;
- 372 • cases of breakthrough infections, which are expected without necessarily indicating a problem with
373 the vaccine, as vaccines and vaccination programmes are not 100% effective; although this issue
374 cannot be fully investigated via spontaneous reporting, reports of vaccine failure can nonetheless
375 generate signals, and risk factors should be analysed (e.g. obesity, age, smoking status,

⁶ Available on Brighton Collaboration website <http://www.brightoncollaboration.org>.

376 vaccination schedule, concomitant disease); appropriate case definitions and validated analytical
377 tests for confirmation of the infective agents should be used whenever possible and the
378 recommendations of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance should be
379 considered for the definition and classification of cases of vaccination failure;⁷

380 • adverse reaction reports indicating a possible reversion to virulence, especially for new live
381 attenuated vaccines; validated and standardised assays, including assays to distinguish between
382 wild and vaccine strains, should normally be implemented prior to marketing authorisation for
383 appropriate case assessment.-

384 As part of the routine follow-up of adverse reactions, data should be collected (in addition to data on
385 the patient, the adverse reaction and the vaccination history) about:

386 • the vaccination schedule and the route of administration;

387 • the vaccine and the diluent (if applicable), including manufacturer(s) and, batch number(s);

388 • in case of a suspected quality defect, batch release specifications, expiry date(s) and laboratory
389 test results about the batch if appropriate, and distribution and administration-related data, such
390 as storage and handling conditions for vaccines in the healthcare institutions where vaccination
391 took place;

392 • relevant comorbidities in the target population (including autoimmune disorders).

393 • ~~Any arrangements established to promptly investigate any emerging issues, such as access to~~
394 ~~electronic health records, registries (e.g. pregnancy registries) or other data sources, should be~~
395 ~~described in this section., batch release specifications, expiry date(s) and laboratory test results~~
396 ~~about the batch if appropriate;~~

397 • ~~distribution and administration-related data, such as storage and handling conditions for vaccines~~
398 ~~in the healthcare institution where vaccination took place;~~

399 • ~~the vaccination schedule and the route of administration.~~

400 ~~Reversion to virulence after multiplication in the human host might be of particular concern for some~~
401 ~~live attenuated vaccines. Careful investigation of spontaneous suspected adverse reaction reports~~
402 ~~indicating a possible reversion to virulence is essential, especially for new live attenuated vaccines.~~
403 ~~Validated and standardised assays, including assays to distinguish between wild and vaccine strains,~~
404 ~~should be implemented prior to marketing authorisation for appropriate case assessment.~~

405 ~~As vaccines and vaccination programmes are not 100% effective, cases of breakthrough infections are~~
406 ~~expected without necessarily indicating a problem with the vaccine. Although these issues cannot be~~
407 ~~fully investigated via spontaneous reporting, reports of vaccine failure can nonetheless generate~~
408 ~~signals to be further evaluated by other methods. Such signals may need prompt action and further~~
409 ~~investigated through post-authorisation studies as appropriate. Risk factors for vaccine failure should~~
410 ~~be analysed (e.g. obesity, age, smoking status, vaccination schedule, concomitant disease). If there is~~
411 ~~concern that a higher than expected rate of vaccine failures and break-through infections in certain risk~~
412 ~~groups exists, appropriate systematic investigations should be carried out. Appropriate case definitions~~
413 ~~and validated analytical tests for confirmation of the infective agents should be used whenever~~

⁷ Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Genève: CIOMS; 2012.

414 possible. The recommendations of the ~~CIOMS/WHO Working Group on Vaccine Pharmacovigilance~~
415 should be considered for the definition and classification of cases of vaccination failure.⁸

416 ~~As under-reporting of suspected adverse reaction reports is an inherent characteristics of~~
417 ~~pharmacovigilance, including for vaccines, appropriate national communications to optimise and~~
418 ~~facilitate reporting may be proposed in specific situations where mass vaccination takes place and~~
419 ~~prompt identification and evaluation of safety concerns are needed. This communication should involve~~
420 ~~collaboration between national regulatory and public health authorities to ensure provision of~~
421 ~~information to patients to describe which vaccine they have used, the batch number and how events~~
422 ~~can be reported.~~

423 ***P.I.B.1.3.2. RMP section “Additional pharmacovigilance activities”***

424 ~~This section should describe the tools established to promptly investigate any emerging issues, such as~~
425 ~~access to electronic health records, or prior arrangements made with managers or users of registries~~
426 ~~(e.g. pregnancy registries) or other data sources.~~

427 In addition to the investigation of important identified risks, important potential risks or important
428 potential missing information, additional pharmacovigilance activities may be needed in the following
429 situations:

- 430 • to detect strain replacement phenomena (with genotyping of circulating strains as necessary) for
431 vaccines that may protect against only some types of organisms within a species;
- 432 • to address the pattern of shedding, transmissibility to contacts and the potential of the strain to
433 survive in the environment;
- 434 • to establish evidence of safety for novel vaccines or for vaccines with a novel adjuvant, in order to:
 - 435 – assess the risk of induction of rare or delayed onset adverse reactions, local or systemic;
 - 436 – detect occurrence of auto-immune diseases and immune-mediated reactions resulting from a
437 synergistic action of the adjuvant and the biologically active antigen;
 - 438 ~~particular in relation to long-term and delayed-onset adverse reactions;~~
- 439 ~~• to assess the effectiveness of the vaccine, especially where pre-authorisation data are limited;~~
- 440 ~~• in cases where a novel adjuvant has been incorporated into the vaccine formulation;~~
- 441 ~~• to assess the risk of induction of rare or delayed onset adverse reactions, local or systemic;~~
- 442 ~~• to detect occurrence of auto-immune diseases and immune-mediated reactions resulting from a~~
443 ~~synergistic action of the adjuvant and the biologically active antigen.~~
- 444 • to investigate clusters of reported adverse events/reactions:
 - 445 • where spontaneous reports raise concerns that a higher than expected rate of vaccine failures and
447 breakthrough infections in certain risk groups exists.

448 Where additional investigations regarding the impact of different vaccination schedules are needed, it
449 is acknowledged that it might not be feasible to study all recommended priming and booster schedules

⁸ ~~Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine
pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Genève: CIOMS; 2012. Report of
CIOMS/WHO Working Group on Vaccine Pharmacovigilance, CIOMS 2012.~~

450 across the EU, but a rationale for further evaluation should be presented (e.g. studying the most
451 accelerated schedule based on 2 or 3 doses).

452 ~~When initiating an additional pharmacovigilance activity, the marketing authorisation holder should~~
453 ~~investigate) and~~ the availability of systems for collecting data in different countries should be
454 investigated.

455 A pregnancy register may be needed to address risks of the vaccine in pregnant women, in which case
456 the design of the registry should be provided as part of the RMP. It should allow identification of
457 spontaneous abortions, stillbirths and congenital malformations with an adequate duration of follow-up
458 of the offspring. Detailed information on vaccine exposure (including number of doses and gestational
459 age at the time of exposure) before and/or during pregnancy should be collected. The Guideline on the
460 Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation Data⁹ and the
461 Systematic overview of data sources for drug safety in pregnancy research¹⁰ should be consulted.

