



1 24 June 2021  
2 EMA/CHMP/QWP/545525/2017 Rev. 2 \*Corr.  
3 Committee for Medicinal Products for Human Use (CHMP)

4 **Guideline on the requirements to the chemical and**  
5 **pharmaceutical quality documentation concerning**  
6 **investigational medicinal products in clinical trials**  
7 **Draft**

<b>Draft agreed by Quality Working Party</b>	December 2015
<b>Adopted by CHMP for release for consultation</b>	December 2015
<b>Consultation of European Commission ad hoc group on clinical trials</b>	February 2016
<b>Start of public consultation</b>	12 April 2016
<b>End of consultation (deadline for comments)</b>	12 October 2016
<b>Agreed by Quality Working Party</b>	May 2017
<b>Consultation of European Commission ad hoc group on clinical trials</b>	June 2017
<b>Adopted by CHMP</b>	14 September 2017
<b>Date of coming into effect</b>	1 April 2018
<b>Draft update of Chapter 9 agreed by Quality Working Party</b>	6 June 2021
<b>Draft Rev. 2 Adoption by CHMP for release for consultation</b>	24 June 2021
<b>Start of public consultation</b>	1 July 2021
<b>End of consultation (deadline for comments)</b>	31 August 2021

8 This guideline replaces the "Guideline on the requirements to the chemical and pharmaceutical quality  
9 documentation concerning investigational medicinal products in clinical trials"  
10 (CHMP/QWP/185401/2004 final)  
11 \*Document reference number corrected.



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

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<b>Keywords</b>	<b>Guideline, Clinical Trial, Quality</b>
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16 Guideline on the requirements to the chemical and  
17 pharmaceutical quality documentation concerning  
18 investigational medicinal products in clinical trials

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## 199 **1. Introduction**

### 200 **1.1. Objectives of the guideline**

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

204 Since clinical trials will often be designed as multi -centre studies, potentially involving different  
205 Member States, it is the aim of this guideline to define harmonised requirements for the documentation  
206 to be submitted throughout the European Union.

207 It should be clearly differentiated between the requirements for a dossier for a clinical trial and a  
208 marketing authorisation dossier. Whilst the latter ones have to ensure a state-of-the-art quality of a  
209 product for wide use in patients, information to be provided for investigational medicinal products  
210 (IMPs) should focus on the risk aspects and should consider the nature of the product, the state of  
211 development/clinical phase, patient population, nature and severity of the illness as well as type and  
212 duration of the clinical trial itself. As a consequence, it will not be possible to define very detailed  
213 requirements applicable to all sorts of different products. However, guidance on standard information  
214 which should normally be presented in the quality part of an IMPD is provided in this guideline.

### 215 **1.2. Scope of the guideline**

216 This guideline addresses the documentation on the chemical and pharmaceutical quality of IMPs and  
217 Auxiliary Medicinal Products containing chemically defined drug substances, synthetic peptides,  
218 synthetic oligonucleotides, herbal substances, herbal preparations and chemically defined radio-  
219 active/radio-labelled substances to be submitted to the competent authority for approval prior to  
220 beginning a clinical trial in humans. It includes the requirements for IMPs and Auxiliary Medicinal  
221 Products to be tested in phase I, phase II, phase III and phase IV studies as well as the requirements  
222 for modified and unmodified comparator products and IMPs to be tested in generic bioequivalence  
223 studies.

224 When compiling the quality part of the IMPD for phase II and phase III clinical studies, the larger and  
225 longer exposure of patients to the product have to be taken into account compared to phase I clinical  
226 studies. Based on the diversity of products to be used in the different phases of clinical trials, the  
227 requirements defined in this guideline can only be of an illustrative nature and cannot be expected to  
228 present an exhaustive list. IMPs based on innovative and/or complex technologies may need more  
229 detailed data to be submitted. For certain situations, e.g. where the drug substance from the specific  
230 source to be used for an IMP is already included in a medicinal product authorised within the EU, not  
231 all the documentation outlined in the following chapters need to be submitted in the IMPD, but a  
232 simplified IMPD will suffice.

### 233 **1.3. General points concerning all IMPs**

234 IMPs should be produced in accordance with the principles and the detailed guidelines of Good  
235 Manufacturing Practices for Medicinal Products.



236 **1.4. Submission of data**

237 The IMPD should be provided in a clearly structured format following the numbering system as given in  
238 the chapters 2 to 8 of this Guideline. However, the first Arabic number being introduced only to  
239 facilitate the Guideline's use should be omitted.

240 The IMPD should include the most up-to-date information relevant to the clinical trial available at time  
241 of submission of the clinical trial application.

242 **1.5. General considerations**

243 For drug substances or IMPs to be used in clinical trials as described in chapters 2 to 8, reference to  
244 either the European Pharmacopoeia (Ph. Eur.), the Pharmacopoeia of an EU Member State, the United  
245 States Pharmacopoeia (USP) or the Japanese Pharmacopoeia (JP) is acceptable. For active substances,  
246 the suitability of the referenced monograph to adequately control the quality of the active substance  
247 (impurity profile) will have to be demonstrated by the applicant/sponsor. Suitability of monographs of  
248 the European Pharmacopoeia (Ph. Eur.) can be demonstrated with certificates of suitability (CEP)  
249 issued by the European Directorate for the Quality of Medicines (EDQM). In other cases, information on  
250 the synthesis of the drug substance, including reagents, solvents, catalysts and processing aids, should  
251 be provided.

252 For generic bioequivalence studies as described in chapter 5 which will support a Marketing  
253 Authorisation Application (MAA) in the EU, applicants/sponsors are advised that reference to the Ph.  
254 Eur. will facilitate future licensing activities in the EU.

255 For impurities in IMPs, a justification that the product is safe for its intended use, considering the  
256 anticipated exposure of volunteers and patients, respectively, will be required.

257 When compiling the documentation, the difference between "analytical procedure" and "analytical  
258 method" should be kept in mind. The term "analytical procedure" is defined in ICH Q 2 (A) and refers  
259 to the way of performing the analysis. The term "analytical method" refers to the principles of the  
260 method used.

261 **2. Information on the chemical and pharmaceutical quality**  
262 **concerning investigational medicinal products in clinical trials**

263 **2.2.1.S Drug substance**

264 Reference to an Active Substance Master File or a Certificate of Suitability of the European Directorate  
265 for the Quality of Medicines is acceptable. The procedure as described in the "Guideline on Active  
266 Substance Master File Procedure – CPMP/QWP/227/02 Rev 3 corr" and the "Guideline on Summary of  
267 Requirements for Active Substances in the Quality Part of the Dossier – CHMP/QWP/297/97 Rev 1" in  
268 their current version should be followed, even though no specific reference to clinical trials application  
269 is included.

270 For reference to pharmacopoeial monographs, see chapter 1.5 General Considerations.

271 If the Active substance used is already authorised in a drug product within the EU/EEA or in one of the  
272 ICH-regions, reference can be made to the valid marketing authorisation. A statement from Marketing  
273 Authorisation Holder or drug substance manufacturer should be provided that the active substance has  
274 the same quality as in the approved product.

275 Name of the drug product, marketing authorisation number or its equivalent, marketing authorisation  
276 holder and the country that granted the marketing authorisation should be given.

## 277 **2.2.1.S.1 General information**

### 278 **2.2.1.S.1.1 Nomenclature**

279 Information concerning the nomenclature of the drug substance (e.g. INN-name (if approved),  
280 pharmacopoeial name, chemical name (IUPAC, CAS-RN), laboratory code, other names or codes, if  
281 any) should be given. In the case of radio-nuclides or radio-labelled substances which are used in  
282 phase I studies in humans to develop a non-radioactive medicinal product, the radio-nuclide or the  
283 radio-labelled substance should be stated additionally.

284 For radio-nuclides, the isotope type should be stated (IUPAC-nomenclature).

285 In the case of radio-nuclide generators, both parent radio-nuclide and daughter radio-nuclide are  
286 considered as drug substances. For kits, which are to be radio-labelled, the part of the formulation  
287 which will carry or bind the radio-nuclide should be stated as well as the radio-labelled product. For  
288 organic-chemical precursors, the same information should be provided as for drug substances.

289 For herbal substances the binominal scientific name of the plant (genus, species, variety and author)  
290 and the chemotype as well as the parts of the plant, the definition of the herbal substance, other  
291 names (synonyms mentioned in other Pharmacopoeias) and the laboratory code should be provided.

292 In addition, for herbal preparations the ratio of the herbal substance to the herbal preparation as well  
293 as the extraction solvent(s) used for extraction should be stated.

### 294 **2.2.1.S.1.2 Structure**

295 The data available at the respective stage of clinical development should be presented. They should  
296 include the structural formula, molecular weight, chirality/stereochemistry as far as elucidated.

297 In the case of radio-nuclides or radio-labelled substances which are used in phase I studies in humans  
298 to develop a non-radioactive medicinal product, the structural formula before and – if known – after  
299 the radio-labelling should be given. For kits for radiopharmaceutical preparations, the ligand's  
300 structural formula before and, if known, after the radio-labelling should be given.

301 In addition, the physical state, the extract type, if known the constituent(s) relevant for the  
302 therapeutic activity or the analytical marker substance(s) used should be stated for herbal substances  
303 and herbal preparations. Information about excipients in the final herbal preparations should be  
304 provided.

### 305 **2.2.1.S.1.3 General properties**

306 A list of physico-chemical and other relevant properties of the active substance should be provided, in  
307 particular physico-chemical properties that could affect pharmacological or toxicological safety, such as  
308 solubilities, pKa, polymorphism, isomerism, log P, permeability etc..

309 For radio-nuclides, the nuclear and radiophysical properties should be stated. Their source should be  
310 also specified, i.e. whether fission or non-fission.

## 311 **2.2.1.S.2 Manufacture**

### 312 **2.2.1.S.2.1 Manufacturer(s)**

313 The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and  
314 each proposed site involved in manufacture and testing should be provided.

315 In the case of radio-nuclides or radio-labelled substances which are used in phase I studies in humans  
316 to develop a non-radioactive medicinal product, the manufacturer should be stated. For  
317 radiopharmaceuticals, the manufacturer of the radiopharmaceutical precursors and of non-radioactive  
318 precursors should be stated, as well as the source of any cyclotron irradiation target materials and  
319 production site(s) at which irradiation occurs.

