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4 **Guideline on influenza vaccines – submission and**
5 **procedural requirements**
6 Regulatory and procedural requirements module - Draft

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7
8 This module will replace the procedural requirements of the following guidelines:

- 9 • Procedural advice on the submission of variations for annual update of human influenza
10 inactivated vaccines applications in the centralised procedure (EMA/CHMP/BWP/99698/2007
11 Rev. 2)
- 12 • Guideline on submission of marketing authorisation applications for pandemic influenza
13 vaccines through the centralised procedure (EMA/CPMP/4986/03)

14

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

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Keywords	<i>Submission and procedural requirements, influenza vaccines, inactivated, LAIV, seasonal, pre-pandemic, pandemic, annual strain update, pandemic strain update</i>
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18 **procedural requirements**

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50 **1. Introduction (background)**

51 The need to update the current guidelines regarding the development of influenza vaccines was
52 recognised in the wake of the 2009-2010 influenza pandemic, as the Agency conducted its "*lessons*
53 *learned*" exercise. Since then, experience has also been gained through the evaluation of scientific
54 advice and marketing authorisation applications for influenza vaccines.

55 As announced in the Concept paper,¹ the revision of the guidelines on influenza vaccines has been
56 organised with the aim of developing a consolidated influenza guideline that covers the regulatory,
57 quality, non-clinical and clinical aspects of influenza vaccine development and dossier submission. The
58 present module compiles with the regulatory and procedural requirements for the different types of
59 influenza vaccines, in line with the scope described under section 2.

60 Subject to the eligibility criteria, marketing authorisation applications for influenza vaccines can be
61 submitted either at centralised or national level. The centralised procedure is mandatory where the
62 application falls within the scope of the Annex of Regulation (EC) No 726/2004, in particular where the
63 vaccine virus has been prepared using one of the techniques mentioned in the Annex, e.g. reverse
64 genetics.

65 This guideline lays down the procedural aspects related to the submission of marketing authorisation
66 applications for influenza vaccines and subsequent updates of vaccine composition in the centralised
67 procedure.

68

69 **2. Scope**

70 This module provides guidance on marketing authorisation applications and subsequent updates of
71 vaccine composition for influenza vaccines in the centralised procedure to be used in seasonal, pre-
72 pandemic or pandemic settings.

73

74 **3. Legal basis and relevant guidelines**

75 This module should be read in conjunction with Directive 2001/83/EC and its Annex I ; Regulation (EC)
76 No 726/2004 ; Regulation (EC) No 1234/2008 and [Chapter 5 of the Notice to Applicants](#).

77 This module should also be read in conjunction with the corresponding scientific guidelines on influenza
78 vaccines and the European Pharmacopoeia.

79

80 **4. Regulatory and procedural requirements for influenza** 81 **vaccines**

82 **4.1. Seasonal influenza vaccines**

83 This section provides an overview of the procedures that would apply to a marketing authorisation
84 application (MAA) for this type of product and for subsequent strain changes.

¹ [Concept paper on the revision of guidelines for influenza vaccines](#)

85 **4.1.1. Requirements for marketing authorisation application**

86 A MAA for a seasonal influenza vaccine can be submitted to the Agency, upon confirmation of eligibility
87 to the centralised procedure. For any seasonal vaccines manufactured by means of one of the
88 techniques mentioned in the Annex of Regulation (EC) No 726/2004, e.g. reverse genetics, the use of
89 the centralised procedure is mandatory.

90 Submission of a new seasonal vaccine is expected to be based upon a comprehensive dossier. The
91 Notice to Applicants, Volume 2B on the Presentation and format of the dossier Common Technical
92 Document (CTD) should be followed.

93 A standard evaluation process is intended to be followed, unless a request for accelerated assessment
94 is justified by the applicant and accepted by the CHMP. Once adopted by the CHMP, the opinion is
95 forwarded to the Commission for the decision-making process.

96 Applicants are advised to consult the relevant aspects of the pre-authorisation procedural advice on
97 the submission of centralised MAAs as published on the Agency website, with regard to practical
98 aspects such as the number of applications or the fees.

99 **4.1.2. Requirements for applications to change vaccine composition** 100 **(seasonal strain update)**

101 ***4.1.2.1. Selection of the seasonal strains in the EU***

102 Seasonal influenza vaccines for human use authorised via the centralised procedure may be varied
103 annually according to Article 18 of Regulation (EC) No 1234/2008 in order to update their strain
104 composition in preparation for the influenza season.