462 Where adverse events of special interest (AESIs) are presented in the safety specification as important
463 potential risks and baseline/background incidence rates of those AESIs in the target population are not
464 available, it may be necessary to design a study to collect this information in order to provide rapid
465 answers to vaccine safety concerns emerging from spontaneous reports of suspected adverse
466 reactions. The types of data sources (e.g. in-patient or out-patient databases) available to estimate
467 background incidence rates will differ across countries and is likely to impact diagnostic validity in
468 terms of sensitivity and specificity. ~~Follow-up time~~The study design should ~~be sufficient for allowing~~
469 differentiation between prevalent and incident cases. Furthermore, bias could arise from
470 misclassification of disease type or changes in diagnostic criteria and disease management over the
471 study period. Whenever possible, data should be stratified by age, sex, geographical region as well as
472 by other potentially relevant risk factors or confounders. If relevant, seasonal variability should be
473 taken into account.

474 In exceptional circumstances (for example in a pandemic with mass vaccination), competent
475 authorities and marketing authorisation holders may agree on an additional ~~communication~~ system to
476 rapidly exchange information on emerging safety data whose submission timelines would depend on
477 the extent of vaccine exposure, epidemiological situation and emerging risk. For example, a structured
478 worksheet could present the observed and expected numbers of cases and integrate simple signal
479 detection methods discussed in P.I.B.4., such as observed-to-expected analyses. Where such an
480 additional ~~communication~~ system has been agreed, its inclusion –as an additional pharmacovigilance
481 activity in the RMP, along with information on its rationale, format and periodicity, should be discussed
482 between the marketing authorisation holder and the competent authority.

483 As under-reporting of suspected adverse reaction reports is an inherent characteristics of
484 pharmacovigilance, including for vaccines, appropriate national communications to optimise and
485 facilitate reporting may be proposed in specific situations where mass vaccination takes place and
486 prompt identification and evaluation of safety concerns are needed. This communication should involve
487 collaboration between national regulatory and public health authorities to ensure provision of
488 information to patients to describe which vaccine they have used, the batch number and how events
489 can be reported. –

⁹ EMEA/CHMP/313666/2005, available on EMA website <http://www.emea.europa.eu>.

¹⁰ Charlton R and de Vries C, for the European Medicines Agency. Available at
<http://www.encepp.eu/encepp/openAttachment.htm?field=documents.otherDocument%5b0%5d&id=2756>.

490 **P.I.B.1.4.RMP part IV “Plans for post-authorisation efficacy studies”**

491 ~~Any Plans~~ for post-authorisation efficacy studies (PAES) ~~should be included in this section may include~~
492 ~~the assessment of vaccine efficacy/effectiveness and immunogenicity in the post-authorisation phase~~
493 ~~may be particularly important~~ in order to get additional information on waning immunity, long-term
494 protection, cross-protective efficacy/effectiveness and the most appropriate use of the vaccine (e.g.
495 the need for booster doses in at least some population groups, such as immunodeficient individuals, to
496 maintain adequate protection over time).

497 **P.I.B.1.5. RMP part V “Risk minimisation measures”**

498 In principle, regulatory tools and risk minimisation activities for vaccines are similar to those used for
499 other medicinal products (see Module XVI). ~~However, the~~The use of additional risk minimisation
500 activities might be challenging given the diverse settings of use of vaccines within and outside (e.g.
501 travel clinics) vaccination programmes.

502 Appropriate communication to healthcare professionals by marketing authorisation holders and
503 regulatory and public health authorities is a critical component of risk minimisation aiming to avoid
504 errors in vaccine handling and vaccine administration and to reiterate warnings and precautions.
505 Routine risk minimisation measures such as the Summary of Product Characteristics and the Package
506 Leaflet are the most used channels of communication to the healthcare professionals (SmPC) and the
507 patients for vaccines. To further minimise the risks associated with the vaccination (e.g. medication
508 errors) and to facilitate the traceability of vaccine’s brandname and batch number in the reporting of
509 adverse events, the MAH should also consider labelling and packaging as risk minimisation tools.

510 ~~Pre-defined criteria for batch recall or quarantine should be included in this RMP section (see P.I.B.5.).~~

511 ***P.I.B.2. Periodic safety update report***

512 In addition to information which should be provided in the periodic safety update report (PSUR) for all
513 medicinal products (see Module VII-), special consideration should be given in PSURs for vaccines to
514 any potential impact on safety of ~~major as well as minor~~ changes in the manufacturing process. Issues
515 related to batch(es), as well as age-related adverse reactions should be evaluated. ~~Safety aspects in~~
516 ~~subpopulations (such as pregnant women) should be analysed.~~ If relevant, the potential for local and
517 systemic adverse reactions should be analysed for different doses of the vaccine and also across
518 different vaccination schedules. ~~Sub-analyses of spontaneous reports with regard to possible~~
519 ~~differences in the adverse reaction profile linked to different vaccination schedules are considered~~
520 ~~important but do not replace clinical investigations.~~

521 The following data should also be summarised and analysed in the PSUR:

- 522 • reports of vaccine failure, lack of efficacy/effectiveness;
- 523 • vaccination errors;
- 524 • vaccination anxiety-related reactions such as syncope;
- 525 • literature data with information relevant to other similar vaccines and vaccine components such as
526 stabilisers, preservatives and adjuvants.

527 If concomitant vaccination with another vaccine is specifically mentioned in the SmPC, co-
528 administration of vaccines should be analysed separately and the analysis be summarised in the PSUR
529 if there is a safety concern. The data should also be analysed for new concerns regarding concomitant
530 vaccination, independently of whether concomitant use is mentioned in the SmPC or not.

531 **P.I.B.2.1. Integrated benefit-risk analysis**

532 When a new or changing risk is identified, it is important to re-evaluate the benefit of the medicinal
533 product using all available data and estimate the impact of the new or changing risk on the benefit-risk
534 balance of the vaccine. Benefits may include prevention of the target disease, severity of symptoms,
535 hospitalisation, complications, effect of target disease on offspring (in case of vaccination of pregnant
536 women) and any other clinical outcome relevant for individual patients.

537 **P.I.B.3. Post-authorisation safety studies**

538 Objectives, methods and procedures for post-authorisation safety studies (PASS) as described in
539 **Module VIII** should be followed.

540 **P.I.B.3.1. Aspects of study design**

541 **Appendix 1 of Module VIII** presents a range of methods for post-authorisation safety studies (PASS).
542 Controlled clinical trials and prospective cohort studies are considered to provide the highest level of
543 evidence but may not be possible to conduct in many cases, especially for rare or long-term risks
544 which may only become evident several years or even decades after vaccination. In this case, cohort
545 studies based on secondary data collection could be designed, whereby the group in whom the adverse
546 events/reactions is studied is defined at the time the study is initiated rather than at the time of
547 vaccination.

