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3 Committee for Medicinal Products for Human Use (CHMP)

4 **Guideline on the requirements for quality documentation**
5 **concerning biological investigational medicinal products in**
6 **clinical trials**

7 Draft

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10 from the European Commission, to facilitate the implementation of Regulation (EU) No. 536/2014

11

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

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14 Guideline on the requirements for quality documentation
15 concerning biological investigational medicinal products in
16 clinical trials

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57 **1. Introduction (background)**

58 ***1.1. Objectives of the guideline***

59 The following guideline is to be seen in connection with Regulation (EU) No. 536/2014 on clinical trials
60 on medicinal products for human use, and repealing Directive 2001/20/EC, which came into force on
61 June 20, 2014

62 Since clinical trials can be designed as multi-centre studies potentially involving different Member
63 States, it is the aim of this guideline to define harmonised requirements for the documentation to be
64 submitted throughout the European Union.

65 Most available guidelines on the quality of biological / biotechnological medicinal products address
66 quality requirements for marketing authorisation applications. Whilst these guidelines may not be fully
67 applicable in the context of a clinical trial application, the principles outlined are applicable and should
68 be taken into consideration during product development. The guidelines on Virus safety evaluation of
69 biotechnological investigational medicinal products (EMA/CHMP/BWP/398498/05) and Strategies to
70 identify and mitigate risks for first-in-human clinical trials with investigational medicinal products
71 (EMA/CHMP/SWP/28367/07) should also be consulted.

72 Assuring the quality of biological medicinal products is challenging, as they often consist of a number
73 of product variants and process related impurities whose safety and efficacy profiles are difficult to
74 predict. However, unlike chemical entities, toxic impurities are generally not an issue, and the safety
75 issues of biological / biotechnological products are more often related to the mechanism of action of
76 the biological product or to immunogenicity.

77 In the context of an overall development strategy, several clinical trials, using products from different
78 versions of the manufacturing process, may be initiated to generate data to support a Marketing
79 Authorisation Application. The objective of this document is to address the quality requirements of an
80 investigational medicinal product for a given clinical trial and not to provide guidance on a Company's
81 overall development strategy for a medicinal product.

82 Nevertheless, for all clinical development phases, it is the responsibility of the applicant (sponsor) to
83 ensure protection of the clinical trial subjects using a high quality investigational medicinal product
84 (IMP) that is suitable for its intended purpose, and to appropriately address those quality attributes
85 that may impair patients' safety (e.g. microbiological aspects, viral contamination, dose).

86 Due to the diversity of products to be used in the different phases of clinical trials, the requirements
87 defined in this guideline can only be taken as illustrative and are not presented as an exhaustive list.
88 IMPs based on innovative and/or complex technologies may require a more detailed data package for
89 assessment.

90 ***1.2. Scope***

91 This guideline addresses the specific documentation requirements on the biological, chemical and
92 pharmaceutical quality of IMPs containing biological / biotechnology derived substances.

93 Moreover, this guideline lists, as regards documentation on the biological, chemical and pharmaceutical
94 quality of the IMP, examples of modifications which are typically considered as 'substantial'.

95 The guidance outlined in this document applies to proteins and polypeptides, their derivatives, and
96 products of which they are components (e.g. conjugates). These proteins and polypeptides are
97 produced from recombinant or non-recombinant cell-culture expression systems and can be highly
98 purified and characterised using an appropriate set of analytical procedures. The guideline also applies
99 to Auxiliary Medicinal Products containing these proteins and polypeptides as active substances. The
100 requirements depend on the type of the product (authorised / not authorised / modified / non-modified
101 medicinal product).

102 The principles may also apply to other product types such as proteins and polypeptides isolated from
103 tissues and body fluids.

104 Advanced Therapy Medicinal Products are excluded from this guideline.

105 **1.3. General points concerning all IMPs**

106 IMPs should be produced in accordance with the principles and the detailed guidelines of good
107 manufacturing practices for medicinal products (The rules governing medicinal products in the
108 European Community, Volume IV).

109 **1.4. Submission of data**

110 The investigational medicinal product dossier (IMPD) should be provided in a clearly structured format
111 following the CTD format of Module 3 and include the most up-to-date available information relevant to
112 the clinical trial at time of submission of the clinical trial application.

113 If the active substance used is already authorised in a finished product within the EU/EEA or in one of
114 the ICH regions reference can be made to the valid marketing authorisation. However, depending on
115 the nature of the product additional information might be necessary. A statement should be provided
116 that the active substance has the same quality as in the approved product.

117 The name of the finished product, the marketing authorisation number or its equivalent, the marketing
118 authorisation holder and the country that granted the marketing authorisation should be given.
119 (Reference is made to Table 1 of Regulation 536/2014)

120 **2. Information on the biological, chemical and** 121 **pharmaceutical quality concerning biological investigational** 122 **medicinal products in clinical trials**

123 **S Active substance**

124 Reference to an Active Substance Master File or a Certificate of Suitability (CEP) of the European
125 Directorate for the Quality of Medicines is neither acceptable nor applicable for biological /
126 biotechnological active substances.

127 **S.1. General information**

128 **S.1.1. Nomenclature**

129 Information concerning the nomenclature of the active substance (e.g. recommended International
130 Non-Proprietary Name (INN), pharmacopoeial name, proprietary name, company code, other names or
131 codes, if any) should be given.

132 **S.1.2. Structure**

133 A brief description of the predicted structure should be provided. Higher order structure, schematic
134 amino acid sequence indicating glycosylation sites or other post-translational modifications and relative
135 molecular mass should be included, as appropriate.

136 **S.1.3. General properties**

137 A list of physico-chemical and other relevant properties of the active substance should be provided
138 including biological activity (i.e. the specific ability or capacity of a product to achieve a defined
139 biological effect). The proposed mechanism of action should be discussed.

140 **S.2. Manufacture**

141 **S.2.1. Manufacturer(s)**

142 The name(s) and address(es) and responsibilities of each manufacturer, including contractors, and
143 each proposed production site or facility involved in manufacture, testing and batch release should be
144 provided.

145 **S.2.2. Description of manufacturing process and process controls**

146 The manufacturing process and process controls should be adequately described. The manufacturing
147 process typically starts with one or more vials of the cell bank and includes cell culture, harvest(s),
148 purification, modification reactions and filling. Storage and shipping conditions should be outlined.

149 A flow chart of all successive steps including relevant process parameters and in-process-testing
150 should be given. The control strategy should focus on safety relevant in-process controls (IPCs) and
151 acceptance criteria for critical steps (e.g. ranges for process parameters of steps involved in virus
152 removal) should be established for manufacture of phase I/II material. These in-process controls
153 (process parameters and in process testing as defined in ICH Q11) should be provided with action
154 limits or preliminary acceptance criteria. For other IPCs, monitoring might be appropriate and
155 acceptance criteria or action limits do not need to be provided. Since early development control limits
156 are normally based on a limited number of development batches, they are inherently preliminary.
157 During development, as additional process knowledge is gained, further details of IPCs should be
158 provided and acceptance criteria reviewed.