### 320 **2.2.1.S.2.2 Description of manufacturing process and process controls**

321 For chemical substances: A brief summary of the synthesis process, a flow chart of the successive  
322 steps including, for each step, the starting materials, intermediates, solvents, catalysts and critical  
323 reagents used should be provided. Drug substance manufacturing process should be described in the  
324 IMPD in such extent so it is understood how impurities are introduced in the process, and why the  
325 proposed control strategy is suitable. This will typically include a description of multiple chemical  
326 transformation steps. Any relevant process controls should be indicated. Where critical steps in the  
327 synthesis have been identified, a more detailed description may be appropriate. The stereo-chemical  
328 properties of starting materials should be discussed, where applicable. For substances which comply to  
329 the European Pharmacopoeia (Ph. Eur.), the Pharmacopoeia of an EU Member State, the United States  
330 Pharmacopoeia (USP) or the Japanese Pharmacopoeia (JP) reference to the monographs is acceptable,  
331 but suitability of the referenced monograph to adequately control the quality of the active substance  
332 (impurity profile) should be discussed by submission of sufficient information on the manufacturing  
333 process of the active substance (see chapter 1.5 General Considerations).

334 For radio-nuclides, the manufacturing process, as well as nuclear reactions should be described,  
335 including possible undesired nuclear reactions. The conditions for irradiation should be given. The  
336 cleaning and segregation processes for the radiopharmaceutical preparation and the organo-chemical  
337 precursors should be stated.

338 For herbal substances or herbal preparations, a brief summary of the manufacturing process and a flow  
339 chart of the successive steps, starting with the plant cultivation or the plant collection, should be  
340 provided. The in-process controls carried out should be documented. The main production steps should  
341 be indicated.

### 342 **2.2.1.S.2.3 Control of materials**

343 Materials used in the manufacture of the drug substance (e.g. raw materials, starting materials,  
344 solvents, reagents, catalysts) should be listed together with a brief summary on the quality and control  
345 of any attributes anticipated to be critical, for example, where control is required to limit an impurity in  
346 the drug substance, e.g. chiral control, metal catalyst control or control of a precursor to a potential  
347 genotoxic impurity. For radio-nuclides, details on the target material should be given.

348 **2.2.1.S.2.4 Control of critical steps and intermediates**

349 In case of critical steps in the synthesis, tests and acceptance criteria for their control should be briefly  
350 summarised.

351 **2.2.1.S.2.5 Process validation and/or evaluation**

352 Not applicable for drug substances to be used in clinical trials.

353 **2.2.1.S.2.6. Manufacturing process development**

354 It should be documented if the manufacturing process significantly differs from that used for the  
355 production of the batches used in the non-clinical studies. In this case, a flow chart of the  
356 manufacturing process used for the drug substance used in the non-clinical studies should be  
357 presented.

358 Significant changes in the manufacturing process, which may impact on quality, should be discussed  
359 (e.g. change of route of synthesis).

360 **2.2.1.S.3 Characterisation**

361 **2.2.1.S.3.1 Elucidation of structure and other characteristics**

362 The structure of chemically defined substances should be established with suitable methodology;  
363 relevant data should be provided.

364 For radiopharmaceutical substances, the analogous non-radioactive substances should be used to  
365 determine the structure. For radiopharmaceutical kits the structure of the radiolabelled compound  
366 should be described where possible.

367 For herbal substances, information should be given on the botanical, macroscopic and microscopic and  
368 phytochemical characterisation. Where applicable, details should be given on the biological activity. For  
369 herbal preparations, details should be provided on the physical and phytochemical characterisation.  
370 Where applicable, details should be given on the biological activity.

371 **2.2.1.S.3.2 Impurities**

372 For substances which comply with a monograph of the Ph. Eur., the pharmacopoeia of an EU Member  
373 State, USP or JP, no further details are required, provided its suitability to adequately control the  
374 quality of the active substance from the specific source has been discussed.

375 In cases where reference to a pharmacopoeial monograph listed above cannot be made, impurities  
376 (e.g. degradation products, residual solvents) deriving from the manufacturing process or starting  
377 materials relevant to the drug substance used for the clinical trial, should be stated.

378 Discussion on (potential) mutagenic impurities according to ICH M7 should be provided (structure,  
379 origin, limit justification). The level of detail necessary depends on the phase of the clinical trial.

380 Absence of routine control for solvents/catalysts used in the manufacturing process should be justified.

381 In the case of radio-nuclides or radio-labelled substances which are used in phase I studies in humans  
382 to develop a non-radioactive medicinal product, the radiochemical purity and the chemical purity  
383 should be indicated describing any assumptions made, e.g. as a consequence of the determination

384 being made prior to dilution with cold material. For radiopharmaceutical substances, the radio-nuclidic  
385 purity, the radiochemical purity and the chemical purity should be stated and discussed.

386 For herbal substances or herbal preparations, data on potential contamination by micro-organisms,  
387 products of micro-organisms, aflatoxins, pesticides, toxic metals, radioactive contamination, fumigants,  
388 etc. should be stated. The general requirements of the Ph. Eur. should be fulfilled.

#### 389 **2.2.1.S.4 Control of the Drug Substance**

##### 390 **2.2.1.S.4.1 Specification(s)**

391 The specifications, the tests used as well as their acceptance criteria should be specified for the  
392 batch(es) of drug substance(s) used in the clinical trial. Tests for identity, impurities and assay are  
393 mandatory. Upper limits, taking safety considerations into account, should be set for the impurities.  
394 They may need to be reviewed and adjusted during further development. The limits should be  
395 supported by the impurity profiles of batches of active substance used in non-clinical and clinical  
396 studies. If ICH or Ph.Eur. requirements are met, no further limit justification is expected.

397 Where specifications are set for (potential) mutagenic impurities, the guidance given in relevant  
398 guidelines should be taken into consideration.

399 The microbiological quality for drug substances used in aseptically manufactured products should be  
400 specified.

401 For substances which comply with a monograph of the Ph. Eur., the pharmacopoeia of an EU Member  
402 State, USP or JP, reference to the relevant monograph will be sufficient, provided its suitability to  
403 adequately control the quality of the active substance from the specific source has been demonstrated.  
404 The specification should, however, include acceptance criteria for any relevant residual solvent or  
405 catalyst.

406 For radiopharmaceutical drug substances, the level of radio-nuclidic impurities, radiochemical  
407 impurities as well as the chemical impurities should be addressed.

#### 408 **Additional information for phase II and phase III clinical trials**

409 Specifications and acceptance criteria set for previous phase I or phase II trials should be reviewed  
410 and, where appropriate, adjusted to the current stage of development.

##### 411 **2.2.1.S.4.2 Analytical procedures**

412 The analytical methods used for the drug substance should be described for all tests included in the  
413 specification (e.g. reverse-phase-HPLC-UV, potentiometric titration, head-space-GC-FID, etc.). It is not  
414 necessary to provide a detailed description of the analytical procedures (see definition of analytical  
415 methods vs. analytical procedures in chapter 1.5 General Considerations).

416 For radiopharmaceutical substances, the method used for the measurement of radioactivity should be  
417 described.

418 For substances which comply with a monograph of the Ph. Eur., the pharmacopoeia of an EU Member  
419 State, USP or JP, reference to the relevant monograph will be sufficient.

420 **2.2.1.S.4.3 Validation of analytical procedures**

421 **Information for phase I clinical trials**

422 The suitability of the analytical methods used should be confirmed. The acceptance limits (e.g.  
423 acceptance limits for the determination of the content of impurities, where relevant) and the  
424 parameters (specificity, linearity, range, accuracy, precision, quantification and detection limit, as  
425 appropriate) for performing validation of the analytical methods should be presented in a tabulated  
426 form.

427 **Information for phase II and III clinical trials**

428 The suitability of the analytical methods used should be demonstrated. A tabulated summary of the  
429 results of the validation carried out should be provided (e.g. results or values found for specificity,  
430 linearity, range, accuracy, precision, quantification and detection limit, as appropriate). It is not  
431 necessary to provide a full validation report.

432 For substances which comply with a monograph of the Ph. Eur., the pharmacopoeia of an EU Member  
433 State, USP or JP, reference to the relevant monograph will be sufficient.

434 In case of major changes in analytical methods, cross-validation data should be presented especially  
435 for specified unknown impurities identified by their relative retention time (RRT) unless otherwise  
436 justified. A re-analysis of preclinical batch with the new method should also be considered, where  
437 relevant.

438 **2.2.1.S.4.4 Batch analyses**

439 Batch results in a tabulated form or certificate of analysis for batches to be used in the current clinical  
440 trial, for batches used in the non-clinical studies and, where needed, for representative batches used in  
441 previous clinical trials (e.g. in case the comparable quality of batches manufactured by previous  
442 processes has to be demonstrated), should be supplied. If data are not available for the batches to be  
443 used in the current clinical trial, data for representative batches for each drug substance manufacturer  
444 may be submitted instead. The batch number, batch size, manufacturing site, manufacturing date,  
445 control methods, and the test results should be listed.

446 The manufacturing process used for each batch should be assigned as stated under 2.2.1.S.2.2.

447 **2.2.1.S.4.5 Justification of specification(s)**

448 For substances for which reference to a pharmacopoeial monograph listed under 2.2.1.S.4.1 cannot be  
449 made, a brief justification of the specifications and acceptance criteria for impurities and any other  
450 parameters which may be relevant to the performance of the drug product should be provided based  
451 on safety and toxicity data, as well as the methods used for the control of impurities. The solvents and  
452 catalysts used in the synthesis should be taken into consideration.

453 **2.2.1.S.5 Reference standards or materials**

454 The parameters characterising the batch of drug substance established as reference standard should  
455 be presented, where applicable.

456 For radiopharmaceuticals, data on the standards used for calibration and the non-radioactive (cold)  
457 standards should be provided.

458 For herbal preparations, the parameters characterising the primary reference standards should be  
459 given. In cases where the herbal substance is not described in a monograph of the Ph. Eur. or a  
460 monograph in the pharmacopoeia of an EU Member State, a characterised herbarium sample should be  
461 available.