548 Traditional study designs such as cohort and case-control studies may however be difficult to
549 implement where they involve populations with high vaccine coverage rates ~~and~~ an appropriate
550 unvaccinated group is lacking or adequate information on covariates at the individual level is lacking.
551 See the ENCePP Guide on Methodological Standards in Pharmacoepidemiology for alternative study
552 designs that can be used in such cases.¹¹ ~~A frequent source of confounding to be considered in vaccine~~
553 ~~studies comparing vaccinated and unvaccinated individuals is the underlying health status influencing~~
554 ~~the probability of being vaccinated. Epidemiological methods involving cases only are useful in such~~
555 ~~situations. These methods include some ecological methods, case coverage methods, case crossover~~
556 ~~and self-controlled case series methods.~~¹²

557 Safety parameters in PASS should be appropriate for the specific vaccine. A pre-requisite is the use of
558 globally accepted standards for case definitions (e.g. those published by the Brighton Collaboration¹³)
559 to compare the frequency of adverse reactions across different studies.

560 **P.I.B.3.2. Case-only designs**

561 ~~In the self-controlled case series (SCCS) design,~~¹⁴ ~~the observation period following each vaccine dose~~
562 ~~for each case is divided into risk period(s) (e.g. the days immediately following each vaccination) and~~
563 ~~control period (the remaining observation period). Incidence rates within the risk period after~~
564 ~~vaccination are compared with incidence rates within the control period, under the null hypothesis that~~
565 ~~incidence rates would be equivalent if no association with vaccination is present, taking age into~~
566 ~~account. A SCCS analysis adjusting for age effects has the advantage of an implicit control of any~~
567 ~~known or unknown confounders which are stable over time. For unique events, this method requires~~

¹¹ See http://www.encepp.eu/standards_and_guidances/index.shtml

¹² Farrington CP. Control without separate controls: evaluation of vaccine safety using case-only methods. *Vaccine*. 2004;22(15-16):2064-70.

¹³ Available on Brighton Collaboration website <http://www.brightoncollaboration.org>.

¹⁴ Weldeselassie YC, Whitaker HJ, Farrington CP. Use of the self-controlled case series method in vaccine safety studies: review and recommendations for best practice. *Epidemiol Infect*. 2011;139(12):1805-17.

568 ~~the additional assumption that the cumulative incidence of events in the population over the observed~~
569 ~~period is low. Data analyses may be performed early and time efficiently. Like cohort or case-control~~
570 ~~studies, the SCCS method remains however susceptible to bias if vaccination is timed to minimise the~~
571 ~~risk of an adverse event. Moreover, relevant time intervals for the risk and control periods need to be~~
572 ~~defined and this may become complex with primary vaccination with several doses.~~

573 ~~Case-coverage methods make use of exposure information on cases, supplemented by data on~~
574 ~~vaccination coverage in the population. This design may be considered as an unmatched case-control~~
575 ~~study with the entire population serving as control. Therefore, no individual data on non-cases or~~
576 ~~denominators are required. Three main shortcomings should be considered: reliable coverage data are~~
577 ~~needed; the population for which vaccination statistics are available may not correspond exactly to~~
578 ~~that from which cases are drawn, which may lead to biased estimates; and the aggregated coverage~~
579 ~~data generally do not permit control of confounding by stratified analysis.¹²~~

580 **~~P.I.B.3.3. Other designs~~**

581 ~~Ecological studies examine the correlation between the trends in an indicator of vaccine coverage and~~
582 ~~the trends in incidence of a disease that is a presumed effect of the vaccine. These trends can be~~
583 ~~examined over time or across geographical regions. In such analysis, it is hypothesised that a strong~~
584 ~~correlation between the two trends is consistent with a causal relationship, while a weak correlation~~
585 ~~would indicate a weak relationship. This comparison at the population level limits the possibility to~~
586 ~~control for confounding variables. Their results should therefore be interpreted with caution. Ecological~~
587 ~~studies may be however useful to generate hypotheses.~~

588 Vaccination registries established in many countries may be used in vaccine safety by creating a source
589 population for large cohort studies. Using a vaccination registry as a source population for studies
590 should be made with caution where enrolment may be biased or there is no systematic collection of
591 exposure in the population. Moreover, a large number of vaccinated individuals is required for the
592 active surveillance of rare adverse reactions by follow-up of a cohort recruited at the time of
593 vaccination.

594 Non-clinical studies and experimental investigations should also be considered to address safety
595 concerns. This may include virological, bacteriological and/or immunological experiments and other
596 methods to elucidate the aetiology of an adverse reaction.

597 ***P.I.B.4. Signal management***

598 The signal management process (see **Module IX**) covers all steps from detecting signals to
599 recommending actions. A signal is information arising from one or multiple sources, including
600 observations and experiments, which suggests a new potentially causal association, or a new aspect of
601 a known association between an intervention and an event or set of related events, ~~either adverse or~~
602 ~~beneficial,~~ that is judged to be of sufficient likelihood to justify verificatory action [IR Art 19(1)]. In the
603 field of vaccines, a signal may also relate to evidence of reduced efficacy ~~or~~ effectiveness, vaccine
604 failures and quality deviations with potential impact on safety ~~or~~ efficacy ~~or~~ effectiveness (which may
605 be batch-specific).

606 **P.I.B.4.1. Standard case definitions**

607 Standardised case definitions of adverse events are a key element for signal validation and evaluation
608 as they provide a common terminology and understanding of adverse events/reactions and thus allow

609 for comparability of data. Definitions published by the Brighton Collaboration¹⁵ should be used where
610 available. If a Brighton Collaboration definition is not available, the definition which is used should be
611 carefully chosen based on scientific criteria and amenable for justification. Adverse reactions should
612 however be reported even if no standard definition exists.

613 Standardised MedDRA (Medical Dictionary for Regulatory Activities) Queries (SMQs)¹⁶ may be used in
614 the process of signal detection, validation and evaluation. Sensitivity and specificity testing of SMQs for
615 vaccines needs to be done beforehand in order to adequately interpret the results.

616 **P.I.B.4.2. Single report of a serious adverse event**

617 A single report of a serious adverse event occurring in temporal association with the vaccination,
618 especially if the event is unexpected or fatal, could have a detrimental impact on vaccination
619 programmes due to perception of unsubstantiated risks or risk amplification.

620 A single report of a serious adverse event should be processed as a signal only if there is a possible
621 causal association to the vaccine. This requires adequate information on the clinical course of the event
622 (time to onset, signs and symptoms, results of relevant laboratory and diagnostic tests, evolution,
623 treatment of the event, autopsy report in case of a fatal event and pathophysiological mechanism),
624 medical history, vaccination history, co-medication and details of the vaccine(s) administered
625 (including brandname, batch number, route of administration and dose). Signal validation should also
626 be based on contextual information. Relevant data to be collected for this purpose should include the
627 number of reported cases of a similar event and the probability of occurrence of the event in a non-
628 vaccinated population of the same age category, calculated from clinical trials and observational
629 studies. If adequate data are available on the number of vaccinated individuals of the same age
630 category, the observed and expected numbers of cases should be estimated.