159 Batch(es) and scale should be defined, including information on any pooling of harvests or
160 intermediates.

161 Any reprocessing during manufacture of the active substance (e.g. filter integrity test failure) should
162 be described and justified. Reprocessing could be considered in exceptional circumstances. For
163 biological products, these situations are usually restricted to certain re-filtration and re-concentration
164 steps upon technical failure of equipment or mechanical breakdown of a chromatography column.

165 **S.2.3. Control of materials**

166 **Raw and starting materials**

167 Materials used in the manufacture of the active substance (e.g. raw materials, starting materials, cell
168 culture media, growth factors, column resins, solvents, reagents) should be listed identifying where
169 each material is used in the process. Reference to quality standards (e.g. compendial monographs or
170 manufacturers' in-house specifications) should be made. Information on the quality and control of non-
171 compendial materials should be provided. Information demonstrating that materials (including
172 biologically-sourced materials, e.g. media components, monoclonal antibodies, enzymes) meet
173 standards applicable for their intended use should be provided, as appropriate.

174 For all raw materials of human or animal origin (including those used in the cell bank generation), the
175 source and the respective stage of the manufacturing process where the material is used should be
176 indicated. Summaries of safety information on adventitious agents for these materials should be
177 provided in Appendix A.2.

178 **Source, history and generation of the cell substrate**

179 A brief description of the source and generation (flow chart of the successive steps) of the cell
180 substrate, analysis of the expression vector used to genetically modify the cells and incorporated in the
181 parental / host cell used to develop the Master Cell Bank (MCB), and the strategy by which the
182 expression of the relevant gene is promoted and controlled in production should be provided, following
183 the principles of ICH Q5D.

184 **Cell bank system, characterisation and testing**

185 A MCB should be established prior to the initiation of phase I trials. It is acknowledged that a Working
186 Cell Bank (WCB) may not always be established.

187 Information on the generation, qualification and storage of the cell banks is required. The MCB and/or
188 WCB if used should be characterised and results of tests performed should be provided. Clonality of the
189 cell banks should be addressed for mammalian cell lines. The generation and characterisation of the
190 cell banks should be performed in accordance with the principles of ICH Q5D.

191 Cell banks should be characterised for relevant phenotypic and genotypic markers so that the identity,
192 viability, and purity of cells used for the production are ensured.

193 The nucleic acid sequence of the expression cassette including sequence of the coding region should be
194 confirmed prior to the initiation of clinical trials.

195 As for any process change, the introduction of a WCB may potentially impact the quality profile of the
196 active substance and comparability should be considered (see section S.2.6. Manufacturing process
197 development).

198 The safety assessment for adventitious agents and qualification of the cell banks used for the
199 production of the active substance should be provided in A.2, if appropriate.

200 **Cell substrate stability**

201 Any available data on cell substrate stability should be provided.

202 **S.2.4. Control of critical steps and intermediates**

203 Tests and acceptance criteria for the control of critical steps in the manufacturing process should be
204 provided. Cross reference to section S 2.2 might be acceptable for acceptance criteria or action limits.
205 It is acknowledged that due to limited data at an early stage of development (phase I/II) complete
206 information may not be available. Hold times and storage conditions for process intermediates should
207 be justified and supported by data, if relevant.

208 **S.2.5. Process validation**

209 Process validation data should be collected throughout development, although they are not required to
210 be submitted in the IMPD.

211 For manufacturing steps intended to remove or inactivate viral contaminants, the relevant information
212 should be provided in the section A2, Adventitious agents safety evaluation.

213 **S.2.6. Manufacturing process development**

214 **Process improvement**

215 Manufacturing processes and their control strategies are continuously being improved and optimised,
216 especially during the development phase and early phases of clinical trials. Changes to the
217 manufacturing process and controls should be summarized. This description should allow a clear
218 identification of the process versions used to produce each batch used in non-clinical and clinical
219 studies, in order to establish an appropriate link between pre-change and post-change batches.
220 Comparative flow charts and/or list of process changes may be used to present the process evolution.
221 If process changes are made to steps involved in viral clearance, justification should be provided as to
222 whether a new viral clearance study is required, or whether the previous study is still applicable.

223 **Comparability exercise**

224 Depending on the consequences of the change introduced and the stage of development, a
225 comparability exercise may be necessary to demonstrate that the change would not adversely impact
226 the quality of the active substance. In early phases the main purpose of this exercise is to provide
227 assurance that the post-change product is suitable for the forthcoming clinical trials and that it will not
228 raise any concern regarding safety of the patients included in the clinical trial. In addition, for later
229 phases, it should be assessed if the post-change material could impact the efficacy of the IMP.

230 This comparability exercise should normally follow a stepwise approach, including comparison of
231 quality attributes of the active substance and relevant intermediates, using suitable analytical
232 methods. Analytical methods usually include routine tests, and may be supplemented by additional
233 characterisation tests (including orthogonal methods), as appropriate. Where the manufacturers'
234 accumulated experience and other relevant information are not sufficient to assess the risk introduced

235 by the change, or if a potential risk to the patients is anticipated, a comparability exercise based only
236 on quality considerations may not be sufficient. During early phases of non-clinical and clinical studies,
237 comparability testing is generally not as extensive as for an approved product. In the case of first in
238 human clinical trials, an IMP representative of the material used in non-clinical studies should be used
239 (see Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with
240 investigational medicinal products (EMA/CHMP/SWP/28367/07)).

241 **S.3. Characterisation**

242 **S.3.1. Elucidation of structure and other characteristics**

243 Characterisation of a biotechnological or biological substance (which includes the determination of
244 physico-chemical properties, biological activity, immuno-chemical properties, purity and impurities) by
245 appropriate techniques is necessary to allow a suitable specification to be established. Reference to
246 literature data only is not acceptable, unless otherwise justified by prior knowledge from similar
247 molecules for modifications where there is no safety concern (e.g. C-terminal lysine for monoclonal
248 antibodies). Adequate characterisation should be performed in the development phase prior to phase I
249 and, where necessary, following significant process changes.

250 All relevant information available on the primary, secondary and higher-order structure including post-
251 translational (e.g. glycoforms) and other modifications of the active substance should be provided.
252 Details should be provided on the biological activity (i.e. the specific ability or capacity of a product to
253 achieve a defined biological effect). Usually, prior to initiation of phase I studies, the biological activity
254 should be determined using an appropriate, reliable and qualified method. Lack of such an assay
255 should be justified. It is recognised that the extent of characterisation data will increase during
256 development.