#### 462 **2.2.1.S.6 Container closure system**

463 The immediate packaging material used for the drug substance should be stated. If non-compendial  
464 materials are used, a description and specifications should be provided.

#### 465 **2.2.1.S.7 Stability**

466 The stability data available at the respective stage of development should be summarised in tables.  
467 Stability data should be provided for batch(es) manufactured according to the representative process  
468 (the same/very similar synthesis, comparable batch size) and can be supported by data from batch(es)  
469 manufactured by previous processes. The parameters known to be critical for the stability of the drug  
470 substance need to be presented, i.e. chemical and physical sensitivity, e.g. photosensitivity,  
471 hygroscopicity. Potential degradation pathways should be described. Alternatively, for active  
472 substances covered by a pharmacopoeial monograph, confirmation that the active substance will meet  
473 specifications at time of use will be acceptable.

474 The retest period should be defined based on the available stability data and should be clearly stated.  
475 For drug substances covered by a Certificate of Suitability (CEP) which does not include a retest date,  
476 supporting stability data and a retest period should be provided. In case no retest period is defined,  
477 statement should be included that the drug substance is tested immediately before the drug product  
478 manufacture.

479 The retest period can be extended without a substantial modification submission, if a stability protocol,  
480 retest period extension plan and a statement that in case of any significant negative trend the Sponsor  
481 will inform the competent authority are provided. The stability protocol should cover the maximum  
482 planned re-test period.

483 For herbal preparations, results of stress testing may be omitted, where justified.

### 484 **2.2.1.P Investigational medicinal product under test**

#### 485 **2.2.1.P.1 Description and composition of the investigational medicinal** 486 **product**

487 The complete qualitative and quantitative composition of the IMP should be stated. For proprietary  
488 prefabricated components (e.g. capsule shells), flavours and excipient mixtures (e.g. film-coating  
489 mixtures), a qualitative composition is sufficient. A short statement or a tabulation of the dosage form  
490 and the function of each excipient should be included. Standard terminology from the EDQM standard  
491 terms database should be preferably used for dosage forms, where applicable.

492 In addition, the radioactivity per unit should be specified for radiopharmaceuticals. Radioactivity should  
493 only be expressed in Becquerel at a given date, and time if appropriate. If a calibration time is stated,  
494 the time zone used should be stated (e.g. GMT/CET).



495 **2.2.1.P.2 Pharmaceutical development**

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

498 For early development, there may be no or only limited information to include in this section.

499 The medicinal product components, the dosage form and the administration device if any should be  
500 safe and suitable for the patient population.

501 Where applicable, the compatibility with solvents used for reconstitution, diluents and admixtures  
502 should be demonstrated. For products to be reconstituted or diluted prior to their use, the method of  
503 preparation should be summarised and reference made to a full description in the clinical protocol or  
504 associated handling instructions which will be available at the clinical site should be provided.

505 For kits for radiopharmaceutical preparations, the suitability of the method used for the radio-labelling  
506 for the intended use should be demonstrated (including results on the physiological distribution after  
507 radio-labelling in rats/rodents). For radio-nuclide generators, the suitability of the elution medium  
508 should be proven. For radiopharmaceuticals, the effect of radiolysis on the purity should be addressed.

509 **Additional information for phase II and phase III clinical trials**

510 If changes in the formulation or dosage form compared to the IMP used in earlier clinical trials have  
511 been made, the relevance of the earlier material compared to the product under testing should be  
512 described. Special consideration should be given to dosage form specific changes in quality parameters  
513 with potential clinical relevance, e.g. in vitro dissolution rate.

514 **2.2.1.P.2.1 Manufacturing process development**

515 Changes in the current manufacturing process compared to the ones used in earlier clinical trials are to  
516 be explained. Special consideration should be given to dosage form specific changes in quality  
517 parameters with potential clinical relevance, e.g. in vitro dissolution rate.

518 **2.2.1.P.3 Manufacture**

519 **2.2.1.P.3.1 Manufacturer(s)**

520 The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and  
521 each proposed site involved in manufacture, packaging/assembly and testing should be provided. In  
522 case that multiple manufacturers contribute to the manufacture of the IMP, their respective  
523 responsibilities need to be clearly stated. Site(s) responsible for import or/and QP release in the EEA  
524 should be also stated.

525 When re-packaging and or re-labelling is carried out at a hospital, health centre or clinic where the  
526 investigational medicinal product is to be used for the trial exclusively at those institutions, and where  
527 an exemption from the need to hold a manufacturing authorisation, as provided for in article 61 (5) of  
528 the Regulation (EU) No. 536/2014 applies, it is not necessary to provide the names and addresses of  
529 those institutions in this section. If relevant, it is sufficient to indicate that these activities will take  
530 place.



531 **2.2.1.P.3.2 Batch formula**

532 The batch formula for the batch to be used for the clinical trial should be presented. Where relevant,  
533 an appropriate range of batch sizes may be given.

534 **2.2.1.P.3.3 Description of manufacturing process and process controls**

535 A flow chart of the successive steps, indicating the components used for each step and including any  
536 relevant in-process controls, should be provided. In addition, a brief narrative description of the  
537 manufacturing process should be included.

538 Non-standard manufacturing processes or new technologies and new packaging processes should be  
539 described in more detail (c.f. Annex II to Note for Guidance on Process Validation: Non-Standard  
540 Processes (CPMP/QWP/2054/03)).

541 **2.2.1.P.3.4 Controls of critical steps and intermediates**

542 Information is not required for phase I and II clinical trials, with the exception of:

- 543 • Non-standard manufacturing processes; and  
544 • Manufacturing processes for sterile products.

545 For sterilisation by filtration the maximum acceptable bioburden prior to the filtration must be stated in  
546 the application. In most situations NMT 10 CFU/100 ml will be acceptable, depending on the volume to  
547 be filtered in relation to the diameter of the filter. If this requirement is not met, a pre-filtration  
548 through a bacteria-retaining filter should be carried out in order to obtain a sufficiently low bioburden.  
549 If availability of the formulated medicinal product is limited, a prefiltration/filtration volume of less than  
550 100 ml may be tested if justified.

551 Statement that aseptic processing operations were validated using media fill runs should be provided.

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

553 If critical manufacturing steps have been identified; their control as well as possible intermediates  
554 should be documented.

555 Should intermediates be stored, assurance should be provided that duration and conditions of storage  
556 are appropriately controlled.

557 **2.2.1.P.3.5 Process validation and/or evaluation**

558 Data are not required during the development phases, i.e. clinical phases I to III, except for non-  
559 standard sterilisation processes not described in the Ph. Eur., USP or JP. In this case, the critical  
560 manufacturing steps, the validation of the manufacturing process as well as the applied in process  
561 controls should be described.

562 **2.2.1.P.4 Control of excipients**

563 **2.2.1.P.4.1 Specifications**

564 References to the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP should be indicated.  
565 For excipients not described in one of the mentioned pharmacopoeias, reference to the relevant food-  
566 chemical regulations (e.g. FCC) can be made. For excipient mixtures composed of pharmacopoeial  
567 substances, e.g. pre-fabricated dry mix for film-coating, a general specification of the mixture will  
568 suffice. For excipients not covered by any of the afore-mentioned standards, an in-house monograph  
569 should be provided. Specification for capsule shells should be provided.

570 **2.2.1.P.4.2 Analytical procedures**

571 In cases where reference to a pharmacopoeial monograph listed under 2.2.1.P.4.1 cannot be made,  
572 the analytical methods used should be indicated.

573 **2.2.1.P.4.3 Validation of the analytical procedures**

574 Not applicable.

575 **2.2.1.P.4.4 Justification of specifications**

576 Not applicable.

577 **2.2.1.P.4.5 Excipients of animal or human origin**

578 Cf. section 7.2.1.A.2.

579 **2.2.1.P.4.6 Novel excipients**

580 For novel excipients, details are to be given on their manufacturing process, characterisation and  
581 control in relevance to product safety. Information as indicated in section 3.2.S of the CTD should be  
582 provided in annex 2.1.A.3 consistent with the respective clinical phase (c.f. section 7.2.1.A.3), details  
583 are to be included on e.g. their manufacturing process, characterisation and stability.

584 **2.2.1.P.5 Control of the investigational medicinal product**

585 **2.2.1.P.5.1 Specifications**

586 The chosen release and shelf-life specifications should be submitted, including test methods and  
587 acceptance criteria. At least, tests on identity, assay and degradation products should be included for  
588 any pharmaceutical form.

589 Upper limits may be set for both individual degradation products and the sum of degradation products.  
590 Safety considerations should be taken into account. The limits should be supported by the impurity  
591 profiles of batches of active substance used in non-clinical/clinical studies. The specifications and  
592 acceptance criteria should be reviewed and adjusted during further development.

593 Drug product specific tests and acceptance criteria should be included in the specifications in line with  
594 the pharmaceutical form used (e.g. dissolution/disintegration for oral solid dosage forms; uniformity of  
595 dosage units; or pH, bacterial endotoxins and sterility for parenteral dosage forms).

596 The omission of drug product specific tests should be justified.

597 For radiopharmaceuticals, it should be specified which tests are carried out prior to batch release and  
598 which tests are carried out retrospectively. For kits for radiopharmaceutical preparations, appropriate  
599 tests after radioactive radio-labelling should be stated.

600 For medicinal products to be reconstituted or diluted prior to their use, the acceptable quality standard  
601 after preparation should be stated and documented by development testing.

## 602 **Additional information for phase II and phase III clinical trials**

603 Specifications and acceptance criteria set for previous phase I or phase II trials should be reviewed  
604 and, where appropriate, adjusted to the current stage of development.

### 605 **2.2.1.P.5.2 Analytical procedures**

606 The analytical methods should be described for all tests included in the specification (e.g. dissolution  
607 test method). It is not necessary to provide a detailed description of the analytical procedures (see  
608 definition of analytical methods vs. analytical procedures in chapter 1.5 General considerations).