631 **P.I.B.4.3. Signal detection in mass vaccination programmes**

632 In mass vaccination programmes which involve large exposure over a relatively short time period,
633 signal detection should be as real-time as possible, ideally to inform decision-making as the
634 vaccination progresses. It should be ~~and~~ adapted to the specific circumstances of the vaccination
635 programme. A particular challenge is the association of such vaccination programmes with very high
636 numbers of spontaneously reported adverse reactions over a relatively short time period. Quickly
637 analysing and communicating the significance of such data is critical. The priority is to rapidly identify
638 possible new signals, but also to rapidly assess the likelihood that the number of reports may be
639 consistent with the expected background incidence in the vaccinated cohort, and thereby possibly
640 coincidental.

641 **P.I.B.4.4. Disproportionality analyses**

642 A statistic of disproportionate reporting (SDR) refers to a statistical association between medicinal
643 products and adverse events. There are several statistical methods used to identify SDRs, such as the
644 proportional reporting ratio (PRR) and Bayesian approaches. Of note, a statistical association does not

¹⁵ Available on Brighton Collaboration website <http://www.brightoncollaboration.org>.

¹⁶ Council for International Organizations of Medical Sciences (CIOMS).

Development and rational use of Standardised MedDRA Queries (SMQs). Geneva: CIOMS; 2004.

Available ~~at~~ ~~on~~ CIOMS website <http://www.cioms.ch/>.

645 imply any kind of causal relationship between the administration of the vaccine and the occurrence of
646 the adverse events.¹⁷

647 Vaccines may require special consideration when applying such ~~tools~~methods (see P.I.-A.). Intrinsic
648 differences between vaccines and other medicinal products should be considered, for example frequent
649 reporting of unrelated adverse events in the target population (e.g. Sudden Infant Death Syndrome
650 (SIDS) and infant vaccination, cardiorespiratory events and influenza vaccines). Furthermore, the
651 safety profile of a vaccine may differ substantially within the target population (e.g. higher risks in the
652 youngest age groups). In order to reduce background noise, estimates of disproportionality should be
653 calculated based on a comparison across groups that have a similar age-specific background risk for
654 illness. The choice of the comparator group will depend on the objectives of the analysis and the
655 information available in the database. A comparison with all medicinal products may result in the
656 detection of reactions specifically related to vaccines, but may also identify a high number of false
657 signals (e.g. SIDS in infants) or already known mild and expected reactions (e.g. local reactions). On
658 the other hand, using only vaccine-related reports available in the database may result in signals of
659 age-related reactions (e.g. cardio-vascular disorders if the vaccine of interest is used in the elderly). In
660 a first step, it may therefore be appropriate to examine results of statistical methods using both
661 comparator groups, or to use reports for other vaccines as the comparator group with a stratification
662 made at least by age.

663 Stratification by geographical region may also be considered and seasonality of vaccine administration
664 may be relevant for some vaccines and needs consideration. When stratification is performed, ~~it may~~
665 ~~be wise to examine the~~ results of both adjusted and non-adjusted analyses should be examined.
666 Results could be inspected in each stratum as pooled result of a stratified analysis may miss signals.

667 **P.I.B.4.5. Observed to expected analyses**

668 When there is little time to validate signals, it is essential to make best use of suspected adverse
669 reaction reports. Observed vs. expected (O/E) analyses based on good-quality data can optimise the
670 utility of passive surveillance data, allowing determination of the strength of a signal for prioritisation
671 and further evaluation, and can help in communication of these data (particularly when serious, rare
672 reported events are well within an expected range). -O/E analyses are particularly useful during mass
673 vaccination programmes where there is little time to review individual cases and prompt decision-
674 making about a safety concern is required. Although such analyses cannot exclude risks or determine
675 causality, they can help put suspected adverse reaction reports into context and should be used as a
676 routine tool for real-time surveillance. They can also be useful in signal validation and, in the absence
677 of robust epidemiological data, in preliminary signal evaluation.

678 Key requirements of O/E analyses and statistical methods are described in the ENCePP Guide on
679 Methodological Standards in Pharmacoepidemiology.¹⁸

680

681 ~~O/E analyses are particularly useful during mass vaccination programmes where there is little time to~~
682 ~~review individual cases, and prompt decision-making about a safety concern is required. Although such~~
683 ~~analyses cannot exclude risks or determine causality, they can help put suspected adverse reaction~~
684 ~~reports into context and should be used as a routine tool for real-time surveillance. They can also be~~
685 ~~useful in signal validation and, in the absence of robust epidemiological data, in preliminary signal~~
686 ~~evaluation.~~

¹⁷ Guideline on the use of statistical signal detection methods in the Eudravigilance data analysis system, available at
[http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011434.p](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011434.pdf)
df.

¹⁸ See http://www.encepp.eu/standards_and_guidances/index.shtml.

687 It should be kept in mind that certain characteristics of an adverse event increase its probability of
688 being reported, such as when the outcome is unexpected, severe or disabling, when it is poorly
689 understood and when it affects a previously healthy person. Also, the shorter the time that has elapsed
690 between the vaccination procedure and the event, the more likely it is to be perceived as a trigger and
691 subsequently be reported. Conversely, events that are expected, common and mild, or occur late after
692 vaccination, are less likely to be reported.

693

694 ***P.I.B.4.5.1. Key requirements of O/E analyses***

695 ~~The key requirements of O/E analyses are the ‘observed’ number of cases detected in a passive or~~
696 ~~active surveillance system, appropriately stratified background incidence data (the ‘expected’) and~~
697 ~~near real-time exposure data (to determine the observed rate and expected incidence). Optimal use of~~
698 ~~O/E analyses therefore requires a high level of preparedness. The following aspects should be carefully~~
699 ~~considered before the start of and during a vaccination programme:~~

- 700 ~~• under-reporting and under-ascertainment of the observed number of cases should be reduced by~~
701 ~~stimulating reporting and optimising data capture; diagnostic certainty should be assured by~~
702 ~~gathering relevant clinical and laboratory test results and using standardised and validated case~~
703 ~~definitions (e.g. case definitions (see P.I.B.4.1));~~
- 704 ~~• background incidence rates of defined adverse events of special interest (AESIs) should be~~
705 ~~collected or compiled before vaccination starts; this should be complemented by securing easy~~
706 ~~access to one or several data sources allowing quick estimation of incidence rates of other~~
707 ~~(unexpected) events;~~
- 708 ~~• mechanisms should be put in place to collect, compile and make available stratified (e.g. age, risk~~
709 ~~group, country/region) and up-to-date vaccine exposure data.~~

710 ***P.I.B.4.5.2. Statistical aspects of O/E analyses***

711 ~~From information on a vaccinated population and baseline incidences of events, it is possible to~~
712 ~~estimate the numbers of new cases that will occur purely by chance within various time windows after~~
713 ~~a vaccination (e.g. cases/100 000 vaccinated persons within 6 weeks). However, these rates of new~~
714 ~~cases occurring purely by chance cannot directly be translated to anticipated rates of spontaneous~~
715 ~~reporting.~~

716 ~~When comparing spontaneous reporting rates and baseline incidence rates, secular trends gives~~
717 ~~information on the validity of such a comparison. If baseline trends indicate a significant increase or~~
718 ~~decrease, discrepancies between reports and baseline rates should be interpreted in this context. The~~
719 ~~inclusion of sex ratio adds information which can be used when comparing baseline incidences in~~
720 ~~periods before and after a vaccination program is introduced. Any changes in the sex ratio indicate that~~
721 ~~the degree of exposure of certain sex-specific risk factors for a given disease has changed.~~

722 Given uncertainties around the ‘observed’ number of cases, the levels of diagnostic certainty, the level
723 of vaccine exposure and the background incidence rates, sensitivity analyses should be applied in
724 statistical analyses around assumed levels of under-reporting, numbers of ‘confirmed’ and ‘non-
725 confirmed’ cases (using several categories of diagnostic certainty as appropriate), numbers of
726 vaccinated individuals or vaccine doses administered and confidence intervals of incidence rates.