257 The rationale for selection of the methods used for characterisation should be provided and their
258 suitability should be justified.

259 **S.3.2. Impurities**

260 Process related impurities (e.g. host cell proteins, host cell DNA, media residues, column leachables)
261 and product related impurities (e.g. precursors, cleaved forms, degradation products, aggregates)
262 should be addressed. Quantitative information on impurities should be provided including maximum
263 amount for the highest clinical dose. For certain process-related impurities (e.g. antifoam agents), an
264 estimation of clearance may be justified.

265 In case only qualitative data are provided for certain impurities, this should be justified.

266 **S.4. Control of the active substance**

267 When process validation data are incomplete, the quality attributes used to control the active
268 substance are important to demonstrate pharmaceutical quality, product consistency and comparability
269 after process changes. Therefore the quality attributes controlled throughout the development process
270 should not be limited to the tests included in the specification for which preliminary acceptance criteria
271 have been set.

272 **S.4.1. Specification**

273 The specification for the batch(es) of active substance to be used in the clinical trial should define
274 acceptance criteria together with the tests used to exert sufficient control of the quality of the active
275 substance. Tests and defined acceptance criteria are mandatory for quantity, identity and purity and a
276 limit of 'record' or 'report results' will not be acceptable for these quality attributes. A test for biological
277 activity should be included unless otherwise justified. Upper limits, taking into account safety
278 considerations, should be set for the impurities. Microbiological quality for the active substance should
279 be specified.

280 As the acceptance criteria are normally based on a limited number of development batches and
281 batches used in non-clinical and clinical studies, they are by their nature inherently preliminary and
282 may need to be reviewed and adjusted during further development.

283 Product characteristics that are not completely defined at a certain stage of development (e.g.
284 glycosylation, charge heterogeneity) or for which the available data is too limited to establish relevant
285 acceptance criteria, should also be recorded. As a consequence, such product characteristics could be
286 included in the specification, without pre-defined acceptance limits. In such cases, a limit of 'record' or
287 'report results' is acceptable. The results should be reported in the Batch Analyses section (S.4.4).

288 **Additional information for phase III clinical trials**

289 As knowledge and experience increases, the addition or removal of parameters and modification of
290 analytical methods may be necessary. Specifications and acceptance criteria set for previous trials
291 should be reviewed and, where appropriate, adjusted to the current stage of development.

292 **S.4.2. Analytical procedures**

293 The analytical methods used for all tests included in the active substance specification (e.g.
294 chromatographic methods, biological assay, etc.) should be listed including those tests reported
295 without acceptance limits. A brief description of all non-compendial analytical procedures, i.e. the way
296 of performing the analysis, should be provided, highlighting controls used in the analysis.

297 For methods which comply with a monograph of the European Pharmacopoeia (Ph. Eur.), the
298 pharmacopoeia of an EU Member State, the United States Pharmacopoeia (USP) or the Japanese
299 Pharmacopoeia (JP), reference to the relevant monograph will be acceptable.

300 **S.4.3. Validation of analytical procedures**

301 Validation of analytical procedures during clinical development is seen as an evolving process.

302 Analytical procedures, which are either described in Ph. Eur., the pharmacopoeia of a Member State,
303 USP or JP, or are linked to a product specific monograph, are normally considered as validated.

304 Proposed modifications or alternatives to compendial methods must be validated

305 For phase I and II clinical trials, the suitability of the analytical methods used should be confirmed. The
306 acceptance limits (e.g. acceptance limits for the determination of the content of impurities, where
307 relevant) and the parameters (specificity, linearity, range, accuracy, precision, quantification and
308 detection limit, as appropriate) for performing validation of the analytical methods should be presented

309 in a tabulated form. If validation studies have been undertaken for early phase trials, a tabulated
310 summary of the results of analytical method validation studies could be provided for further assurance.

311 **Information for phase III clinical trials**

312 Validation of the analytical methods used for release and stability testing should be provided. A
313 tabulated summary of the results of the validation carried out should be submitted (e.g. results or
314 values found for specificity, linearity, range, accuracy, precision, quantification and detection limit, as
315 appropriate). By the end of phase III full method validation must be completed, including confirmation
316 of robustness. It is not necessary to provide a full validation report.

317 **S.4.4. Batch analyses**

318 As the specification may initially be very wide, actual batch data are important for quality assessment.
319 For quantitative parameters, actual numerical values should be presented.

320 The focus of this section is to demonstrate the quality of the batches (conformance to established
321 preliminary specification) to be used in the clinical trial. For early phase clinical trials where only a
322 limited number of batches of active substance have been manufactured, test results from relevant
323 clinical and non-clinical batches should be provided, including those to be used in the clinical trial
324 supported by the IMPD. For active substances with a longer production history, it could be acceptable
325 to provide results for only a number of representative batches, if appropriately justified.

326 Batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance
327 criteria and the test results should be listed together with the use of the batches. The manufacturing
328 process used for each batch and any differences in these processes should be identified.

329 A statement should be included whether the batch analyses data presented are from the batches that
330 will be used in the clinical trial, or whether additional batches not yet manufactured at time of
331 submission of the IMPD might be used.

332 **S.4.5. Justification of specification**

333 A justification for the quality attributes included in the specification and the acceptance criteria for
334 purity, impurities, biological activity and any other quality attributes which may be relevant to the
335 performance of the medicinal product should be provided. The justification should be based on relevant
336 development data, the batches used in non-clinical and/or clinical studies and data from stability
337 studies, taking into account the methods used for their control. It is acknowledged that during clinical
338 development, the acceptance criteria may be wider and may not reflect process capability. However,
339 for those quality attributes that may impact patient safety, the limits should be carefully considered
340 taking into account available knowledge (e.g. process capability, product type, dose, duration of dosing
341 etc.). The relevance of the selected potency assay and its proposed acceptance limits should be
342 justified.

343 Changes to a previously applied specification (e.g. addition or removal of parameters, widening of
344 acceptance criteria) should be indicated and justified.

345 **S.5. Reference standards or materials**

346 Due to the nature of biologically / biotechnology derived active substances, a well characterised
347 reference material is essential to ensure consistency between different batches but also to ensure the
348 comparability of the product to be marketed with that used in clinical studies and to provide a link
349 between process development and commercial manufacturing. The characterisation of the reference
350 material should be performed with reliable state-of-the-art analytical methods, which should be
351 adequately described. Information regarding the manufacturing process used to establish the reference
352 material should be provided.

353 If more than one reference standard has been used during the clinical development, a qualification
354 history should be provided describing how the relationship between the different standards was
355 maintained.