609 For complex or innovative pharmaceutical forms, a higher level of detail may be required.

### 610 **2.2.1.P.5.3 Validation of analytical procedures**

611 For phase I clinical trials, the suitability of the analytical methods used should be confirmed. The  
612 acceptance limits (e.g. acceptance limits for the determination of the content of impurities, where  
613 relevant) and the parameters (specificity, linearity, range, accuracy, precision, quantification and  
614 detection limit, as appropriate) for performing validation of the analytical methods should be presented  
615 in a tabulated form.

## 616 **Additional information for phase II and III clinical trials**

617 The suitability of the analytical methods used should be demonstrated. A tabulated summary of the  
618 results of the validation should be provided (e.g. results or values found for specificity, linearity, range,  
619 accuracy, precision, quantification and detection limit, as appropriate). It is not necessary to provide a  
620 full validation report.

### 621 **2.2.1.P.5.4 Batch analyses**

622 Batch results in a tabulated form or certificates of analysis for representative batches (same  
623 manufacturing site, same manufacturing process, same composition, and comparable batch size,  
624 unless otherwise justified,) to be used in the clinical trial should be provided. The results should cover  
625 the relevant strengths to be used in the trial.

626 The batch number, batch size, manufacturing site, manufacturing date, control methods, and the test  
627 results should be listed.

628 In case of more than one bulk manufacturing sites, it is necessary to provide results for batches which  
629 have been produced by each of the bulk manufacturing sites relevant for the current trial unless  
630 otherwise justified, (e.g. where one legal entity has multiple sites (in the same country), then batch  
631 analysis data from one site only would be sufficient).

632 Results for batches controlled according to previous, wider specifications are acceptable if the results  
633 comply with the specifications for the planned clinical trial.

#### 634 **2.2.1.P.5.5 Characterisation of impurities**

635 Additional impurities/degradants observed in the IMP, but not covered by section 2.2.1.S.3.2, should  
636 be stated.

#### 637 **2.2.1.P.5.6 Justification of specification(s)**

638 For IMPs in phase I clinical trials, it will be sufficient to briefly justify the specifications and acceptance  
639 criteria for degradation products and any other parameters that may be relevant to the performance of  
640 the drug product. Toxicological justification should be given, where appropriate.

#### 641 **Additional information for phase II and phase III clinical trials**

642 The choice of specifications and acceptance criteria for parameters which may affect efficacy or safety  
643 should be briefly justified.

#### 644 **2.2.1.P.6 Reference standards or materials**

645 The parameters for characterisation of the reference standard should be submitted, where applicable.  
646 Section 2.2.1.S.5 - Reference Standards or Materials - may be referred to, where applicable. For  
647 radiopharmaceuticals, information should be provided on radioactive standards used in the calibration  
648 of radioactivity measurement equipment.

#### 649 **2.2.1.P.7 Container closure system**

650 The intended immediate packaging and additionally, where relevant for the quality of the drug product,  
651 the outer packaging to be used for the IMP in the clinical trial, should be stated. Where appropriate,  
652 reference should be made to the relevant pharmacopoeial monograph. If the product is packed in a  
653 non-standard administration device, or if non-compendial materials are used, a description and  
654 specifications should be provided. For dosage forms that have a higher potential for interaction  
655 between filling and container closure system (e.g. parenterals, ophthalmic products, oral solutions),  
656 more details may be needed for phase III studies (e.g. extractables, leachables). For dosage forms  
657 where an interaction is unlikely, e.g. solid oral dosage forms, a justification for not providing any  
658 information may suffice.

#### 659 **2.2.1.P.8 Stability**

660 The shelf-life and storage conditions of the IMP should be defined based on the stability profile of the  
661 active substance and the available data on the IMP. Stability data for representative batch(es) should  
662 be provided in a tabulated form. Extrapolation may be used, provided that stability studies are  
663 conducted in parallel to the clinical studies and throughout its entire duration. Shelf life extrapolation  
664 can be made under the following conditions:

- 665
- Results at long-term as well as at accelerated storage conditions are available;
  - No significant changes in stability behaviour are observed. If any observed, justification should be provided;
- 667

- 668 • Stability protocol covering the proposed extrapolated shelf life should be provided;
- 669 • Criteria used to extrapolate data should be clearly defined; and
- 670 • Depending on the data available:
- 671 - A fourfold extrapolation of accelerated stability data may be acceptable up to a shelf life of
- 672 12 months
- 673 - An extrapolation of + max 12 months to long-term stability data available (at least 6-
- 674 months) may be acceptable for a shelf life of more than 12 months
- 675 - Other schemes may be possible but should be justified.

676 Furthermore, bracketing and matrixing designs of appropriate IMPs may be acceptable, where justified.

677 The batches of drug product must meet specification requirements throughout the period of use. If

678 issues arise, then the Competent Authorities should be informed of the situation, including any

679 corrective action proposed.

680 In case the drug product is stored in a bulk for a significant time period, relevant stability data should

681 be provided as well as shelf life, storage conditions and packaging material for the bulk. In case the

682 final drug product shelf life is calculated not from the first mixing of the drug substance with excipients

683 but from the time of packaging into the primary package, this should be clearly stated and justified.

684 Any proposal for a future shelf life extension without substantial modification submission should be

685 stated in the IMPD. Stability protocol, shelf life extension plan and a statement that in case of any

686 significant negative trend the Sponsor will inform the competent authority should be provided. The

687 stability protocol should cover the maximum planned shelf life.

688 For preparations intended for applications after reconstitution, dilution or mixing, and products in

689 multi-dose containers, excluding oral solid dosage forms, in-use stability data should be presented. In-

690 use stability studies should cover the practice described in the clinical protocol. Relevant parameters

691 should be monitored within the in-use stability studies (e.g. appearance, assay, impurities, visible and

692 sub-visible particles, microbial contamination). Shelf life and storage conditions after first opening

693 and/or after reconstitution and/or dilution should be defined. These studies are not required if the

694 preparation is to be used immediately after opening or reconstitution and if it can be justified that no

695 negative influence on the quality of the preparation through instabilities is to be expected.

696 For radiopharmaceuticals, the time of calibration should be specified, since the stability also depends

697 on the half-life of the radioactive isotope.

## 698 **Information for phase I clinical trials**

699 For phase I clinical trials, it should be confirmed that an ongoing stability program will be carried out

700 with the relevant batch(es) and that, prior to the start of the clinical trial, at least studies under

701 accelerated and long-term storage conditions will have been initiated. Where available, the results

702 from these studies should be summarised in a tabulated form. Supportive data from development

703 studies should be summarised in a tabular overview. An evaluation of the available data and

704 justification of the proposed shelf-life to be assigned to the IMP in the clinical trial should be provided.

## 705 **Additional information for phase II and phase III clinical trials**

706 The available stability data should be presented in a tabulated form. An evaluation of the available  
707 data and justification of the proposed shelf- life to be assigned to the IMP in the clinical trial should be  
708 provided. Data should include results from studies under accelerated and long-term storage conditions.

709 For radiopharmaceuticals, the time of calibration should be specified. The general stability guidelines  
710 are not fully applicable for ready-for-use radiopharmaceuticals, radio-nuclide generators and  
711 radioactive precursors. However, the aspects reflected in the Guideline on Radiopharmaceuticals  
712 (EMA/CHMP/QWP/306970/2007) should be taken into consideration.

## 713 **3. Information on the chemical and pharmaceutical quality of** 714 **authorised, non-modified test and comparator products in** 715 **clinical trials**

716 For test and comparator products to be used in clinical trials which have already been authorised in the  
717 EU/EEA or in one of the ICH-regions (and are sourced from these countries), it will be sufficient to  
718 provide the name of the MA-holder and the MA-number as proof for the existence of a MA, incl. copy of  
719 the SmPC/Summary of Product Characteristics or its equivalent e.g. Prescribing information. For  
720 repackaged/modified authorised products, see following chapter.

721 The applicant or sponsor of the clinical trial has to ensure that the IMP is stable at least for the  
722 anticipated duration of the clinical trial in which it will be used. For authorised, not modified products,  
723 it will be sufficient to state that the respective expiry date assigned by the manufacturer will be used.

724 For IMPs sourced from outside of the EU/EEA or ICH regions, a full documentation, according to the  
725 requirements stated in chapter 2 of this guideline, should be submitted.

## 726 **4. Information on the chemical and pharmaceutical quality of** 727 **modified authorised test and comparator products in clinical** 728 **trials**

729 In preparing supplies for clinical trials, applicants often modify or process medicinal products which  
730 have already been authorised in order to use them as test/comparator products in blinded studies.

731 As the marketing authorisation holder (MAH) of a authorised product is only responsible for the un-  
732 changed product in its designated and authorised packaging, there is a need to ensure that the quality  
733 of the product is not negatively affected by the modifications performed by the applicant or sponsor of  
734 the clinical trial, with special emphasis on the biopharmaceutical properties.

### 735 **4.2.1.P Modified test/comparator product**

#### 736 **4.2.1.P.1 Description and composition**

737 In the case of any modification of the authorised product other than repackaging, the complete  
738 quantitative composition of the preparation should be specified. All additional substances/materials  
739 added to the authorised product should be listed with reference to pharmacopoeial or in-house  
740 monographs. For the authorised product itself, reference to the name and marketing authorisation  
741 (MA) number will suffice, including a copy of the SPC/PIL in Module 1.

742 **4.2.1.P.2 Pharmaceutical development**

743 The modifications carried out on the authorised product should be described and their influence on the  
744 quality of the product discussed. Special focus should be assigned to all parameters relevant for the  
745 function, stability and efficacy of the medicinal product, such as in vitro-dissolution and pH-value. It  
746 should be demonstrated that these parameters remain comparable to those of the unmodified product.

747 Compatibility with other solvents (that are not stated in the original SmPC) used for drug product  
748 reconstitution and dilution should be demonstrated. Compatibility studies reflecting the practice  
749 described in the clinical protocol (e.g. dispersion of a tablet or content of the hard capsule in  
750 water/juice/food) should be performed in case of unstable products and/or in case of preparation in  
751 advance.

752 In case of solid oral dosage forms, comparative dissolution profiles of both original and modified  
753 product should be provided to ensure unchanged bio-pharmaceutical properties. In those cases where  
754 comparability cannot be established in vitro, additional clinical data to support equivalence may be  
755 necessary.