727 ~~Calculations should be appropriately stratified. Analyses should be performed regularly (e.g. weekly),~~
728 ~~ideally with statistical methods applied for sequential analysis with signal thresholds.~~

729 Specific statistical methods may include:

730 • a 'snapshot' method for ad hoc analyses using an appropriate risk period post vaccination to
731 calculate the expected number of cases, and comparing it to the observed number of cases to
732 calculate an O/E ratio with a 95% confidence interval; this method can be applied with a simple
733 worksheet displaying for each reaction of interest the expected rate, the observed number of cases
734 and the vaccine exposure, with regular updates; sensitivity analyses can be added; the method is
735 easy to understand and results are easy to communicate, but it may not be fully appropriate for
736 continuous monitoring and signal detection due to issues of multiplicity;

737 • a sequential method (for example, the Maximised Sequential Probability Ratio Test (MaxSPRT) for
738 weekly surveillance¹⁹) allowing to perform O/E analyses with adjustment for multiplicity; the O/E
739 ratio can therefore be calculated on a weekly basis using cumulative data; sequential methods are
740 more complex to perform than the 'snapshot' method and are less easy to understand and
741 communicate to a non-statistical audience.

742 Combination of sequential and snapshot methods may be helpful: while the 'snapshot' method
743 provides a method that is preferable to use for communication purpose, the sequential method
744 provides a more robust method for continuous surveillance.

745 P.I.B.4.6. Signal evaluation

746 For the evaluation of validated signals based on individual case reports of suspected adverse reactions,
747 complete and accurate individual records documenting administration of all vaccines should be
748 provided, together with information on the date of vaccination, product administered, manufacturer,
749 batch number, site and route of administration, detailed description and course of the adverse
750 event/reaction as well as therapeutic intervention. Information on ~~dechallenge and~~
751 ~~rechallenge~~ rechallenge, where are often not applicable, to vaccines, but where they are, such data
752 should be recorded. The investigation of clusters of reported adverse events or adverse reactions is
753 described in the report of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance.²⁰

754 Appropriate follow-up of serious suspected adverse reactions is essential, including data on possible
755 alternative causes. It may be helpful to develop pre-defined check lists or formats for those reactions
756 which may be anticipated from experience with similar vaccines in order to consistently ascertain
757 relevant clinical information and support the quality of causality assessment for individual cases (see
758 also Module VI).

759 The following aspects need to be considered for signal evaluation:

- 760 • the incidence of the natural disease in the target population for vaccination and its seasonality, as
761 this population is usually large and heterogeneous and coincident adverse events are likely to
762 occur;
- 763 • additives and excipients used for the production, inactivation, preservation, and stabilisation of the
764 vaccine;
- 765 • past experience with similar vaccines, adjuvants and types of antigens, in order to identify adverse
766 reactions which are unexpected and for which a causal relationship remains to be elucidated;

¹⁹ Brown JS, Kulldorf M, Chan KA et al. Early detection of adverse drug events within population-based health networks: application of sequential testing methods. *Pharmacoepidemiology and Drug Safety* 2007;16(12): 1275–1284.

²⁰ Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Genève: CIOMS; 2012. See http://whqlibdoc.who.int/publications/2012/9789290360834_eng.pdf

- 767 • distinction between suspected adverse reactions to the vaccine and those reflecting the clinical
768 picture of the disease for which vaccination has been given (e.g. rash following measles
769 vaccination);
- 770 • public information (public campaign, press) that may favour certain reports in some periods.

771 ***P.I.B.5. Batch recall and quarantine***

772 In order to protect public health, it may become necessary to implement urgent measures such as to
773 recall or halt the distribution (quarantine) of (a) batch(es) of a vaccine due to a suspected batch-
774 specific signal or defect.²¹ The legal reference for batch recall is the **Good manufacturing practice and**
775 **good distribution practice**.²²

776 The principle of public health protection may be particularly relevant in certain situations, e.g. vaccines
777 for healthy children, particularly in case of a localised incident. A vaccine batch recall or quarantine is
778 sometimes taken in the absence of the full facts and evidence and before the assessment of the issue
779 is finalised. However, batch recall or quarantine may have a detrimental impact on the vaccination
780 programme itself, even if absence of association between the suspected batch(es) and the severe
781 adverse events is later demonstrated, and may cause more harm than good. As with any mass
782 intervention, vaccination programmes are inevitably associated with serious adverse events in
783 temporal association with vaccine administration but many of these are coincidental. As a batch recall
784 may also lead to issues of vaccine supply and sometimes a shortage of vaccines, the possibility of a
785 chance association and the availability of a sufficient amount of vaccines or of alternative vaccines
786 for the vaccination programme should also be considered in this context.

787 In situations where a batch-specific quality or safety issue has not been confirmed, measures other
788 than recall or quarantine may be warranted initially whilst an investigation is on-going, e.g. providing
789 recommendations on patient surveillance and follow-up post-vaccination. This may be considered when
790 recall or quarantine may lead to vaccine supply shortages and alternatives are not widely available.

791 The following sections present elements that should be taken into account when considering recalling
792 or quarantining batches.

793 **P.I.B.5.1. Data requirements**

794 The following data should be collected as soon as possible and should ideally be available when taking
795 a decision about a batch recall or quarantine:

- 796 – detailed description of the case(s) presented in CIOMS format with narrative(s), including any
797 additional information as appropriate (e.g. laboratory results, autopsy reports, literature);
- 798 – characteristics of the adverse event, e.g. severity, expectedness (new adverse reaction vs.
799 increased frequency of a known adverse reaction), outcome;
- 800 – characteristics of patients presenting the adverse event, e.g. age, concomitant diseases,
801 concomitant vaccination;

²¹ Compilation of community procedures on inspection and exchange of information. Procedure for handling rapid alerts rising from quality defects. London 18 May 2009. EMEA/INS/GMP/313510/2006 Rev 1.
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004713.pdf

²² [European Medicines Agency](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000154.jsp&mid=WC0b01ac0580027088). Good manufacturing practice and good distribution practice compliance [webpage].
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000154.jsp&mid=WC0b01ac0580027088.