356 If available, an international or Ph. Eur. standard should be used as primary reference material. Each
357 in-house working standard should be qualified against this primary reference material. However, it
358 should be noted that the use of an international or Ph. Eur. standard might be limited to certain
359 defined test methods, e.g. biological activity. If an international or Ph. Eur. standard is not available,
360 an in-house standard should be established during development as primary reference material. The
361 stability of the reference material should be monitored. This can be handled within the quality system
362 of the company

363 **S.6. Container closure system**

364 The immediate packaging material used for the active substance should be stated. Possible interactions
365 between the active substance and the immediate packaging should be considered.

366 **S.7. Stability**

367 **Stability summary and conclusions (protocol / material and method)**

368 A stability protocol covering the proposed storage period of the active substance should be provided,
369 including specification, analytical methods and test intervals. The testing interval should normally
370 follow the guidance given in ICH Q5C.

371 The quality of the batches of the active substance placed into the stability program should be
372 representative of the quality of the material to be used in the planned clinical trial.

373 The active substance entered into the stability program should be stored in a container closure system
374 of the same type and made from the same materials as that used to store active substance batches to
375 be used in the clinical trial. Containers of reduced size are usually acceptable for the active substance
376 stability testing.

377 Studies should evaluate the active substance stability under the proposed storage conditions.
378 Accelerated and stress condition studies are recommended as they may help understanding the
379 degradation profile of the product and support an extension of the shelf-life.

380 The methods used for analysing the stability-indicating properties of the active substance should be
381 discussed, or cross-reference to S.4.3 made, to provide assurance that changes in the purity /

382 impurity profile and potency of the active substance would be detected. A potency assay should be
383 included in the protocol, unless otherwise justified.

384 A re-test period (as defined in ICH Q1A guideline) is not applicable to biological / biotechnology derived
385 active substances.

386 **Stability data / results**

387 Stability data should be presented for at least one batch made by a process representative of that used
388 to manufacture material for use in the clinical trial. In addition, supportive stability data on relevant
389 development batches or batches manufactured using previous manufacturing processes should be
390 provided, if available. Such batch data may be used in the assignment of shelf life for the active
391 substance provided an appropriate justification of the representative quality for the clinical trial
392 material is given.

393 The relevant stability data should be summarised in tabular format, specifying the batches tested, date
394 of manufacture, process version, composition, storage conditions, time-points, test methods,
395 acceptance criteria and results.

396 For quantitative parameters, actual numerical values should be presented. Any observed data trends
397 should be discussed.

398 Progressive requirements will need to be applied to reflect the amount of available data and emerging
399 knowledge about the stability of the active substance during the different phases of clinical
400 development. By phase III the applicant should have a comprehensive understanding of the stability
401 profile of the active substance.

402 **Shelf-life determination**

403 The claimed shelf-life of the active substance under the proposed storage conditions should be stated
404 and accompanied by an evaluation of the available data. Any observed trends should be discussed.

405 The requested storage period should be based on long term, real time and real temperature stability
406 studies, as described in ICH Q5C. However, extension of the shelf-life beyond the period covered by
407 real-time stability data may be acceptable, if supported by relevant data, including accelerated stability
408 studies and/or relevant stability data generated with representative material.

409 The maximum shelf-life after the extension should not be more than double, or more than twelve
410 months longer than the period covered by real time stability data obtained with representative
411 batch(es). However, extension of the shelf life beyond the intended duration of the long term stability
412 studies is not acceptable.

413 Where extensions of the shelf-life are planned, the applicant should commit to perform the proposed
414 stability program according to the presented protocol, and, in the event of unexpected issues, to
415 inform Competent Authorities of the situation, and propose corrective actions.

416 Prior knowledge including platform technologies could be taken into consideration when designing a
417 stability protocol. However, on its own this data is not considered sufficient to justify the shelf-life of
418 the actual active substance.

419 For shelf-life extension by way of substantial modification, see section 6.

420 **P Investigational medicinal product under test**

421 ***P.1. Description and composition of the investigational medicinal***
422 ***product***

423 The qualitative and quantitative composition of the IMP should be stated. The information provided
424 should include:

- 425 • a short statement or a tabulation of the dosage form
- 426 • composition, i.e. list of all components of the dosage form and their amount on a per-unit basis
427 (including overages, if any), the function of the components, and a reference to their quality
428 standards (e.g. compendial monographs or manufacturer's specifications)
- 429 • description of accompanying diluents(s)
- 430 • an outline of the type of container and closure used for the dosage form and for any accompanying
431 reconstitution diluent and devices, if applicable. A complete description should be provided in
432 section P.7.

433 ***P.2. Pharmaceutical development***

434 For early development there may be only limited information to include in this section.

435 A short description of formulation development, including justification of any new pharmaceutical form
436 or excipient, should be provided.

437 For products requiring additional preparation (e.g. reconstitution, dilution, mixing), compatibility with
438 the used materials (e.g. solvents, diluents, matrix) should be demonstrated and the method of
439 preparation should be summarised (reference may be made to a full description in the clinical
440 protocol).

441 It should be documented that the combination of intended formulation and packaging material does
442 not impair correct dosing, ensuring for example that the product is not adsorbed to the wall of the
443 container or infusion system. This is particularly relevant for low dose and highly diluted presentations.
444 Where applicable, the reliable administration of very small doses in first-in-human studies should be
445 addressed as laid down in the Guideline on strategies to identify and mitigate risks for first-in-human
446 clinical trials with investigational medicinal products (EMA/CHMP/SWP/28367/07).

447 **Manufacturing process development**

448 Changes in the manufacturing process including changes in formulation and dosage form compared to
449 previous clinical trials should be described. An appropriate comparability exercise should support
450 significant changes, e.g. formulation changes. In this regard, expectations are similar to those
451 described in S.2.6. This data should be sufficiently detailed to allow an appropriate understanding of
452 the changes and assessment of possible consequences to the safety of the patient.

453 Any changes in the formulation during the clinical phases should be documented and justified with
454 respect to their impact on quality, safety, clinical properties, dosing and stability of the medicinal
455 product.

456 **P.3. Manufacture**

457 **P.3.1. Manufacturer(s)**

458 The name(s), address(es) and responsibilities of all manufacturer(s) and each proposed production site
459 involved in manufacture, testing and batch release should be provided. In case multiple manufacturers
460 contribute to the manufacture of the IMP, their respective responsibilities should be clearly stated.

461 **P.3.2. Batch formula**

462 The batch formula for the batch(es) to be used for the clinical trial should be presented. This should
463 include a list of all components. The batch sizes or range of batch sizes should be given.

464 **P.3.3. Description of manufacturing process and process controls**

465 A flow chart showing all steps of the manufacturing process, including relevant IPCs (process
466 parameters and in-process-tests), should be provided accompanied by a brief process description. The
467 IPCs may be recorded as action limits or reported as preliminary acceptance criteria and the focus
468 should be on safety relevant attributes. For other IPCs, monitoring might be appropriate and
469 acceptance criteria and action limits do not need to be reported. During development, as additional
470 process knowledge is gained, further details of IPCs should be provided and acceptance criteria
471 reviewed.