105 Twice a year, typically in February for the northern hemisphere and in September for the southern
106 hemisphere, WHO recommends the influenza A and B virus strains which should be used for the
107 production of seasonal vaccine for the coming influenza season. However, there remains flexibility
108 within these recommendations to take into consideration the specificities of the epidemiological
109 situation in the European Union and to adapt these recommendations as appropriate. In this respect,
110 the European Medicines Agency (hereinafter the 'Agency') publishes every year, usually in March, an
111 EU recommendation, including the recommended reassortants for the manufacture of seasonal
112 influenza vaccines.

113 Based on the EU recommendation, any strain replacements for authorised vaccines are approved via
114 the procedure described in Section 4.1.2.2 (see section on seasonal strain update; quality and clinical
115 modules of the influenza guideline).

116 ***4.1.2.2. Details of the procedure***

117 The variation application should be submitted as a type II B.I.a.5 by the recommended target annual
118 deadline, which will be published every year together with the EU annual strain(s) recommendations
119 on the EMA website. The guideline on the details of the various categories of variations to the terms of
120 marketing authorisations for medicinal products for human use and the Notice to Applicants, Volume
121 2B on the Presentation and format of the dossier Common Technical Document (CTD) should be
122 followed.

123 The content of the application is defined in Annex I of this module. No changes other than the ones
124 related to the new strains may be introduced in the product information.

125 Applicants are advised to consult the post-authorisation procedural advice on the handling of variations
126 as published on the Agency website, with regard to some practical aspects such as the number of
127 applications or the fees.

128 The scope of the variation to be mentioned in the variation application form is “annual update of Union
129 human influenza vaccine strain(s)”.

130 In accordance with Article 18 of Commission Regulation (EC) No 1234/2008, a ‘two step’ approach
131 submission is foreseen i.e. submission of the quality documentation, followed, if necessary, by the
132 submission of additional data:

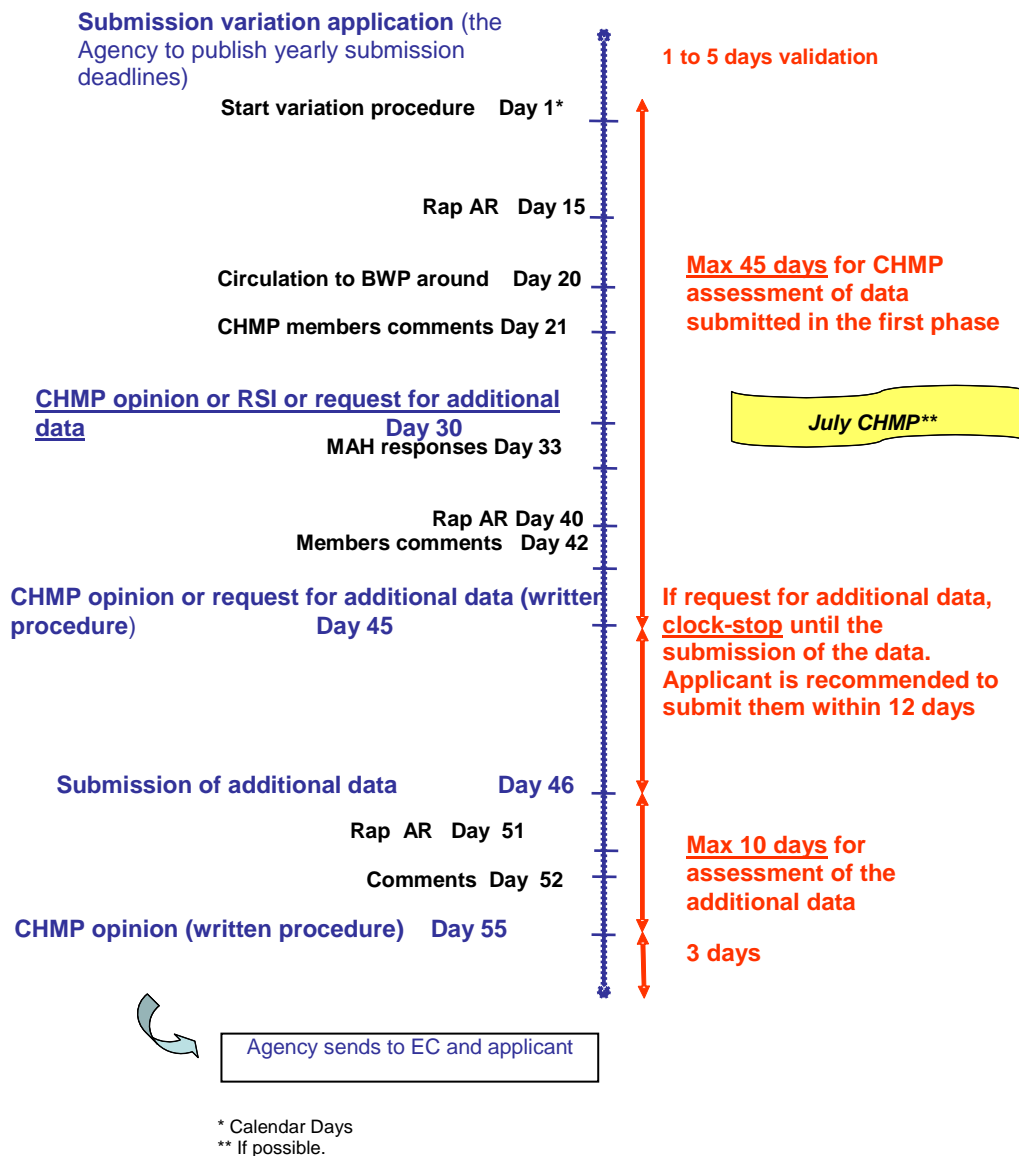
- 133 • First step: within 45 days of the validation, the CHMP adopts an opinion to approve or refuse the
134 variation application or the CHMP suspends the procedure (clock-stop) by adopting a request for
135 additional data A request for supplementary information (RSI) without suspending the procedure
136 may be issued at D30.
- 137 • Second step: where a request for additional data has been adopted, the marketing authorisation
138 holder (MAH) is recommended to submit these additional data within 12 days from the adoption of
139 the request for additional data. Upon receipt of this data, the procedure is restarted and the CHMP
140 adopts an opinion within 10 days.