- 802 - crude number of cases and reporting rate or incidence rate of the adverse event in the vaccinated
803 population using, if possible, actual vaccine usage data rather than sales data and observed vs.
804 expected calculations of the event observed;
- 805 - time and space clustering of cases, e.g. cases reported by a single hospital, physician or
806 locality region;
- 807 - geographical distribution (both spatial and numbers of doses used) of the suspected batch(es);
- 808 - manufacturing records of the suspected batch(es) (certificates of analysis, information on
809 deviations observed at in-process controls or manufacturing steps, documentation of recent
810 changes to the manufacturing process);
- 811 - storage and administration conditions of the suspected batch(es);
- 812 - re-analysis of retained samples of the suspected batch(es), focussing, if necessary, on additional
813 parameters to those required for the release of the product.
- 814 Time is a critical factor in the evaluation of potential batch-related issues. Marketing authorisation
815 holders should therefore continuously maintain a high level of preparedness to provide the information
816 needed for a quick evaluation of batch-related safety issues. Competent authorities should investigate
817 any other available source of information that may promptly provide information on similar events
818 (including batch-related information), and provide a preliminary assessment of all available data within
819 a short timeframe.

820 **P.I.B.5.2. Action based on clinical events in the absence of a known quality**
821 **issue**

822 A batch-specific signal based on an observed clinical event is often based on spontaneous reporting. In
823 the absence of a known quality issue, decision making on a precautionary recall or quarantine is
824 difficult, as a causal association with the vaccine can rarely be established at the time when an initial
825 decision is required.

826 In the absence of a known quality issue and where there is an apparent increase in frequency or
827 severity of known adverse reactions without serious clinical risk, consideration should be given to the
828 geographical distribution of the suspected batch and of the case(s) at the origin of the signal. If it is
829 established that a suspected batch has been used to a significant extent in many regions/countries and
830 a signal is apparent in only one geographical area, this could potentially indicate a false signal.
831 Conversely, an apparent signal in more than one locality may potentially strengthen the signal and
832 support a recall or quarantine.

833 For single fatal adverse events, particularly where the cause of death is unknown, the reporting rate of
834 the event relative to both the usage of the vaccine batch and the 'expected' age-specific all-cause
835 mortality should be considered before deciding on a recall or quarantine action (see also **P.I.B.4.2**).
836 The probability of a chance association should be considered. If a fatal event is initially thought to be a
837 consequence of a known adverse reaction (e.g. due to anaphylaxis), it would not necessarily imply a
838 batch-specific issue requiring a recall or a quarantine. On the other hand, where contamination of a
839 batch is suspected based on individual case details or a localised cluster, due to possible cold chain and
840 handling deviations, localised action should be considered before escalation to a national recall or
841 quarantine.

842 **P.I.B.5.3. Action due to identified quality deviations**

843 Identified quality deviations may be associated with no apparent clinical risks, and may not warrant
844 recall or quarantine. However, quality deviations may result in increased reactogenicity and/or
845 increased frequency of expected adverse reactions (such as severity and frequency of febrile reactions,
846 localised reactions and allergic reactions), or reduced potency, which may necessitate recall of a given
847 batch(es). In the case of a confirmed quality deviation, the decision to recall or quarantine can often
848 be relatively straightforward and supported by the likelihood of clinical risk and availability of
849 alternative batches or products.

850 **P.I.B.6. Safety communication**

851 Appropriate communication about the benefit-risk balance and safe use of vaccines to the target
852 population, vaccinated individuals, their parents/carers, healthcare professionals, health policy makers
853 and the general public is essential for ensuring the appropriate use of vaccines as well as for the
854 implementation of the vaccination programme.

855 Principles and guidance on safety communication, its planning and effectiveness evaluation is provided
856 in Modules XV and XII. In addition, the following principles should be considered for vaccines.±

857 Being transparent and providing explicit information in lay language to the public regarding the use of
858 (a) vaccine(s) should be fundamental to the communication approach. Incomplete or unclear
859 messages may lead to confusion of the general public and the decision not to vaccinate or not to be
860 vaccinated on unsubstantiated grounds. Communication should help preventing anxiety-related
861 reactions (see Annex I). Any potential risks for specific population groups should be clearly
862 communicated.

863 Specific safety communication objectives in relation to vaccines may also aim at avoiding errors in
864 vaccine handling and administration and at reiterating warnings and precautions for use.

865 Safety communication about a vaccine should also describe the benefits of vaccines, explain the risks
866 for individuals and the population of a decrease in vaccination coverage, and explain its impact on
867 disease control. When drafting communication texts, it should be considered that, as vaccination
868 programmes mature, incidence rates of the targeted diseases decrease substantially, and so does
869 personal experience with the disease in a given population. This may result in an increased attention to
870 concerns related to vaccine safety, and information on the target disease itself may need to be
871 provided. It should be considered that risk perceptions may differ between stakeholders, especially
872 when there is uncertainty about a risk. Public confidence in vaccination programmes may only be
873 maintained by knowledge that systems are in place to ensure complete and rapid assessment and to
874 take precautionary measures if needed. Therefore, safety communication about vaccines may also
875 profit from describing key functions of the pharmacovigilance systems.

876 Communication about vaccines may also include informing vaccinators/healthcare professionals on the
877 management of vaccine-related anxiety and associated reactions, particularly in individuals with special
878 conditions (e.g. pregnancy, puberty, immunosensitive conditions, general anxiety or other mood
879 disorders, epilepsy).

880 Communication to the public should be a collaborative task undertaken by the industry, regulators and
881 public health organisations, with input from other stakeholders (see Module XII for collection of data on
882 information needs and public concerns and see Module XI for mechanisms for public participation).

883 The processes for planning and implementing safety communication at the level of marketing
884 authorisation holders and competent authorities described in Modules XII and XV apply and are
885 interlinked with the risk assessment and communication effectiveness evaluation processes also

886 described in these Modules. Communication interventions may be part of a risk management plan
887 | ([RMP](#)) (see [Modules V and XVI](#)). During the communication planning and implementing phases,
888 international collaboration (see [Module XIV](#)) should be facilitated as necessary. Special planning should
889 be undertaken in case of public health emergencies (see [Module I](#)) or pandemics.

890 Communication planning should include being prepared for frequent public communication needs, such
891 as those regarding excipients, residues, identified or potential risks for individuals with special
892 conditions, coincidental events, temporal versus causal association, a single case of an adverse event
893 rarely identified as a risk, safety monitoring requirements being different to identified risk, or the
894 mock-up concept not being related to an experimental/not tested/not authorised vaccine. For the
895 | purpose of quantifying safety concerns, relevant background rates, [by age group and sex](#), of signs and
896 symptoms which are also present in adverse events, whether known to be causally related, suspected
897 to be causally related or likely to be coincidental, should be kept up-to-date, as well as exposure data.
898 Communication planning should also include preparing standard texts. Frequently needed explanations
899 should be ideally tested by representatives of likely target audiences. Concerns raised by the public
900 should also be addressed by proactively communicating results of benefit-risk evaluations.

901 Competent authorities should ensure appropriate communication with the public and in particular the
902 media. Media monitoring should be especially conducted for vaccines. The media can play an important
903 role in influencing the public perception of vaccine safety, in both a negative and positive way, and
904 information to the media should be given in timely and meaningful manner (see [Module XII](#)). In this
905 respect, it is essential to maintain a high level of transparency on how regulatory decisions were
906 reached and on the roles and responsibilities of each stakeholder. In communication materials,
907 reference should be made to published documents.