756 **4.2.1.P.3 Manufacture**

757 **4.2.1.P.3.1 Manufacturer(s) related to the modification**

758 The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and  
759 each proposed site involved in the modification, packaging/assembly and testing of the modified  
760 product should be provided. In case that multiple manufacturers contribute to the manufacture of the  
761 IMP, their respective responsibilities need to be clearly stated. Sites responsible for import or/and QP  
762 release in the EEA should be also stated.

763 When re-packaging and or re-labelling is carried out at a hospital, health centre or clinic where the  
764 investigational medicinal product is to be used for the trial exclusively at those institutions, and where  
765 an exemption from the need to hold a manufacturing authorisation, as provided for in article 61 (5) of  
766 the Regulation (EU) No. 536/2014 applies, it is not necessary to provide the names and addresses of  
767 those institutions in this section. If relevant, it is sufficient to indicate that these activities will take  
768 place.

769 **4.2.1.P.3.2 Batch formula**

770 The batch formula for the batch intended to be used during the clinical trial should be presented. This  
771 does not apply to authorised products which are only re-packaged.

772 **4.2.1.P.3.3 Description of manufacturing process and process controls**

773 All steps of the modification of the authorised medicinal product should be described, including in-  
774 process controls that are carried out. For details, reference is made to section. 2.2.1.P.3.3).

775 **4.2.1.P.4 Control of excipients**

776 **4.2.1.P.4.1 Specifications**

777 References to the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP should be indicated.  
778 For excipients not described in one of the mentioned pharmacopoeias, reference to the relevant food-

779 chemical regulations (e.g. FCC) can be made. For excipient mixtures composed of pharmacopoeial  
780 substances, e.g. pre-fabricated dry mix for film-coating, a general specification of the mixture will  
781 suffice. For excipients not covered by any of the afore-mentioned standards, an in-house monograph  
782 should be provided. Specification for capsule shells should be provided.

#### 783 **4.2.1.P.4.2 Analytical procedures**

784 In cases where reference to a pharmacopoeial monograph listed under 4.2.1.P.4.1 cannot be made,  
785 the analytical methods used should be indicated.

#### 786 **4.2.1.P.4.3 Validation of analytical procedures**

787 Not applicable.

#### 788 **4.2.1.P.4.4 Justification of specifications**

789 Not applicable.

#### 790 **4.2.1.P.4.5 Excipients of animal or human origin**

791 Cf. Appendix 7.2.1.A.2.

#### 792 ***4.2.1.P.5 Control of the modified authorised product***

##### 793 **4.2.1.P.5.1 Specifications**

794 The chosen release and shelf-life specifications of the modified authorised product should be  
795 submitted, including test methods and acceptance criteria. Generally, they should include description  
796 and identification of the drug substance as well as the control of important pharmaceutical and  
797 technological properties, such as dissolution. Where an intact solid oral dosage form that is easily  
798 identifiable by its colour, shape and marking is encapsulated, identification of the active substance may  
799 not be necessary, and visual examination may suffice for identification. Depending on the degree of  
800 modification of the authorised product, additional quality criteria, e.g. determination of the drug  
801 substance(s) and impurities/degradants, may need to be specified and tested.

##### 802 **4.2.1.P.5.2 Analytical procedures**

803 For parameters relevant to the performance of the modified authorised product, e.g. dissolution, the  
804 methods should be described. It is not necessary to provide a detailed description of the analytical  
805 procedures (see definition of analytical methods vs. analytical procedures in chapter 1.5 General  
806 considerations).

##### 807 **4.2.1.P.5.3 Validation of analytical procedures**

808 The suitability of the analytical methods used should be demonstrated. A tabulated summary of the  
809 results of validation of the analytical methods should be provided (e.g. results or values found for  
810 specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate). It is  
811 not necessary to provide a full validation report.



#### 812 **4.2.1.P.5.4 Batch analyses**

813 Results or certificates of analysis for the batch of modified authorised product to be used in the clinical  
814 trial or of a representative batch should be provided.

815 In case of more than one bulk manufacturing sites, it is necessary to provide results for batches which  
816 have been produced by each of the bulk manufacturing sites relevant for the current trial unless  
817 otherwise justified, (e.g. where one legal entity has multiple sites (in the same country), then batch  
818 analysis data from one site only would be sufficient).

819 The batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance  
820 criteria and the test results should be listed.

#### 821 **4.2.1.P.5.5 Characterisation of impurities**

822 In those cases, where the authorised product has undergone significant modification by the sponsor,  
823 e.g. has been processed with an excipient hitherto not present in the formulation with a likely impact  
824 on product stability, and the original product is not known to be stable under normal conditions, special  
825 emphasis should be given to demonstrating that the impurity profile has not changed compared to the  
826 original product. For stable authorised products, where a small degree of modification has been  
827 undertaken by the sponsor, e.g. where an intact tablet is encapsulated using the ingredients already  
828 present in the tablet, justification for not quantifying impurities will suffice (for definition of "stable" cf.  
829 Note for Guidance on Stability Testing of New Drug Substances and Products (CPMP/QWP/2736/99),  
830 section 2.2.7 "Storage conditions"). This is not required for authorised products which are only re-  
831 packaged.

#### 832 **4.2.1.P.5.6 Justification of specification(s)**

833 A justification of specification(s) will only be required in cases where a significant modification of the  
834 authorised product may affect the product's performance or safety.

#### 835 **4.2.1.P.7 Container closure system**

836 The type of immediate packaging, material and package size(s) should be specified. If materials other  
837 than those authorised are used, a description and specifications should be provided. Where  
838 appropriate, reference should be made to the relevant pharmacopoeial monograph. If the  
839 test/comparator product is packed in a non-standard administration device, or if non-compendial  
840 materials are used, a description and specifications should be provided.

#### 841 **4.2.1.P.8 Stability**

842 The applicant or sponsor of the clinical trial has to ensure that the modified test/comparator product is  
843 stable for at least the anticipated duration of the clinical trial in which it will be used.

844 In the case of any modification with a likely significant impact on product stability, a minimum of  
845 stability data on the modified authorised product should be available, depending on the length of the  
846 planned clinical trial, prior to the start of the clinical trial in order to allow an assessment of the impact  
847 of the modifications on product safety and stability. The available stability data should be presented in  
848 a tabulated form. An evaluation of the available data and justification of the proposed shelf-life to be

849 assigned to the IMP in the clinical trial should be provided. Any degree of extrapolation may not exceed  
850 the shelf-life originally assigned to the specific batch of authorised product by its MAH.

851 Shelf life extension without a substantial modification submission can be approved under the same  
852 conditions as described in the section 2.2.1.P.8.

853 In the case of only minor modifications, a justification of the stability over the intended trial period  
854 may be acceptable.

855 In-use stability studies should be performed in case of use of the comparator product in different  
856 conditions as those described in the SPC (according to the clinical protocol), if not otherwise justified  
857 (the same requirements as defined in section 2.2.1.P.8 apply).

## 858 **5. Information on the chemical and pharmaceutical quality of** 859 **investigational medicinal products containing existing active** 860 **substances used in bio-equivalence studies, e.g. generics** 861 **(chemical substances)**

862 This section of the guideline is only relevant for the test product. Information on the  
863 comparator/innovator product to be provided in the IMPD should meet the requirements as outlined in  
864 sections 3 and 4, respectively.

### 865 **5.2.1.S Drug substance**

866 Reference to an Active Substance Master File or a Certificate of Suitability of the European Directorate  
867 for the Quality of Medicines is acceptable. The procedure as described in the "Guideline on Active  
868 Substance Master File Procedure – CPMP/QWP/227/02 Rev 3 corr" and the "Guideline on Summary of  
869 Requirements for Active Substances in the Quality Part of the Dossier – CHMP/QWP/297/97 Rev 1" in  
870 their current version should be followed, even though no specific reference to clinical trials application  
871 is included.

872 For reference to pharmacopoeial monographs, see chapter 1.5 General Considerations.

873 If the Active substance used is already authorised in a drug product within the EU/EEA or in one of the  
874 ICH-regions, reference can be made to the valid marketing authorisation. A statement should be  
875 provided that the active substance has the same quality as in the approved product.

876 Name of the drug product, marketing authorisation number or its equivalent, marketing authorisation  
877 holder and the country that granted the marketing authorisation should be given.

#### 878 **5.2.1.S.1 General information**

##### 879 **5.2.1.S.1.1 Nomenclature**

880 Information concerning the nomenclature of the drug substance (e.g. (proposed) INN-name,  
881 pharmacopoeial name, chemical name, code, and other names, if any) should be given.

##### 882 **5.2.1.S.1.2 Structure**

883 The structural formula should be presented.

884 **5.2.1.S.1.3 General Properties**

885 The main physicochemical and other relevant properties of the drug substance should be indicated.

886 **5.2.1.S.2 Manufacture**

887 **5.2.1.S.2.1 Manufacturer(s)**

888 The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and  
889 each proposed site involved in manufacture and testing should be provided.

890 **5.2.1.S.2.2 Description of manufacturing process and process controls**

891 For substances which comply to the European Pharmacopoeia (Ph. Eur.), the Pharmacopoeia of an EU  
892 Member State, the United States Pharmacopoeia (USP) or the Japanese Pharmacopoeia (JP) reference  
893 to the monographs is acceptable, but suitability of the referenced monograph to adequately control the  
894 quality of the active substance (impurity profile) should be discussed by submission of sufficient  
895 information on the manufacturing process of the active substance (see section 1.5).

896 In cases where reference to a pharmacopoeial monograph listed above cannot be made, a brief  
897 summary of the synthesis process, a flow chart of the successive steps including, for each step, the  
898 starting materials, intermediates, solvents, catalysts and reagents used should be provided. The  
899 stereo-chemical properties of starting materials should be discussed, where applicable.

900 **5.2.1.S.3 Characterisation**

901 **5.2.1.S.3.2 Impurities**

902 For substances which comply with a monograph of the Ph. Eur., the pharmacopoeia of an EU Member  
903 State, USP or JP, no further details are required, provided its suitability to adequately control the  
904 quality of the active substance from the specific source has been discussed.

905 Discussion on (potential) mutagenic impurities should be provided (structure, origin, limit justification),  
906 if relevant.