472 Most products containing recombinant proteins and monoclonal antibodies are manufactured by an
473 aseptic process, which is considered to be non-standard. Non-standard manufacturing processes or
474 new technologies and new packaging processes should be described in sufficient detail (see the
475 Guideline on process validation for finished products - information and data to be provided in
476 regulatory submissions, EMA/CHMP/CVMP/QWP/BWP/70278/2012).

477 Reprocessing may be acceptable for particular manufacturing steps (e.g. re-filtration) only if the steps
478 are adequately described and appropriately justified.

479 **P.3.4. Control of critical steps and intermediates**

480 Tests and acceptance criteria for the control of critical steps in the manufacturing process should be
481 provided. It is acknowledged that due to limited data at an early stage of development (phase I/II)
482 complete information may not be available.

483 If holding times are foreseen for process intermediates, duration and storage conditions should be
484 provided and justified by data in terms of physicochemical, biological and microbiological properties.

485 For sterilisation by filtration the maximum acceptable bioburden prior to the filtration must be stated in
486 the application. In most situations NMT 10 CFU/100 ml will be acceptable. Test volumes of less than
487 100 ml may be used if justified.

488 **P.3.5. Process validation**

489 The state of validation of aseptic processing and lyophilisation should be briefly described, if applicable.
490 Taking into account EudraLex Vol. 4, Annex 13, the validation of sterilising processes should be of the
491 same standard as for product authorised for marketing. The dossier should particularly include
492 information directly relating to the product safety, i.e. on bioburden and media fill runs.

493 **P.4. Control of excipients**

494 **P.4.1. Specification**

495 References to Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP may be made. For
496 excipients not covered by any of the aforementioned standards, an in-house specification should be
497 provided.

498 **P.4.2. Analytical procedures**

499 In cases where reference to a pharmacopoeial monograph listed under P.4.1 cannot be made, the
500 analytical methods used should be indicated.

501 **P.4.3. Validation of the analytical procedures**

502 Not applicable.

503 **P.4.4. Justification of specification**

504 For non-compendial excipients as listed above in P.4.1, the in-house specification should be justified.

505 **P.4.5. Excipients of human or animal origin**

506 For excipients of human or animal origin, information should be provided regarding adventitious agents
507 safety evaluation (e.g. sources, specifications, description of the testing performed) and viral safety
508 data according to the Guideline on virus safety evaluation of biotechnological investigational medicinal
509 products (EMA/CHMP/BWP/398498/05) in Appendix A.2. Furthermore, compliance with the note for
510 guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human
511 and veterinary medicinal products (EMA/410/01) should be documented in section A.2.

512 If human albumin or any other plasma derived medicinal product is used as an excipient, information
513 regarding adventitious agents safety evaluation should follow the relevant chapters of the Guideline on
514 plasma-derived medicinal products (CPMP/BWP/706271/2010). If the plasma derived component has
515 already been used in a product with a Marketing Authorisation then reference to this can be made.

516 **P.4.6. Novel excipients**

517 For excipients used for the first time in a medicinal product or by a new route of administration, full
518 details of manufacture, characterisation and controls, with cross references to supporting safety data

519 (non-clinical and/or clinical), should be provided according to the active substance format (details in
520 A.3).

521 **P.5. Control of the investigational medicinal product**

522 **P.5.1. Specification**

523 The same principles as described for setting the active substance specification should be applied to the
524 medicinal product. In the specification, the tests used as well as their acceptance criteria should be
525 defined for the batch(es) of the product to be used in the clinical trial to enable sufficient control of
526 quality of the product. Tests for content, identity and purity are mandatory. Tests for sterility and
527 endotoxins are mandatory for sterile products. A test for biological activity should be included unless
528 otherwise justified. Upper limits, taking safety considerations into account, should be set for impurities.
529 They may need to be reviewed and adjusted during further development.

530 Acceptance criteria for IMP quality attributes should take into account safety considerations and the
531 stage of development. Since the acceptance criteria are normally based on a limited number of
532 development batches and batches used in non-clinical and clinical studies, their nature is inherently
533 preliminary. They may need to be reviewed and adjusted during further development.

534 The analytical methods and the limits for content and bioactivity should ensure a correct dosing.

535 For the impurities not covered by the active substance specification, upper limits should be set, taking
536 into account safety considerations.

537 **Additional information for Phase III clinical trials**

538 As knowledge and experience increases the addition or removal of parameters and modification of
539 analytical methods may be necessary. The specification and acceptance criteria set for previous trials
540 should be reviewed for phase III clinical trials and, where appropriate, adjusted to the current stage of
541 development.

542 **P.5.2. Analytical procedures**

543 The analytical methods for all tests included in the specification should be described. For some proteins
544 and complex or innovative pharmaceutical forms, a higher level of detail may be required.

545 For further requirements refer to S.4.2.

546 **P.5.3. Validation of analytical procedures**

547 For requirements refer to S.4.3.

548 **P.5.4. Batch analysis**

549 As specifications may initially be very wide, actual batch data are important for quality assessment. For
550 quantitative parameters, actual numerical values should be presented.

551 The focus of this section is to demonstrate the quality of the batches (conformance to established
552 preliminary specification) to be used in the clinical trial. For early phase clinical trials where only a
553 limited number of batches have been manufactured, test results from relevant clinical and non-clinical
554 batches should be provided, including those to be used in the clinical trial supported by the IMPD. For
555 products with a longer production history, it could be acceptable to provide results for only a number
556 of representative batches, if appropriately justified.

557 Batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance
558 criteria and the test results should be listed together with the use of the batches. The manufacturing
559 process used for each batch should be identified.

560 A statement should be included whether the batch analyses data presented are from the batches that
561 will be used in the clinical trial, or whether additional batches not yet manufactured at time of
562 submission of the IMPD might be used.

563 **P.5.5. Characterisation of impurities**

564 Additional impurities and degradation products observed in the IMP, but not covered by section S.3.2,
565 should be identified and quantified as necessary.

566 **P.5.6. Justification of specification**

567 A justification for the quality attributes included in the product specification should be provided mainly
568 based on the active substance specification. Stability indicating quality attributes should be considered.
569 The proposed acceptance criteria should be justified.

570 **P.6. Reference standards or materials**

571 The parameters for characterisation of the reference standard should be submitted, where applicable.
572 Section S.5 may be referred to, where applicable.