141 Within 3 days from the adoption of the opinion, the Agency sends the opinion to the MAH and the
142 European Commission. This will be followed by a Commission decision to amend the terms of the
143 marketing authorisation.

144 MAHs are advised to liaise with the Agency in advance of the submission of the variation, especially in
145 view of possible deviation from the recommended deadlines.

146

Fast track procedure for human influenza vaccines annual strain(s) update



147

148

149 **4.2. Pre-pandemic (zoonotic) influenza vaccines**

150 **4.2.1. Requirements for marketing authorisation application for a pre-**
 151 **pandemic (zoonotic) influenza vaccine**

152 Zoonotic influenza vaccines (also known as pre-pandemic vaccines) are intended for immunisation in
 153 the context of outbreaks of zoonotic influenza viruses with pandemic potential, including use when
 154 there is anticipation of a possible pandemic due to the same or a similar strain.

155 A MAA for a zoonotic influenza vaccine can be submitted to the Agency, upon confirmation of eligibility
156 to the centralised procedure. For any zoonotic vaccines manufactured by means of one of the
157 techniques mentioned in the Annex of Regulation (EC) No 726/2004, e.g. reverse genetics, the use of
158 the centralised procedure is mandatory.

159 Submission of a new pre-pandemic vaccine is expected to be based upon a comprehensive dossier. The
160 Notice to Applicants, Volume 2B on the Presentation and format of the dossier Common Technical
161 Document (CTD) should be followed.

162 A standard evaluation process is intended to be applied, unless a request for accelerated assessment is
163 justified by the applicant and accepted by the CHMP. Once adopted by the CHMP, the opinion is
164 forwarded to the Commission for the decision-making process.

165 Applicants are advised to consult the relevant aspects of the pre-authorisation procedural advice on
166 the submission of centralised MAA as published on the Agency website, with regard to practical aspects
167 such as the number of applications or the fees.

168 **4.2.2. Requirements for applications to change vaccine composition** 169 **(zoonotic strain change)**

170 Replacement of the vaccine virus in a zoonotic influenza vaccine should be processed via a type II
171 B.I.a.5 variation application.

172 The Notice to Applicants, Volume 2B on the Presentation and format of the dossier Common Technical
173 Document (CTD) should be followed.

174 Applicants are advised to consult the relevant aspects of the post-authorisation procedural advice on
175 the handling of variations as published on the Agency website, with regard to some practical aspects
176 such as the number of applications or the fees.