907 In cases where reference to a pharmacopoeial monograph listed above cannot be made, impurities  
908 (e.g. possible degradation products and residual solvents), deriving from the manufacturing process or  
909 starting materials relevant to the drug substance used for the bio-equivalence study should be stated.

910 Absence of routine control for solvents/catalysts used in the manufacturing process should be justified.

911 **5.2.1.S.4 Control of the drug substance**

912 **5.2.1.S.4.1 Specifications**

913 The microbiological quality of drug substances used in aseptically manufactured products should be  
914 specified.

915 For substances which comply with a monograph of the Ph. Eur., the pharmacopoeia of an EU Member  
916 State, USP or JP, no further details are required, provided its suitability to adequately control the  
917 quality of the active substance from the specific source has been demonstrated. The specification  
918 should, however, include acceptance criteria for any relevant residual solvents and catalysts.

919 In cases where reference to a pharmacopoeial monograph listed above cannot be made, specifications,  
920 tests used as well as the acceptance criteria should be provided for the batch(es) of the drug  
921 substance(s) intended for use in the bio-equivalence study. Tests for identity and assay are  
922 mandatory. Upper limits, taking safety considerations into account, should be set for the impurities.  
923 Where specifications are set for (potential) mutagenic impurities, the guidance given in relevant  
924 guidelines should be taken into consideration.

#### 925 **5.2.1.S.4.2 Analytical procedures**

926 For substances for which reference to a pharmacopoeial monograph listed under 5.2.1.S.4.1 of this  
927 chapter cannot be made, the analytical methods used for the drug substance (e.g. reverse- phase-  
928 HPLC-UV, potentiometric titration, head-space-GC-FID, etc.) should be provided. It is not necessary to  
929 provide a detailed description of the analytical procedures (see definition of analytical methods vs.  
930 analytical procedures in chapter 1.5 General Considerations).

#### 931 **5.2.1.S.4.3 Validation of analytical procedures**

932 For substances for which reference to a pharmacopoeial monograph listed under 5.2.1.S.4.1 of this  
933 chapter cannot be made, the suitability of the analytical methods used should be demonstrated. A  
934 tabulated summary of the results of validation of the analytical methods should be provided (e.g.  
935 values found for repeatability, limit of quantification etc.). It is not necessary to provide a full  
936 validation report.

#### 937 **5.2.1.S.4.4 Batch analyses**

938 Certificates of analyses or batch analysis data for the batch(es) intended for use in the planned bio-  
939 equivalence study or, in their absence, for representative batches, should be supplied. The batch  
940 number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and  
941 test results should be listed.

#### 942 **5.2.1.S.4.5 Justification of specifications**

943 For substances for which reference to a pharmacopoeial monograph listed under 5.2.1.S.4.1 cannot be  
944 made, a brief justification of the specifications and acceptance criteria for impurities and any other  
945 parameters which may be relevant to the performance of the drug product should be provided based  
946 on safety and toxicity data, as well as the methods used for the control of impurities. The solvents and  
947 catalysts used in the synthesis should be taken into consideration.

#### 948 **5.2.1.S.5 Reference Standards or materials**

949 For substances for which reference to a pharmacopoeial monograph listed under 5.2.1.S.4.1 cannot be  
950 made, the parameters characterising the batch of drug substance established as reference standards  
951 should be presented.

#### 952 **5.2.1.S.6 Container closure system**

953 The immediate packaging material used for the drug substance should be stated. If non-compendial  
954 materials are used, a description and specifications should be provided.

955 **5.2.1.S.7 Stability**

956 The available stability data should be provided in a tabulated form. The retest period should be defined  
957 based on the available stability data and should be clearly stated. For drug substances covered by a  
958 Certificate of Suitability (CEP) which does not include a retest date, supporting stability data and a  
959 retest period should be provided. In case no retest period is defined, statement should be included that  
960 the drug substance is tested immediately before the drug product manufacture.

961 **5.2.1.P Investigational medicinal product under test**

962 **5.2.1.P.1 Description and composition**

963 The complete qualitative and quantitative composition of the IMP should be stated. For proprietary  
964 prefabricated components (e.g. capsule shells), flavours and excipient mixtures (e.g. film-coating  
965 mixtures), a qualitative composition is sufficient. Standard terminology from the EDQM standard terms  
966 database should be preferably used for dosage forms, where applicable.

967 **5.2.1.P.2 Pharmaceutical development**

968 A brief narrative description of the dosage form should be provided.

969 **5.2.1.P.3 Manufacture**

970 **5.2.1.P.3.1 Manufacturer(s)**

971 The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and  
972 each proposed site involved in manufacture, packaging/assembly and testing should be provided. In  
973 case multiple manufacturers contribute to the manufacture of the IMP, their respective responsibilities  
974 in the manufacturing chain should be clearly indicated. Site(s) responsible for import or/and QP release  
975 in the EEA should be also stated.

976 When re-packaging and or re-labelling is carried out at a hospital, health centre or clinic where the  
977 investigational medicinal product is to be used for the trial exclusively at those institutions, and where  
978 an exemption from the need to hold a manufacturing authorisation, as provided for in article 61 (5) of  
979 the Regulation (EU) No. 536/2014, it is not necessary to provide the names and addresses of those  
980 institutions in this section. If relevant, it is sufficient to indicate that these activities will take place.

981 **5.2.1.P.3.2 Batch formula**

982 The batch formula for the batch to be used in the planned bio-equivalence study should be presented.  
983 Where relevant, an appropriate range of batch sizes may be given.

984 **5.2.1.P.3.3 Description of manufacturing process and process controls**

985 A flow chart of the successive steps, including the components used for each step and including any  
986 relevant in process controls, should be provided. In addition, a brief narrative description of the  
987 manufacturing process should be included.

988 **5.2.1.P.3.4 Control of critical steps and intermediates**

989 If critical manufacturing steps have been identified; their control as well as possible intermediates  
990 should be documented.

991 Should intermediates be stored, assurance should be provided that duration and conditions of storage  
992 are appropriately controlled.

993 **5.2.1.P.3.5 Process validation and/or evaluation**

994 Data are not required, except for non-standard sterilisation processes not described in the Ph. Eur.,  
995 USP or JP. In this case, the critical manufacturing steps, the validation of the manufacturing process as  
996 well as the applied in process controls should be described.

997 **5.2.1.P.4 Control of excipients**

998 **5.2.1.P.4.1 Specifications**

999 References to the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP should be indicated.  
1000 For excipients not described in one of the mentioned pharmacopoeias, reference to the relevant food-  
1001 chemical regulations (e.g. FCC) can be made. For excipient mixtures composed of pharmacopoeial  
1002 substances, e.g. pre-fabricated dry mix for film-coating, a general specification of the mixture will  
1003 suffice. For excipients not covered by any of the afore-mentioned standards, an in-house monograph  
1004 should be provided. Specification for capsule shells should be provided.

1005 **5.2.1.P.4.2 Analytical procedures**

1006 In cases where reference to a pharmacopoeial monograph listed under 5.2.1.P.4.1 cannot be made,  
1007 the analytical methods used should be indicated.

1008 **5.2.1.P.4.3 Validation of analytical procedures**

1009 Not applicable.

1010 **5.2.1.P.4.4 Justification of specifications**

1011 Not applicable.

1012 **5.2.1.P.4.5 Excipients of animal or human origin**

1013 Cf. Appendix 7.2.1.A.2.

1014 **5.2.1.P.4.6 Novel excipients**

1015 For novel excipients, details are to be given on their manufacturing process, characterisation and  
1016 control in relevance to product safety. Information as indicated in section 3.2.S of the CTD should be  
1017 provided in annex 2.1.A.3 consistent with the respective clinical phase (c.f. section 7.2.1.A.3), details  
1018 are to be included on e.g. their manufacturing process, characterisation and stability.

1019 **5.2.1.P.5 Control of the investigational medicinal product**

1020 **5.2.1.P.5.1 Specifications**

1021 The chosen release and shelf-life specifications should be submitted, including test methods and  
1022 acceptance criteria. At least, tests on identity, assay and degradation products should be included for  
1023 any pharmaceutical form. Drug product specific tests defined in the Ph.Eur. monographs for dosage  
1024 forms (see chapter 1.5 General Considerations) and acceptance criteria should be included in the  
1025 specifications in line with the pharmaceutical form used (e.g. dissolution/disintegration for oral solid  
1026 dosage forms; uniformity of dosage units; or pH, bacterial endotoxins and sterility for parenteral  
1027 dosage forms).

1028 The omission of drug product specific tests should be justified.

1029 **5.2.1.P.5.2 Analytical procedures**

1030 The analytical methods should be described for all tests included in the specification (e.g. dissolution  
1031 test method). It is not necessary to provide a detailed description of the analytical procedures (see  
1032 definition of analytical methods vs. analytical procedures in chapter 1.5 General considerations).

1033 For complex or innovative pharmaceutical forms, a higher level of detail may be required.

1034 **5.2.1.P.5.3 Validation of analytical procedures**

1035 The suitability of the analytical methods used should be demonstrated. A tabulated summary of the  
1036 validation results should be provided (e.g. results or values found for specificity, linearity, range,  
1037 accuracy, precision, quantification and detection limit, as appropriate). It is not necessary to provide a  
1038 full validation report.

1039 **5.2.1.P.5.4 Batch analyses**

1040 Certificates of analysis or batch analysis data for the batch(es) intended to be used in the planned bio-  
1041 equivalence study or, in their absence, representative batches, should be provided.

1042 The batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance  
1043 criteria and the test results should be listed.

1044 **5.2.1.P.5.5 Characterisation of impurities**

1045 Additional impurities/degradants observed in the IMP, but not covered by section 5.2.1.S.3.2, should  
1046 be stated.

1047 **5.2.1.P.5.6 Justification of specification(s)**

1048 It will be sufficient to briefly justify the specifications and acceptance criteria for degradation products  
1049 and any other parameters that may be relevant to the performance of the drug product. Toxicological  
1050 justification should be given, where appropriate.

1051 **5.2.1.P.6 Reference standards or materials**

1052 The parameters for characterisation of the reference standard should be submitted, if no compendial  
1053 reference standard is available.