908 **P.I.C. Operation of the EU network**

909 ***P.I.C.1. Roles and responsibilities***

910 Stakeholders involved in the process of vaccine pharmacovigilance in the EU include the target
911 population for the vaccine, consumers of vaccines (vaccinated persons and, in the case of paediatric
912 vaccination, their parents/carers), healthcare professionals, marketing authorisation
913 applicants/holders, sponsors of clinical trials, regulatory authorities, public health authorities
914 recommending vaccination programmes, the European Medicines Agency, the European Centre for
915 Disease Prevention and Control (ECDC) and the World Health Organization (WHO). Each stakeholder
916 has an important contribution to the vaccine pharmacovigilance process. Efficient collaboration
917 between stakeholders is particularly important in situations of mass vaccination where it is anticipated
918 that a large number of suspected reactions may be reported in a short period of time (e.g. during a
919 pandemic) and it is necessary to quickly assess potential safety issues and take regulatory decisions.
920 In such cases, collaborations should be established prior to the start of the vaccination programme to
921 identify source of data and agree on processes to exchange information.

922 All obligations laid down in Regulation (EC) No 726/2004 and Directive 2001/83/EC regarding roles and
923 responsibilities apply to vaccines.

924 **P.I.C.1.1. Vaccinated persons and parents/carers**

925 Vaccinated persons and their parents/carers may report a suspected adverse reaction to a healthcare
926 | professional or directly to the competent authorities in Member States or [to](#) the marketing
927 authorisation holder. Competent authorities in Member States should facilitate reporting, for example
928 through a web platform. They should encourage reporting of complete information on the vaccine and

929 the vaccination, including the invented name and batch number. This can be facilitated by providing
930 adequate and easily retrievable information at the time of vaccination, for example with a patient card.

931 **P.I.C.1.2. Healthcare professionals**

932 Healthcare professionals should follow national guidelines regarding the collection, recording and
933 reporting of suspected adverse reactions to vaccines, ~~and medically confirm the occurrence of any~~
934 ~~severe adverse event occurring after vaccination and reported by a vaccinated person or a~~
935 ~~patient/carer.~~ In vaccination programmes where ~~the a~~ physician diagnosing the adverse reaction was
936 not involved in the administration of the vaccine, this physician should document the product name,
937 batch number and other information relevant for the evaluation of the severe adverse event either
938 from information provided to the vaccinated person or the patient/carer, or by contacting the medical
939 centre or person that provided the vaccine. Any suspected adverse reaction should be reported to the
940 competent authorities in Member States according to national recommendations.

941 **P.I.C.1.3. Marketing authorisation holders**

942 Marketing authorisation holders may establish a specific pharmacovigilance system for vaccines (see
943 ~~Module I.C.1.~~).

944 Marketing authorisation holders should collect and record all available information regarding the
945 distribution of vaccine batches in Member States. ~~Marketing authorisation holders should make an~~
946 ~~effort to collect information on~~ and the numbers of doses of vaccines administered/distributed by
947 batch. They should also take appropriate measures in order to collect and collate all reports of
948 suspected adverse reactions associated with vaccines originating from unsolicited or solicited sources.
949 The definite identification of the concerned product with regard to its manufacturing is of particular
950 importance. Therefore, all appropriate measures should be taken to clearly identify the brandname of
951 the product and the batch number. Where necessary, attempts should be made to contact the patient
952 or healthcare professional reporting the adverse reaction (see ~~GVP Module VI.B~~ and Appendix 1 on the
953 identification of biological medicinal products). Marketing authorisation holders should communicate as
954 an emerging safety issue (see ~~Module VI.C.2.2.6~~) any safety concern related to the vaccine that may
955 impact on its benefit-risk profile.

956 Marketing authorisation holders should continuously maintain a high level of preparedness to quickly
957 document and investigate safety issues and batch-related issues, as precautionary measures may need
958 to be taken by competent authorities in absence of adequate information (see ~~P.I.B.1.3.2~~).

959 **P.I.C.1.4. Competent authorities in Member States**

960 National regulatory and public health authorities should collaborate for recording, collating, exchanging
961 and integrating all information relevant to the safety surveillance of vaccines. This includes information
962 on the distribution of vaccine batches within the Member States and vaccine exposure stratified by
963 batch, age and sex and in the target population (or other characteristics, e.g. pregnant women) where
964 possible. Where a registration system is in place, procedures should allow quick compilation and
965 analyses of data to estimate exposure. Information to be collected and exchanged also include
966 available data on incidence of diseases which may also be adverse events of the vaccine, reports of
967 adverse reactions and their assessment, results arising from specific surveillance programmes, clinical
968 or non-clinical investigations and post-authorisation studies, including safety and efficacy/effectiveness
969 studies, seroepidemiological studies and studies on circulating strains and strain replacement. If the
970 vaccine is anticipated to be used in vaccination programmes, attempts should be made before the start
971 of the vaccination to collect missing data, e.g. background incidence rates of adverse events of special

972 interest. Relevant data sources for vaccine efficacy/effectiveness and benefit-risk evaluation of the
973 vaccine should be identified and data availability should be explored, including possible use by
974 marketing authorisation holders.

975 National regulatory authorities should have in place a web-based reporting system of suspected
976 adverse reactions for patients and healthcare professionals, and should encourage these to provide
977 accurate information on invented names and batch numbers. They should establish channels for an
978 adequate communication to the public and play an important role in unbiased communication, in
979 particular in situations where there is a gap between results of scientific ~~analysis~~ analyses made by
980 experts and public concerns. National regulatory authorities should ensure that the public is given
981 important information on pharmacovigilance concerns relating to the use of the vaccines. Media should
982 receive timely and relevant information on the benefit-risk balance of vaccines.

983 National competent authorities should collaborate with the World Health Organisation in the field of
984 vaccine safety (see **Module XIV**).

985 **P.I.C.1.5. European Medicines Agency**

986 As for all medicinal products, the European Medicines Agency has the responsibility for coordinating the
987 existing scientific resources for the evaluation, supervision and pharmacovigilance for vaccines. It
988 supports Member States in these activities by operating and maintaining the infrastructure needed for
989 the surveillance of vaccines, such as EudraVigilance (see **Module VI**), EPITT (see **Module XII**), the EU
990 PAS register (see **Module VIII**) and by providing reaction monitoring reports to facilitate the monitoring
991 of EudraVigilance data (see **Module IX**). The Agency also facilitates the identification of relevant
992 networks and research groups in the EU in the view of conducting post-authorisation studies.²³

993 The Agency has the responsibility for EudraVigilance data monitoring, signal detection and signal
994 validation for centrally authorised vaccines and for active substances contained in several vaccines
995 where at least one is centrally authorised (see ~~Module IX-C.1~~).

996 For vaccines authorised in more than one Member State, the Agency is responsible for the coordination
997 between national competent authorities of safety announcements (see **P.I.C.5**). For centrally
998 authorised vaccines, the Agency publishes on the European medicines web-portal information including
999 a summary of the risk management plan (RMP), protocols and public abstracts of results of the post-
1000 authorisation safety studies imposed as an obligation and conclusions of assessments,
1001 recommendations, opinions and approvals and decisions taken by its scientific committees.