177

178 **4.3. Pandemic influenza vaccines**

179 **4.3.1. Marketing authorisation granted prior to the recognition of a** 180 **pandemic situation ('pandemic preparedness vaccine')**

181 In order to prepare for a pandemic situation, applicants are recommended to submit a marketing
182 authorisation application for a pandemic vaccine containing a strain with pandemic potential (so-called
183 'pandemic preparedness vaccine').

184 This type of vaccine is based on the concept formerly known as 'mock-up' that mimics the future
185 pandemic influenza vaccine in having the same manufacture and control and being of the same
186 construct, notably the antigen content, excipients and adjuvant system.

187 The marketing authorisation application should be supported by a 'core pandemic dossier' including
188 data on the potential pandemic strain(s) (see relevant modules for data requirements). When a
189 pandemic situation is duly recognised by the WHO or the Union, the MAH should submit a variation
190 application ('pandemic strain update') *as per* Article 21 of Regulation (EC) No 1234/2008 to include the
191 declared pandemic strain in the pandemic vaccine ('pandemic strain update'). This variation will be
192 reviewed under an accelerated timeframe.

193 'Pandemic preparedness vaccines' are indicated for immunization against potential pandemic strain(s)
194 once an official pandemic declaration in the EU has been recognized and after that the variation to
195 include the declared pandemic strain has been authorised.

196 **4.3.1.1. Requirements for marketing authorisation application**

197 Once eligibility to the centralised procedure is confirmed, the applicant can submit an application
198 supported by a 'core pandemic dossier' which will include data on relevant strain(s) (see relevant
199 modules for data requirements).

200 It is expected that a comprehensive dossier could not be generated outside a pandemic situation. A
201 submission of a MAA based on a non-comprehensive dossier under the conditional marketing
202 authorisation may therefore be considered if the applicant is likely to be in a position to provide the
203 comprehensive clinical data after the declaration of a pandemic and if other requirements laid down in
204 Regulation (EC) No 507/2006 are fulfilled ; an appropriate justification on the regulatory framework
205 claimed, the type of data missing and whether these data could be generated should then be included
206 in the dossier.

207 A standard evaluation process is intended to be applied, unless a request for accelerated assessment is
208 justified by the applicant. Once adopted by the CHMP, the opinion is forwarded to the Commission for
209 the decision-making process.

210 Applicants are encouraged to liaise with the European Commission before the grant of the marketing
211 authorisation to request an exemption to the obligation to place the product on the Union market
212 within three years (so-called 'sunset clause'). The MAH should provide a justification based on public
213 health grounds and explaining the exceptional circumstances. A copy of the request should be
214 addressed to the European Medicines Agency.

215 The Notice to Applicants, Volume 2B on the Presentation and format of the dossier Common Technical
216 Document (CTD) should be followed.

217 Applicants are advised to consult the relevant aspects of the pre-authorisation procedural advice on
218 the submission of centralised MAA as published on the Agency website, with regard to some practical
219 aspects such as the number of applications.

220 Special fees incentives apply for applications based on a 'core pandemic dossier.' The [Explanatory note](#)
221 [on fees](#) available on the Agency website should be consulted.

222 In case such application is envisaged, it is recommended to initiate discussions with competent
223 authorities as early as possible.

224 **4.3.1.2. Requirements for applications to change vaccine composition (pandemic strain** 225 **change) during a pandemic situation**

226 Where a pandemic situation is duly recognised by the WHO or the Union, a variation application may
227 be accepted to include the declared pandemic strain in the pandemic vaccine ('pandemic strain
228 update'), if appropriate.

229 *As per* Article 21 of Regulation (EC) No 1234/2008, it may be exceptionally and temporarily acceptable
230 that certain non-clinical or clinical data are missing. In the latter, the MAH will have to submit the
231 missing non-clinical and clinical data within the time limit set in the marketing authorisation.

232 The Notice to Applicants, Volume 2B on the Presentation and format of the dossier Common Technical
233 Document (CTD) should be followed.

234 Applicants are advised to consult the relevant aspects of the pre-authorisation procedural advice on
235 the handling of variations as published on the Agency website, with regard to some practical aspects
236 such as the number of applications.

237 Special fees incentives apply for applications based on a 'core pandemic dossier'. The [Explanatory note](#)
238 [on fees](#) should be consulted.