1054 Section 5.2.1.S.5 – Reference Standards or Materials – may be referred to, where applicable.

1055 **5.2.1.P.7 Container closure system**

1056 The intended immediate packaging and additionally, where relevant for the quality of the drug product,  
1057 the outer packaging to be used for the IMP in the clinical trial, should be stated. Where appropriate,  
1058 reference should be made to the relevant pharmacopoeial monograph. If the product is packed in a  
1059 non-standard administration device, or if non-compendial materials are used, a description and  
1060 specifications should be provided. For dosage forms that have a higher potential for interaction  
1061 between filling and container closure system (e.g. parenterals, ophthalmic products, oral solutions),  
1062 more details may be needed. For dosage forms where an interaction is unlikely, e.g. solid oral dosage  
1063 forms, a justification for not providing any information may suffice.

1064 **5.2.1.P.8 Stability**

1065 For bioequivalence studies, it should be confirmed that an ongoing stability program will be carried out  
1066 with the relevant batch(es) and that, prior to the start of the clinical trial, at least studies under  
1067 accelerated and long-term storage conditions will have been initiated. The results from at least one  
1068 month accelerated studies or the results of the initial phase of studies under long-term storage  
1069 conditions should be summarised in a tabulated form. Supporting data from development studies  
1070 should also be summarised in a tabular overview. An evaluation of the available data and justification  
1071 of the proposed shelf-life and storage conditions to be assigned to the IMP in the bio-equivalence study  
1072 should be provided. Extrapolation may be used, provided a commitment is included to perform an  
1073 ongoing stability study in parallel to the bioequivalence study.

1074 **6. Information on the chemical and pharmaceutical quality**  
1075 **concerning placebo products in clinical trials**

1076 The quality documentation to be submitted for placebos is limited to the following sections of the  
1077 product part.

1078 **6.2.1.P Placebo product in clinical trials**

1079 **6.2.1.P.1 Description and composition**

1080 The complete qualitative and quantitative composition of the placebo should be stated. For proprietary  
1081 prefabricated components (e.g. capsule shells), flavours and excipient mixtures (e.g. film-coating  
1082 mixtures), a qualitative composition is sufficient. A short statement or a tabulation of the dosage form  
1083 and the function of each excipient should be included.

1084 **6.2.1.P.2 Pharmaceutical development**

1085 It should be described how possible differences of the placebo preparation in relation to the  
1086 investigational medicinal product regarding taste, appearance and smell are masked, where applicable.



1087 **6.2.1.P.3 Manufacture**

1088 **6.2.1.P.3.1 Manufacturer(s)**

1089 The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and  
1090 each proposed site involved in manufacture, packaging/assembly and testing should be provided. In  
1091 case that multiple manufacturers contribute to the manufacture of the placebo, their respective  
1092 responsibilities need to be clearly stated.

1093 When re-packaging and or re-labelling is carried out at a hospital, health centre or clinic where the  
1094 investigational medicinal product is to be used for the trial exclusively at those institutions, and where  
1095 an exemption from the need to hold a manufacturing authorisation, as provided for in article 61 (5) of  
1096 the Regulation (EU) No. 536/2014, it is not necessary to provide the names and addresses of those  
1097 institutions in this section. If relevant, it is sufficient to indicate that these activities will take place.

1098 **6.2.1.P.3.2 Batch formula**

1099 The batch formula for the batch to be used for the clinical trial should be presented. Where relevant,  
1100 an appropriate range of batch sizes may be given.

1101 **6.2.1.P.3.3 Description of manufacturing process and process controls**

1102 A flow chart of the successive steps, indicating the components used for each step and including in-  
1103 process controls should be provided. In addition, a brief narrative description of the manufacturing  
1104 process should be included.

1105 **6.2.1.P.3.4 Control of critical steps and intermediates**

1106 Information is not required with the exception of manufacturing processes for sterile products (the  
1107 same requirements as defined in section 2.2.1.P.3.4 apply).

1108 **6.2.1.P.3.5 Process validation and/or evaluation**

1109 Data are not required, except for non-standard sterilisation processes not described in the Ph. Eur.,  
1110 USP or JP. In this case, the critical manufacturing steps, the validation of the manufacturing process as  
1111 well as the applied in process controls should be described.

1112 **6.2.1.P.4 Control of excipients**

1113 **6.2.1.P.4.1 Specifications**

1114 References to the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP should be indicated.  
1115 For excipients not described in one on of the mentioned pharmacopoeias, reference to the relevant  
1116 food-chemical regulations (e.g. FCC) can be made. For excipient mixtures composed of  
1117 pharmacopoeial substances, e.g. pre -fabricated dry mix for film-coating, a general specification of the  
1118 mixture will suffice. For excipients not covered by any of the afore-mentioned standards, an in-house  
1119 monograph should be provided. Specification for capsule shells should be provided.

1120 **6.2.1.P.4.2 Analytical procedures**

1121 In cases where reference to a pharmacopoeial monograph listed under 6.2.1.P.4.1 cannot be made,  
1122 the analytical methods used should be indicated.

1123 **6.2.1.P.4.3 Validation of analytical procedures**

1124 Not applicable.

1125 **6.2.1.P.4.4 Justification of specifications**

1126 Not applicable.

1127 **6.2.1.P.4.5 Excipients of animal or human origin**

1128 Cf. Appendix 7.2.1. A.2.

1129 **6.2.1.P.4.6 Novel excipients**

1130 For novel excipients, details are to be given on their manufacturing process, characterisation and  
1131 control in relevance to product safety. Information as indicated in section 3.2.S of the CTD should be  
1132 provided in annex 2.1.A.3 (c.f. section 7.2.1.A.3) consistent with the respective clinical phase, details  
1133 are to be included on e.g. their manufacturing process, characterisation and stability. If the same novel  
1134 excipient is already described in the IMPD for the respective test product, cross-reference to the  
1135 relevant section will suffice.

1136 **6.2.1.P.5 Control of the placebo product**

1137 **6.2.1.P.5.1 Specifications**

1138 The chosen release and shelf-life specifications should be submitted, including test methods and  
1139 acceptance criteria. The specifications should at minimum include a test which enables to clearly  
1140 differentiate between the respective investigational medicinal product and the placebo.

1141 **6.2.1.P.5.2 Analytical procedures**

1142 The analytical methods should be described for all tests included in the specification. It is not  
1143 necessary to provide a detailed description of the analytical procedures (see definition of analytical  
1144 methods vs. analytical procedures in chapter 1.5 General considerations).

1145 **6.2.1.P.7 Container closure system**

1146 The intended immediate packaging and additionally, where relevant for the quality of the drug product,  
1147 the outer packaging to be used for the placebo in the clinical trial, should be stated.

1148 **6.2.1.P.8 Stability**

1149 The shelf-life and storage conditions of the placebo should be defined. The shelf life of the placebo  
1150 product should preferably cover the anticipated duration of the clinical trial. Stability studies are only  
1151 required in cases where there is reason to suspect that the placebo product will undergo changes in its

1152 physical characteristics or degradation, respectively, e.g. microbial purity of multi-dose containers,  
1153 hardness or appearance. In all other cases, a short justification of the assigned shelf-life will suffice.

## 1154 **7. Appendices**

### 1155 **7.2.1.A.1 Facilities and equipment**

1156 Not applicable.

### 1157 **7.2.1.A.2 Adventitious agents safety evaluation**

1158 All materials of human or animal origin used in the manufacturing process of both drug substance and  
1159 drug product, or such materials coming into contact with drug substance or drug product during the  
1160 manufacturing process, should be identified. Information assessing the risk with respect to potential  
1161 contamination with adventitious agents of human or animal origin should be provided in this section.

#### 1162 ***TSE agents***

1163 Detailed information should be provided on the avoidance and control of transmissible spongiform  
1164 encephalopathy agents. This information can include, for example, certification and control of the  
1165 production process, as appropriate for the material, process and agent.

1166 The "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy  
1167 Agents via Human and Veterinary Medicinal Products, EMEA/410/01" in its current version is to be  
1168 applied.

#### 1169 ***Viral safety***

1170 Where applicable, information assessing the risk with respect to potential viral contamination should be  
1171 provided in this section. The risk of introducing viruses into the product and the capacity of the  
1172 manufacturing process to remove or inactivate viruses should be evaluated.

#### 1173 ***Other adventitious agents***

1174 Detailed information regarding the other adventitious agents, such as bacteria, mycoplasma, and fungi  
1175 should be provided in appropriate sections within the core dossier.

### 1176 **7.2.1.A.3 Novel excipients**

1177 For novel excipients, information as indicated in section.3.2.S of the CTD should be provided,  
1178 consistent with the respective clinical phase.

### 1179 **7.2.1.A.4 Solvents for reconstitution and diluents**

1180 For solvents for reconstitution and diluents, the relevant information as indicated in section 3.2.P of the  
1181 CTD should be provided as applicable.

## 1182 8. Auxiliary medicinal products

1183 For auxiliary medicinal products the same requirements and principles apply as for investigational  
1184 medicinal products. The requirements depend on the type of the product (authorised / not authorised /  
1185 modified / non-modified medicinal product).

## 1186 9. Changes to the investigational medicinal product and 1187 auxiliary medicinal product with a need to request a 1188 substantial modification to the IMPD

1189 In accordance with Good Manufacturing Practice, a Product Specification File should be maintained for  
1190 each IMP/auxiliary medicinal product at the respective site and be continually updated as the  
1191 development of the product proceeds, ensuring appropriate traceability to the previous versions.