573 **P.7. Container closure system**

574 The intended primary packaging to be used for the IMP in the clinical trial should be described. Where
575 appropriate, reference should be made to the relevant pharmacopoeial monograph. If the product is
576 packed in a non-standard administration device, or if non-compendial materials are used, description
577 and specifications should be provided.

578 If a medical device is to be used for administration it should be stated whether the device is CE marked
579 for its intended purpose. In the absence of a CE mark for the intended purpose, a statement of
580 compliance with the relevant essential requirements for medical devices with regards to safety and
581 performance related device features is required. An integral device component of a drug-device
582 combination product, as defined in the Medical Device Directive, is exempt from CE-marking.

583 For products intended for parenteral use where there is potential for interaction between product and
584 container closure system, more details may be needed (e.g. extractable/leachable for phase III
585 studies).

586 **P.8. Stability**

587 The same requirements as for the active substance are applied to the medicinal product, including the
588 stability protocol, stability results, shelf-life determination, including extension of shelf-life beyond the
589 period covered by real-time stability data, stability commitment and post-approval extension. Stability
590 studies should provide sufficient assurance that the IMP will be stable during its intended storage
591 period. The presented data should justify the proposed shelf life of the product from its release to its
592 administration to patients. The stability protocol for the IMP should take into account the knowledge
593 acquired on the stability profile of the active substance.

594 Bracketing and matrixing approaches may be acceptable, where justified.

595 In-use stability data should be presented for preparations intended for use after reconstitution,
596 dilution, mixing or for multidose presentations. These studies are not required if the preparation is to
597 be used immediately after opening or reconstitution.

598 **Appendices**

599 **A.1. Facilities and equipment**

600 Not applicable.

601 **A.2. Adventitious agents safety evaluation**

602 All materials of human or animal origin used in the manufacturing process of both the active substance
603 and the medicinal product, or such materials coming into contact with active substance or medicinal
604 product during the manufacturing process, should be identified. Information assessing the risk with
605 respect to potential contamination with adventitious agents of human or animal origin should be
606 provided in this section.

607 **TSE agents**

608 Detailed information should be provided on the avoidance and control of transmissible spongiform
609 encephalopathy agents. This information can include, for example, certification and control of the
610 production process, as appropriate for the material, process and agent.

611 The note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents
612 via human and veterinary medicinal products (EMA/410/01) in its current version is to be applied.

613 **Viral safety**

614 Where applicable, an assessment of the risk with respect to potential viral contamination should be
615 provided in this section. The documentation should comply with the requirements outlined in the
616 guideline on virus safety evaluation of biotechnological investigational medicinal products
617 (EMA/CHMP/BWP/398498/05).

618 **Other adventitious agents**

619 Detailed information regarding other adventitious agents, such as bacteria, mycoplasma, and fungi
620 should be provided in appropriate sections within the core dossier.

621 **A.3. Excipients**

622 For novel excipients, information as indicated in section S should be provided in line with the
623 respective clinical phase.

624 **A.4. Solvents for reconstitution and diluents**

625 For solvents for reconstitution and diluents, the relevant information as indicated in section P should be
626 provided.

627 **3. Information on the quality of authorised, non-modified
628 biological test and comparator products in clinical trials**

629 Information on the authorised, non-modified test/comparator product provided in the IMPD should
630 meet the requirements as outlined in section 3 of the Guideline on the requirements to the chemical
631 and pharmaceutical quality documentation concerning investigational medicinal products in clinical
632 trials (EMA/CHMP/QWP/834816/2015).

633 In the case when only repackaging is performed without changing the primary packaging, the following
634 information should be included in the simplified IMPD in addition to the requirements listed in section 3
635 of EMA/CHMP/QWP/834816/2015:

- 636 • Information that will satisfy the requirement to ensure that the investigational medicinal
637 product will have the proper identity, strength, quality and purity (e.g. cross-reference to the
638 Summary of Product Characteristics for the EU marketed product).
- 639 • Details on the site of repackaging/relabeling operations.

640 **4. Information on the quality of modified authorised
641 biological comparator products in clinical trials**

642 Information on the modified authorised test/comparator product provided in the IMPD should meet the
643 requirements as outlined in this guideline.

644 Sections not impacted by the modification may cross-refer to the authorised product.

645 **5. Information on the chemical and pharmaceutical quality
646 concerning placebo products in clinical trials**

647 Information on the placebo product to be provided in the IMPD should meet the requirements as
648 outlined in section 6 of the Guideline on the requirements to the chemical and pharmaceutical quality
649 documentation concerning investigational medicinal products in clinical trials
650 (EMA/CHMP/QWP/834816/2015).

651 **6. Changes to the investigational medicinal product and**
652 **auxiliary medicinal product with a need to request a**
653 **substantial modification to the IMPD**

654 In accordance with Good Manufacturing Practice, a Product Specification File should be maintained for
655 each IMP/auxiliary medicinal product at the respective site and be continually updated as the
656 development of the product proceeds, ensuring appropriate traceability to the previous versions. ~~The~~
657 ~~following is a non-exhaustive list of modifications that are typically 'substantial' and need to be notified~~
658 ~~to the competent authorities.~~

- 659 ~~• changes in the manufacturer(s) of the active substance or the medicinal product~~
- 660 ~~• substantial changes in the manufacturing process (such as new expression cell line, addition or~~
661 ~~emission of a purification step, changes of steps affecting viral clearance, any reprocessing not~~
662 ~~described in the IMPD)~~
- 663 ~~• changes leading to the occurrence of new impurities and product related substances~~
- 664 ~~• change in the specification, if acceptance criteria are widened or test procedures are deleted or~~
665 ~~replaced~~
- 666 ~~• change to the formulation including changes in the active substance concentration and~~
667 ~~excipient composition~~
- 668 ~~• changes to immediate packaging material, if the nature of material is changed~~
- 669 ~~• changes in the approved in-use stability recommendations~~
- 670 ~~• any extension of the shelf life outside the agreed stability protocol or without prior~~
671 ~~commitment (see section S.7 and P.8)~~

672 ~~However, shelf life extension based on the agreed protocol is typically not considered as substantial~~
673 ~~modification if:~~

- 674 ~~• each additional extension of the shelf life is not more than double, and is not more than twelve~~
675 ~~months longer than available real time data and does not go beyond the duration as outlined in the~~
676 ~~agreed stability protocol.~~
- 677 ~~• the extension is covered and in compliance with the approved stability protocol~~
- 678 ~~• no significant trends or out-of-specification results (OoS) have been detected in ongoing~~
679 ~~stability studies at the designated storage temperature~~

680 ~~the applicant commits to inform Competent Authorities of unexpected stability issues in the ongoing~~
681 ~~study (including trends and OoS) and to propose corrective action as appropriate~~

682 In compliance with the Clinical Trials Regulation (CTR), a change to IMP/auxiliary medicinal product
683 quality data is either:

- 684 • a substantial modification (Art. 2.2.13);
- 685 • a change relevant to the supervision of the trial (Art. 81.9);
- 686 • a non-substantial modification (changes outside the scope of substantial modifications and
687 changes irrelevant to the supervision of the trial).