239 A pandemic variation will be assessed following an accelerated timetable. It is emphasised that an
240 efficient interaction with the EMA Pandemic Task Force (ETF) to discuss critical issues in advance of the
241 submission would be essential to allow acceleration of the variation procedure.

242 Once adopted by the CHMP, the opinion is forwarded to the Commission for the decision-making
243 process which may be accelerated as appropriate.

244 The post-authorisation procedures to submit the missing data and to vary the terms of the marketing
245 authorisation may be reviewed under an accelerated timeframe if appropriate.

246

247 **4.3.2. Marketing authorisation submitted during a pandemic situation**

248 **4.3.2.1. 'Emergency procedure'**

249 It may become necessary to authorise a new pandemic vaccine in a pandemic situation duly
250 recognised by the WHO or the Union.

251 It is expected that it may be difficult to generate a comprehensive dossier at the time of the MAA. A
252 submission of a MAA based on a non-comprehensive dossier under the conditional marketing
253 authorisation may therefore be considered if the applicant is likely to be in a position to provide the
254 comprehensive clinical data after the declaration of a pandemic and if other requirements laid down in
255 Regulation (EC) No 507/2006 are fulfilled; an appropriate justification on the regulatory framework
256 claimed, the type of data missing and whether these data could be generated should then be included
257 in the dossier.

258 The Notice to Applicants, Volume 2B on the Presentation and format of the dossier Common Technical
259 Document (CTD) should be followed.

260 If a MAA for a pandemic vaccine is submitted in such circumstances, the evaluation will be accelerated
261 as appropriate.

262 Once adopted, the opinion will be forwarded to the Commission for the decision-making process, which
263 will also be accelerated as appropriate.

264 Applicants are advised to consult the relevant aspects of the pre-authorisation procedural advice on
265 the submission of centralised MAA as published on the Agency website, with regard to practical aspects
266 such as the number of applications.

267 In case such application is envisaged, the applicant is recommended to initiate discussions with the
268 competent authorities as early as possible.

269 **4.3.2.2. Other routes of authorisation for a pandemic vaccine**

270 In exceptional circumstances, depending on the emergency of the situation and where no 'pandemic
271 preparedness vaccine' is already authorised for a specific vaccine construct, variations of a relevant

272 seasonal or pre-pandemic influenza vaccine, based on Article 21 of Regulation (EC) No 1234/2008,
273 may be considered during a pandemic, if feasible from a regulatory and scientific perspective.

274 In case such an exceptional situation is envisaged, it is recommended to initiate discussions with
275 competent authorities as early as possible, in particular to discuss the modalities and particulars of
276 these applications.

277

278 5. Annex 1 – Seasonal strain change ('Annual update')

279 5.1. Variation application(s) content

280 IMPORTANT REMARK

281 **Only changes related to the new strains used may be introduced. No other changes are**
282 **allowed to be processed via the 'fast track' procedure.**
283

284

285 The variation should be submitted as a type II variation as stated in the guideline on the details of the
286 various categories of variations to the terms of marketing authorisations for medicinal products for
287 human use and should contain the documentation described below. , by the **Agency recommended**
288 **target annual deadline**, which will be **published every year together with the EU Annual**
289 **strain(s) recommendations**.

290 The variation application should follow the EU recommendations of the Notice to Applicants, Volume 2B
291 on the Presentation and format of the dossier Common Technical Document (CTD).

292 Please note that only relevant sections of the CTD corresponding to the supporting data for the
293 variation application should be submitted. Any absence of a study/test report requires a justification in
294 the appropriate summary/overview.

295 5.1.1. First step submission – quality

296 The supporting documentation described below should be included within the variation application. Any
297 deviation (absence of data or additional data) should be justified and discussed with the competent
298 authorities before the submission of the application.

299 **Module 1: - Administrative Information and Prescribing Information**

300 **1.0** Cover Letter

301 **1.1** Comprehensive Table of Contents (not required if submitted in eCTD format)

302 **1.2** Application Form (European Variation Application Form as published in the NTA, Volume 2C).

303 **1.3** Product Information

304 **1.3.1** SmPC, Labelling and Package Leaflet

305 Note: Only changes related to the strains used for the season may be introduced in these
306 texts.

307 **1.4** Information about the Quality Expert:

308 The relevant expert declaration(s) and signature must be provided, corresponding to the
309 quality overall summary submitted in Module 2.