1002 See Module XIV for the agency's cooperation with the World Health Organization (WHO) on matters of
1003 pharmacovigilance and on transmission of information and suspected cases of adverse reactions to
1004 WHO. The EMA should collaborate with the European Centre for Disease Prevention and Control
1005 (ECDC) and the World Health Organization in order to monitor the efficacy/effectiveness of vaccines
1006 and collect information on their benefit-risk balance.

1007

1008 **P.I.C.2. Reporting of reactions and emerging safety issues**

1009 Reporting of suspected adverse reactions and emerging safety concerns should follow the guidance in
1010 **Module VI**. Communication of signals from EudraVigilance by marketing authorisation holders should
1011 follow the guidance of **Module IX**.

²³ See ENCePP website: <http://www.encepp.eu>.

1012 Reports of vaccination errors with no associated adverse reaction should not be reported as individual
1013 case safety reports. They should be considered in periodic safety update reports as applicable (see
1014 **Module VII**). When those reports and any suspected quality defect or batch-related issues constitute
1015 safety concerns which may impact on the benefit-risk balance of the medicinal product or representing
1016 a significant hazard to public health, they should be notified immediately in writing to the competent
1017 authorities in accordance with the recommendations provided in **Module VI**.

1018 When a batch-related issue is suspected, activities at the level of Agency and competent authorities in
1019 Member States may include as appropriate:

- 1020 • early distribution of information on the issue via the rapid alert system (see **Module XII**) to
1021 national competent authorities; this communication may include questions to Member States (e.g.
1022 on usage of the batch(es) and similar cases reported to the national competent authorities);
- 1023 • triggering of the incident management plan established in the EU ~~if considered necessary~~ (see
1024 **Module XIII**);
- 1025 • interactions with other European agencies, the WHO and non-EU national competent authorities ~~as~~
1026 appropriate (see **Module XIV**).

1027 Where a quality defect is suspected, marketing authorisation holders should follow the procedures
1028 explained on the EMA website²⁴ as well as the applicable national procedures.

1029 ***P.I.C.2.1. Reporting of vaccination failures***

1030 Cases of vaccination failures should be reported as cases of lack of therapeutic efficacy within 15 days,
1031 in particular with the view to highlight potential signals of reduced immunogenicity in a sub-group of
1032 vaccinated individuals, waning immunity or strain replacement. Such a signal may need prompt action
1033 and further investigation through post-authorisation studies as appropriate.

1034 ***P.I.C.3. Risk Management System***

1035 A RMP or an update, as applicable may be submitted at any time during a vaccine's life cycle, i.e.
1036 during both the pre-and post-authorisation phase (see **Module V.C.**). In addition, because a change to
1037 the manufacturing process of a biological product may potentially have an unpredictable impact on
1038 safety, situations where a RMP or RMP update may be required include a significant change in the
1039 marketing authorisation, including, on a case to case basis (depending on the nature of the changes),
1040 changes in the manufacturing process of ~~a the biotechnologically derived~~ vaccine. Therefore, any
1041 potential or theoretical impact on safety, and thereby the possible need to update the RMP, must be
1042 considered with any change to the manufacturing process of a vaccine in this situation.

1043 ***P.I.C.4. Signal management***

1044 Where a signal is based on a single report of a serious adverse event following vaccination, the signal
1045 should be validated by the signal identifier (see **Module IX.B.3.3** and **P.I.B.4**). The validation should be
1046 performed in collaboration with the PRAC Rapporteur or Lead Member State, if appropriate, to facilitate
1047 collection of contextual information. Where the report does not meet the criteria for signal validation, it
1048 should not be communicated as a confirmed signal to the PRAC by the PRAC Rapporteur or Lead
1049 Member State but should be tracked by the signal identifier and special attention should be paid to any
1050 follow-up information or other cases of the same adverse event (see **Module IX.C.1**). If a non-validated
1051 signal has to be shared with the EU regulatory network by a national competent authority for

²⁴ Available on EMA website <http://www.ema.europa.eu> under <http://www.ema.europa.eu/Inspections/Defects.html>.

1052 information or collection of additional data, it may be communicated to the network via a Non Urgent
1053 Information.

1054 Vaccines should be subject to additional monitoring if they have been authorised after 1 January 2011
1055 or at the request of the European Commission or the national competent authority where the optional
1056 scope for additional monitoring is applicable (see **Module X**). In such cases, the periodicity for the
1057 monitoring of data from EudraVigilance ~~will may be every 2 weeks~~ increased to every 2 weeks. for the
1058 duration of the additional monitoring. In some circumstances, more frequent monitoring ~~than every 2~~
1059 ~~weeks~~ may be proposed by national competent authority or the Agency. It should be targeted to a
1060 safety concern of interest especially during public health emergencies (e.g. pandemics) and may be
1061 applied in the context of custom queries conducted in the EudraVigilance Data Analysis System (see
1062 **Module IX**).

1063 ***P.I.C.5. Safety communication about vaccines in the EU***

1064 Further to the guidance in **P.I.B.6.**, the following should be considered for safety communications about
1065 vaccines in the EU. Operational details of communication processes may differ according to different
1066 scenarios of vaccine use among Member States and with regard to different vaccines. Also, benefit-risk
1067 perceptions may vary between Member States and cultures. Hence, these differences and variations
1068 should be accounted for during the EU-wide coordination of safety communication with consistent
1069 messages. Communication in the EU should be underpinned by transparency on how regulatory
1070 decisions were reached and on the roles and responsibilities of each stakeholder in the EU (see
1071 **P.I.C.1.**). Where special planning should be undertaken in case of public health emergencies or
1072 pandemics, the Agency and the national competent authorities should announce requirements and
1073 guidance for marketing authorisation holders ~~and competent authorities in Member States~~ on their
1074 ~~website and the~~ respective webportals.

1075 ***P.I.C.6. Transparency of pharmacovigilance for vaccines in the EU***

1076 The public summary of the RMP is to be made publicly available by the Agency for centrally authorised
1077 vaccines and by national competent authorities for nationally authorised vaccines [REG Art 26(1)(c),
1078 DIR Art 106(c)]. It should be written in lay language and considerations should be given to the target
1079 audience, ~~which that~~ might be different for a vaccine than for a usual medicinal product (e.g. general
1080 population vs. informed patient groups).

1081 ***P.I.C.7. Vaccines intended for markets outside the EU***

1082 In the context of the cooperation of Member States and the Agency with the World Health Organization
1083 (WHO) (see **Module XIV**), the Agency may give a scientific opinion for the evaluation of vaccines for
1084 human use intended exclusively for markets outside the EU [REG Art 58]. -Examples for this procedure
1085 include vaccines to be possibly used in the WHO Expanded Programme on Immunization, vaccines for
1086 protection against a WHO public health priority disease and vaccines that are part of a WHO managed
1087 stockpile for emergency response. Companies that acquire a marketing authorisation in a third country
1088 or are entitled to place the product on the market in a third country on the basis of the Agency's
1089 opinion should implement the pharmacovigilance activities specified in the procedure.²⁵

²⁵ European Medicines Agency. Article 58 applications: Regulatory and procedural guidance.
www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000157.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800240d1.