688 Substantial modification means any change which is likely to have a substantial impact on the safety
689 and rights of the subjects or on the reliability and robustness of the data generated in the clinical trial.
690 Assessment of an IMPD should be focussed on patient safety. Therefore, any modification involving a
691 potential new risk has to be considered a substantial modification. This may be especially the case for
692 changes in impurities profile, microbial contamination, viral safety, TSE and in some particular cases to
693 stability when toxic degradation products may be generated.

694 Non-substantial modifications relevant to the supervision of the trial (Art 81.9 change) are concepts
695 introduced under the CTR, which aims to update certain, specified information in the EU database
696 (CTIS) without the need for a substantial modification application, when this information is necessary
697 for oversight but does not have a substantial impact on patients safety and rights and/or data
698 robustness. Art 81.9 states "The sponsor shall permanently update in the EU database information on
699 any changes to the clinical trials which are not substantial modifications but are relevant for the
700 supervision of the clinical trial by the Member States concerned". Art 81.9 changes can be submitted
701 only if the change does not trigger additional changes, which are expected to be submitted as a
702 substantial modification application. The combination of different Art 81.9 changes can cumulate into a
703 change that needs to be submitted as a substantial modification.

704 For non-substantial modifications, documentation should not be proactively submitted, but the relevant
705 internal and study documentation supporting the change should be recorded within the company and if
706 appropriate, at investigator site. At the time of an overall IMPD update or submission of a substantial
707 modification the non-substantial changes should be incorporated into the updated documentation.
708 However, when submitting a modified IMPD, the sponsor should clearly identify which changes are
709 substantial and which are not.

710 When a modification will become effective with the start of a new clinical trial (e.g. change of name of
711 the IMP, new manufacturing process), the notification will take place with the application for the new
712 trial. Submissions of substantial modifications are only necessary for changes in ongoing clinical trials.

713 In the following table, examples are given for changes in IMPs containing biological active substances,
714 and their classification. This list does not claim to be exhaustive. The sponsor should decide on a case
715 by case basis how to classify the change.

	<u>Changes to IMPD</u>	<u>Substantial Modification (SM)</u>	<u>Art. 81.9 Non-substantial Modification (NSM)</u>	<u>Non-substantial Modification (NSM)</u>
<u>719</u>	<u>Change of name or code of the active substance or investigational medicinal product</u>		<ul style="list-style-type: none"> <u>Change from company code to INN or trade name during ongoing clinical trial (exchange of the label)</u> 	
<u>720</u>	<u>Manufacturer of the active substance</u>	<ul style="list-style-type: none"> <u>Addition or replacement of manufacturing site or testing site</u> <u>Change of manufacturer or change of manufacturing site (within the same company)</u> <u>Deletion of manufacturing, or testing site (for safety reason, GMP non-compliance).</u> 		<ul style="list-style-type: none"> <u>Deletion of manufacturing, or testing site (no safety reason)</u> <u>Name change of manufacturer</u>

	<u>Changes to IMPD</u>	<u>Substantial Modification (SM)</u>	<u>Art. 81.9 Non-substantial Modification (NSM)</u>	<u>Non-substantial Modification (NSM)</u>
<u>721</u>	<u>Manufacturing process of the active substance</u>	<p><u>Changes such as;</u></p> <ul style="list-style-type: none"> • <u>new expression cell line</u> • <u>new cell bank</u> • <u>change of a raw material of biological origin</u> • <u>changes to the viral safety tests performed on cell banks or unprocessed bulk batches,</u> • <u>change of production scale (upstream process),</u> • <u>changes to the cell culture conditions</u> • <u>changes in the purification process (downstream): addition or removal of a purification step</u> • <u>changes in the process</u> 		<ul style="list-style-type: none"> • <u>Addition or tightening of IPC if not due to safety reasons</u> • <u>Modification of the process parameters (same process, analogous raw materials) where no effect on product quality is expected.</u> • <u>reprocessing if adequately described and accepted in the initial submission</u> • <u>minor changes in the manufacturing process which do not require a comparability exercise</u> • <u>changes to the controls of non critical raw materials</u>

	<u>Changes to IMPD</u>	<u>Substantial Modification (SM)</u>	<u>Art. 81.9 Non-substantial Modification (NSM)</u>	<u>Non-substantial Modification (NSM)</u>
		<p><u>conditions of a steps potentially effective on virus removal/inactivation, new virus validation studies (viral clearance studies)</u></p> <ul style="list-style-type: none"> • <u>any reprocessing not described in the IMPD</u> • <u>changes leading to the occurrence of new impurities and product related substances</u> 		
<u>722</u>	<u>Specifications (release and shelf life) of the active substance</u>	<ul style="list-style-type: none"> • <u>change in the specification, if acceptance criteria are widened or test procedures are deleted or replaced</u> • <u>Replacement or deletion of a specification test based on supportive data</u> 		<ul style="list-style-type: none"> • <u>Tightening acceptance criteria (no safety reason)</u>

	<u>Changes to IMPD</u>	<u>Substantial Modification (SM)</u>	<u>Art. 81.9 Non-substantial Modification (NSM)</u>	<u>Non-substantial Modification (NSM)</u>
<u>723</u>	<u>Analytical methods for control of the active substance</u>	<ul style="list-style-type: none"> <u>New test methods and new test conditions</u> 		<ul style="list-style-type: none"> <u>Improvement of the same analytical method (e.g., greater sensitivity, precision, accuracy) provided</u> <ol style="list-style-type: none"> <u>the acceptance criteria are similar or tighter</u> <u>the improved method is suitable for use or validated according to the stage of development, and lead to comparable or better validation results</u> <u>Variation of the method already covered by the IMPD and the new test conditions are validated and lead to comparable or better validation results</u>
<u>724</u>	<u>Batch analysis of the active substance</u>			<ul style="list-style-type: none"> <u>Additional batch data manufactured using the same process described in the IMPD unless it is</u>

	<u>Changes to IMPD</u>	<u>Substantial Modification (SM)</u>	<u>Art. 81.9 Non-substantial Modification (NSM)</u>	<u>Non-substantial Modification (NSM)</u>
				<u>requested otherwise</u>
<u>725</u>	<u>Reference standard</u>			<u>Introduction of new RS, provided equivalence has been established to the previous RS</u>
<u>726</u>	<u>Stability of the active substance</u>	<ul style="list-style-type: none"> • <u>changes in the approved storage conditions</u> • <u>any extension of the shelf-life outside the agreed stability protocol or without prior commitment</u> • <u>Reduction in shelf life due to stability concerns</u> 		<ul style="list-style-type: none"> • <u>Additional intermediate stability timepoint but which is not yet covered (e.g., additional pull point at 42months) without changing the conditions for the extrapolation, leading to corresponding interim shelf life extension</u> • <u>Reduction in Shelf-Life if not safety or quality related</u> <p><u>Shelf-life extension based on the agreed protocol is typically not considered as substantial modification if:</u></p>