310 **Module 2: Common Technical Document Summaries**

311 **2.1** CTD Table of Contents (Module 2 – 3) (not required if submitted in eCTD format)

312 **2.2** CTD Introduction

313 **2.3** Quality Overall Summary (addendum to "previous" Quality Overall Summary)

314

315 **Module 3: Chemical-pharmaceutical and biological information for chemical active** 316 **substances and biological products**

317

318 **3.2.S.2** Manufacture

319 **3.2.S.2.3** Control of Materials

320 - seed lots: history:

321 - passage level

322 - characterisation of Haemagglutinin and Neuraminidase

- 323 - analytical protocols (including test results on seed lots)*
 324
 325 **3.2.S.2.4** Control of Critical Steps and Intermediates
 326 **3.2.S.2.5** Process validation and/or evaluation
 327 - monovalent bulks:
 328 - manufacturing process strain specific changes
 329 - validation of critical manufacturing steps (new strain)
 330 1. inactivation
 331 2. splitting efficiency
 332
 333 **3.2.S.4.1** Specification (copy of approved specifications in a tabular format)
 334 **3.2.S.4.2** Analytical procedures
 335 **3.2.S.4.3** Validation of analytical procedures (validation of SRD test for new strains)
 336 **3.2.S.4.4** Batch analysis results of monovalent bulks: results (including test for neuraminidase)
 337 of the first three monovalent bulks from
 338 - each working seed lot of a new master seed lot of new strains
 339 - each working seed lot from previously approved master seed lot where the procedure
 340 of working seed lot preparation is different from the approved procedure
 341 **3.2.S.7** Drug Substance: Stability (Stability tests on the active substances: results from
 342 monovalent bulks where they are used for more than one year)
 343 **3.2.P.1** Composition
 344 **3.2.P.2.2.1** Pharmaceutical development: formulation development (actual formula (new season's
 345 strains) and Certificate of Analysis of batch(es) used in clinical trial(s) when available
 346 (either in quality or in clinical submission)
 347 **3.2.P.3.2** Batch formula (actual formula)
 348 **3.2.P.5.1** Specifications (Copy of approved specifications and routine tests analytical methods in
 349 a tabular format)
 350 **3.2.P.5.3** Validation of analytical procedures; validation of SRD test for new strains (either using
 351 trivalent bulk or drug product)
 352 **3.2.P.8** Drug Product: Stability
 353 - Stability data from previous season
 354 - Stability commitment(s)
 355 - Post-approval stability protocol for the final lot Stability
 356

357 * Note: Where the seed virus is tested for extraneous agents using PCR, and if further to discussion
 358 with the Agency and rapporteurs the need for additional PCR testing of the seed has been agreed,
 359 these data should be included in this application.

360 **5.1.2. Second step submission –additional data requested**

361 Relevant sections of the CTD variation application should be submitted depending on the type of
 362 additional data submitted.

363 **Module 1: - Administrative Information and Prescribing Information**

- 364 **1.0** Cover Letter
 365 **1.1** Comprehensive Table of Contents (not required if submitted in eCTD format)
 366 **1.4** Information about the Expert(s):
 367 The relevant expert declaration(s) and signature(s) must be provided, corresponding to the
 368 Summary submitted in Module 2

369 **Module 2: Common Technical Document Summaries**

- 370 **2.1** CTD Table of Contents (Module 2 – 5) (not required if submitted in eCTD format)
 371 **2.2** CTD Introduction
 372 **2.3** Quality Overall Summary (revised to first addendum to Quality Overall Summary), if
 373 appropriate
 374 **2.5** Clinical Overview (addendum to the previous Clinical Overview), if appropriate
 375 **2.7** Clinical Summary (addendum to the previous Clinical Summary), if appropriate
 376

377 **Module 3, 4, 5**

378 To be submitted if additional data on quality, non-clinical* and/or clinical* data were requested.

379 * *In principle, there is no need to provide clinical data to support seasonal strain updates. Vaccine*
380 *performance should be monitored by means of product-specific effectiveness studies and enhanced*
381 *safety surveillance. The reactogenicity profile of influenza vaccines after annual strain updates should*
382 *be investigated in the population indicated for each vaccine (including children if applicable) in order*
383 *to confirm acceptable tolerability of the newly recommended strain(s). For details, see Guideline on*
384 *influenza vaccines, non-clinical and clinical module (EMA/CHMP/VWP/457259/2014).*