	<u>Changes to IMPD</u>	<u>Substantial Modification (SM)</u>	<u>Art. 81.9 Non-substantial Modification (NSM)</u>	<u>Non-substantial Modification (NSM)</u>
				<ul style="list-style-type: none"> • <u>each additional extension of the shelf-life is not more than double and is not more than 12 months longer than available real time data and does not go beyond the duration as outlined in the agreed stability protocol</u> • <u>the extension is covered and in compliance with the approved stability protocol</u> • <u>no OOS results or significant trends which may lead to an OOS result during the approved shelf life have been detected in ongoing stability studies at the designated storage temperature</u>

	<u>Changes to IMPD</u>	<u>Substantial Modification (SM)</u>	<u>Art. 81.9 Non-substantial Modification (NSM)</u>	<u>Non-substantial Modification (NSM)</u>
<u>727</u>	<u>Composition of the investigational medicinal product</u>	<ul style="list-style-type: none"> • <u>change to the formulation including changes in the active substance concentration and excipient</u> • <u>change of composition</u> 		
<u>728</u>	<u>Manufacturer of the investigational medicinal product</u>	<ul style="list-style-type: none"> • <u>Addition or replacement of manufacturing site (including primary packaging) or testing site</u> • <u>Deletion of manufacturing, packaging or testing site (for safety reason, GMP non-compliance).</u> • <u>Addition or replacement of secondary packaging or labeling site with valid GMP status</u> • <u>Addition or</u> 		<ul style="list-style-type: none"> • <u>Deletion of manufacturing, packaging or testing site (no safety reason)</u> • <u>Name change of manufacturer</u>

	<u>Changes to IMPD</u>	<u>Substantial Modification (SM)</u>	<u>Art. 81.9 Non-substantial Modification (NSM)</u>	<u>Non-substantial Modification (NSM)</u>
		<ul style="list-style-type: none"> <u>replacement of importation, QP release or QC testing sites</u> 		
<u>729</u>	<u>Manufacturing process of the investigational medicinal product</u>	<ul style="list-style-type: none"> <u>Significant changes to the manufacturing process</u> 		<ul style="list-style-type: none"> <u>Modifications of process parameters (same process) where no effect on product quality is demonstrated.</u> <u>Scale-Up of filling process if supported by appropriate media fills.</u>
<u>730</u>	<u>Specifications (release and shelf life) of the investigational medicinal product</u>	<ul style="list-style-type: none"> <u>change in the specification, if acceptance criteria are widened or test procedures are deleted or replaced</u> <u>Replacement or deletion of specification test based on supportive data</u> 		<ul style="list-style-type: none"> <u>Tightening acceptance criteria (no safety reason)</u>

	<u>Changes to IMPD</u>	<u>Substantial Modification (SM)</u>	<u>Art. 81.9 Non-substantial Modification (NSM)</u>	<u>Non-substantial Modification (NSM)</u>
<u>731</u>	<u>Analytical methods for control of the investigational medicinal product</u>	<ul style="list-style-type: none"> <u>New test methods and new test conditions</u> 		<ul style="list-style-type: none"> <u>Improvement of the same analytical method (e.g., greater sensitivity, precision, accuracy) provided</u> <ol style="list-style-type: none"> <u>the acceptance criteria are similar or tighter</u> <u>the improved method is suitable for use or validated according to the stage of development, and lead to comparable or better validation results</u> <u>Variation of the method already covered by the IMPD and the new test conditions are validated and lead to comparable or better validation results</u>
<u>732</u>	<u>Batch analysis of the investigational medicinal product</u>			<ul style="list-style-type: none"> <u>Additional batch data manufactured using the same process described in the IMPD unless it is</u>

	<u>Changes to IMPD</u>	<u>Substantial Modification (SM)</u>	<u>Art. 81.9 Non-substantial Modification (NSM)</u>	<u>Non-substantial Modification (NSM)</u>
				<u>requested otherwise</u>
<u>733</u>	<u>Container closure system of the investigational medicinal product</u>	<ul style="list-style-type: none"> <u>changes to immediate packaging</u> 		<ul style="list-style-type: none"> <u>Changes to secondary packaging</u> <u>Change of supplier (deletion, replacement or addition) of packaging components if the material is identical and specifications are at least equivalent.</u>
<u>734</u>	<u>Medical devices registered in the IMPD</u>	<ul style="list-style-type: none"> <u>Change to use a different medical device.</u> <u>Changes to a medical device registered in the IMPD if potentially impacting on the quality, safety and/or efficacy.</u> 		<ul style="list-style-type: none"> <u>changes to a medical device registered in the IMPD which is not considered to impact on the quality, safety and/or efficacy.</u>
<u>735</u>	<u>Stability of the investigational medicinal</u>	<ul style="list-style-type: none"> <u>changes in the</u> 		<ul style="list-style-type: none"> <u>Additional intermediate</u>

	<u>Changes to IMPD</u>	<u>Substantial Modification (SM)</u>	<u>Art. 81.9 Non-substantial Modification (NSM)</u>	<u>Non-substantial Modification (NSM)</u>
	product	<p><u>approved in-use stability recommendations</u></p> <ul style="list-style-type: none"> • <u>any extension of the shelf-life outside the agreed stability protocol or without prior commitment</u> • <u>Reduction in shelf life due to stability concerns</u> 		<p><u>stability timepoint but which is not yet covered (e.g., add. pull point at 42m) without changing the conditions for the extrapolation, leading to corresponding interim shelf life extension</u></p> <ul style="list-style-type: none"> • <u>Reduction in Shelf-Life if not safety or quality related</u> <p><u>Shelf-life extension based on the agreed protocol is typically not considered as substantial modification if:</u></p> <ul style="list-style-type: none"> • <u>each additional extension of the shelf-life is not more than double and is not more than 12 months longer than available real time data and does not go beyond the duration as outlined in the agreed stability protocol</u>

	<u>Changes to IMPD</u>	<u>Substantial Modification (SM)</u>	<u>Art. 81.9 Non-substantial Modification (NSM)</u>	<u>Non-substantial Modification (NSM)</u>
				<ul style="list-style-type: none"> • <u>the extension is covered and in compliance with the approved stability protocol</u> • <u>no OOS results or significant trends which may lead to an OOS result during the approved shelf life have been detected in ongoing stability studies at the designated storage temperature</u>