1192 ~~Guidance given in this section relates only to changes that need to be notified to the competent  
1193 authorities and when they should be notified.~~

1194 ~~The following examples of changes to IMP/auxiliary medicinal product quality data concerning:~~

- 1195 ~~• Importation of the medicinal product;~~
- 1196 ~~• Change of name or code of IMPs;~~
- 1197 ~~• Container closure system;~~
- 1198 ~~• Manufacturer(s) of drug substance;~~
- 1199 ~~• Manufacturing process of the drug substance;~~
- 1200 ~~• Specifications of active substance;~~
- 1201 ~~• Manufacturer(s) of medicinal product~~
- 1202 ~~• Manufacturing process of the medicinal product;~~
- 1203 ~~• Specification (release or shelf life) of the medicinal product;~~
- 1204 ~~• Specification of excipients where these may affect product performance;~~
- 1205 ~~• Shelf life including after first opening and reconstitution;~~
- 1206 ~~• Major change to the formulation;~~
- 1207 ~~• Storage conditions;~~
- 1208 ~~• Test procedures of active substance;~~
- 1209 ~~• Test procedures of the medicinal product; and~~
- 1210 ~~• Test procedures of non-pharmacopoeial excipients~~

1211  
1212 ~~In compliance with the Clinical Trial Regulation (CTR), a change to IMP/auxiliary medicinal product  
1213 quality data is either:~~

- 1214 ~~- a substantial modification (art 2.2.13)~~
- 1215 ~~- a change relevant to the supervision of the trial (art 81.9)~~
- 1216 ~~- a non-substantial modification (changes outside the scope of substantial modifications and changes  
1217 irrelevant to the supervision of the trial)~~

1218 ~~•~~

1219  
1220 ~~are only to be regarded as “substantial” where they are likely to have a significant impact on:~~

- 1221 ~~— The safety or physical or mental integrity of the patients;~~
- 1222 ~~— The scientific values of the trial;~~

1223 ~~—The conduct or management of the trial;~~

1224 ~~—The quality or safety of any IMP used in the trial.~~

1225 ~~In all cases, a modification is only to be regarded as “substantial” when one or more of the above~~  
1226 ~~criteria are met. The list is not exhaustive; a substantial modification might occur in some other aspect~~  
1227 ~~of a clinical trial.~~

1228  
1229 Substantial modification means any change which is likely to have a substantial impact on the safety  
1230 and rights of the subjects or on the reliability and robustness of the data generated in the clinical trial.

1231 Assessment of an IMPD should be focussed on patient safety. Therefore, any modification involving a  
1232 potential new risk has to be considered a substantial modification. This may be especially the case for  
1233 changes in impurities profile, microbial contamination, viral safety, TSE and in some particular cases to  
1234 stability when toxic degradation products may be generated.

1235

1236 Non-substantial changes relevant to the supervision of the trial (Art 81.9 change) are concept  
1237 introduced under the CTR, which aims to update certain, specified information in the CTIS without the  
1238 need for an substantial modification application, when this information is necessary for oversight but  
1239 does not have a substantial impact on patients safety and rights and/or data robustness. Art 81.9  
1240 states “The sponsor shall permanently update in the EU database information on any changes to the  
1241 clinical trial which are not substantial modifications but are relevant for the supervision of the clinical  
1242 trial by the Member states concerned”. Art 81.9 changes can be submitted only if the change does not  
1243 trigger additional changes, which are expected to be submitted as an substantial modification  
1244 application. The combination of different art 81.9 changes can cumulate into a change that needs to be  
1245 submitted as an SM.

1246

1247 ~~The modifications refer to the submitted IMPD. Should the changes be covered by the IMPD as~~  
1248 ~~submitted, a notification of a substantial modification will not be necessary.~~

1249 For non-substantial modifications documentation should not be proactively submitted, but the relevant  
1250 internal and study documentation supporting the change should be recorded within the company and if  
1251 appropriate, at investigator site. At the time of an overall IMPD update or submission of a substantial  
1252 modification the non-substantial changes should be incorporated into the updated documentation.  
1253 However, when submitting a modified IMPD, the sponsor should clearly identify which changes are  
1254 substantial and which are not.

1255

1256 When a modification will become effective with the start of a new clinical trial (e.g. change of name of  
1257 the IMP, new manufacturing process), the notification will take place with the application for the new  
1258 trial. Notifications-Submissions of substantial modifications are only necessary for changes in ongoing  
1259 clinical trials.

1260

1261 In the following table, examples are given for changes in IMPs, containing chemically defined or herbal  
1262 drug substances, ~~which should be notified as substantial modifications, and for changes, where a~~  
1263 notification will not be necessary and their classification. This list does not claim to be exhaustive. The  
1264 sponsor should decide on a case by case basis ~~if a modification is to be classified as substantial or~~  
1265 not how to classify the change.-

	Changes to IMPD	Substantial changes	<a href="#">Art. 81.9 non-substantial changes</a>	Non-substantial changes
<a href="#">1266</a>	Change of name or code of <a href="#">drug substance/IMP</a>		<ul style="list-style-type: none"> <li>• <a href="#">Change from company code to INN or trade name during ongoing clinical trial (exchange of the label)</a></li> </ul>	
<a href="#">1267</a>	Manufacturer(s) of drug substance	<ul style="list-style-type: none"> <li>• Change to a <a href="#">completely new manufacturer</a></li> <li>• <a href="#">Deletion of manufacturing or testing site (for safety reason, GMP non-compliance)</a></li> </ul>	<ul style="list-style-type: none"> <li>• <a href="#">Replacement or addition of a testing site provided that the same analytical methods are used, and method transfer has been demonstrated</a></li> </ul>	<ul style="list-style-type: none"> <li>• <a href="#">Alternate sites of manufacture within one company with unchanged manufacturing process and specifications</a></li> <li>• <a href="#">Name change of drug substance manufacturer</a></li> <li>• <a href="#">Deletion of a manufacturing or testing site (no safety reason)</a></li> </ul>
<a href="#">1268</a>	Manufacturing process of drug substance	<ul style="list-style-type: none"> <li>• <a href="#">Different route of synthesis</a></li> <li>• Extension of <a href="#">the process parameters or in-process control</a> acceptance criteria</li> <li>• <a href="#">Changes in the physicochemical properties with influence on the quality of the IMP (e.g., particle size distribution, polymorphism <a href="#">in case of solid dosage forms etc.</a>)</a></li> <li>• <a href="#">Change in the manufacturing process of an herbal substance or herbal preparation</a></li> </ul>		<ul style="list-style-type: none"> <li>• <a href="#">Modifications of the process parameters (same process, <a href="#">similar solvents, slight modifications in temperature, pressure, reaction time, stoichiometry etc.</a>)</a></li> <li>• <a href="#">Scale-up <a href="#">not impacting the physicochemical properties or the impurity profile</a></a></li> </ul>
<a href="#">1269</a>	Specification of drug substance	<ul style="list-style-type: none"> <li>• Extension of acceptance criteria</li> <li>• Deletion of tests</li> <li>• <a href="#">Addition of test(s) for safety/quality reasons, e.g. <a href="#">addition of mutagenic impurity control</a></a></li> </ul>	<ul style="list-style-type: none"> <li>• <a href="#">Deletion of test(s) due to compendial change</a></li> </ul>	<ul style="list-style-type: none"> <li>• Tightening of acceptance criteria (no safety reason)</li> <li>• <a href="#">Addition of test(s) with no safety reason</a></li> </ul>

1270	Test methods of drug substance/ drug product	<ul style="list-style-type: none"> <li>• <u>New test method (e.g. NIR instead of HPLC) or method changes requiring new validation</u></li> </ul>		<ul style="list-style-type: none"> <li>• <u>Variation Minor changes of the analytical method already covered by the IMPD for which no additional validation is necessary</u></li> <li>• <u>Update of the test procedure to comply with revised PhEur, USP, or JP monograph</u></li> </ul>
1271	Retest period of drug substance	<ul style="list-style-type: none"> <li>• <u>Reduction of retest period due to safety concern and/or restriction of the storage conditions</u></li> <li>• <u>Extension of retest period not based on a scheme approved within the initial submission</u></li> <li>• <u>Extension of protocol duration through additional timepoints to extend retest period</u></li> </ul>		<ul style="list-style-type: none"> <li>• <u>Extension of retest period based on the scheme approved within the initial submission</u></li> </ul>
1272	Major change to the formulation of medicinal product	<ul style="list-style-type: none"> <li>• <u>Change in the qualitative or quantitative composition in one or more excipients that may have a significant impact on the quality or safety of the IMP (including exchange of excipients to excipients with same functional characteristics, e.g., disintegrant)</u></li> </ul>		<ul style="list-style-type: none"> <li>• <u>Qualitatively identical but quantitatively different composition of non-functional tablet coating if there is no impact on blinding</u></li> <li>• <u>Different form shape of an IR-tablet, e.g. round to capsule shaped, with no clinical impact (e.g. dissolution profile of the new form shape is comparable to the old one)</u></li> </ul>

				<a href="#">and if there is no impact on blinding</a>
<a href="#">1273</a>	Manufacturer(s) of medicinal product	<ul style="list-style-type: none"> <li>• Addition of manufacturing, packaging, or testing site</li> <li>• <a href="#">Deletion of manufacturing, packaging, or testing site (for safety reason, GMP non-compliance)</a></li> </ul>		<ul style="list-style-type: none"> <li>• Deletion of manufacturing, packaging, or testing site (no safety reason)</li> <li>• <a href="#">Name change of the manufacturer</a></li> </ul>
<a href="#">1274</a>	Importation of medicinal product	<ul style="list-style-type: none"> <li>• <a href="#">Addition/change of importing site</a></li> </ul>		
<a href="#">1275</a>	<a href="#">Drug product batch release</a>	<ul style="list-style-type: none"> <li>• <a href="#">Addition/change of batch release certification site (QP certification)</a></li> </ul>		
<a href="#">1276</a>	Manufacture of medicinal product	<ul style="list-style-type: none"> <li>• <a href="#">Significant changes to the manufacturing process (e.g., dry compacting vs. wet granulation, conventional granulation vs. fluid-bed-granulation) and critical process controls (e.g. bioburden limit)</a></li> <li>• <a href="#">Scale-up for non-standard processes (e.g. lyophilization, aseptic manufacturing) or for large scale-ups</a></li> </ul>		<ul style="list-style-type: none"> <li>• Modifications of the process parameters (same process)</li> <li>• <a href="#">Limited scale-up (i.e. such that the multiplication factor for the scale-up does not exceed 10) for standard manufacturing processes</a></li> </ul>
<a href="#">1277</a>	Specification of excipients where these may affect product performance	<ul style="list-style-type: none"> <li>• <a href="#">Changes in the particle size distribution with influence on in-vitro dissolution</a></li> </ul>		
<a href="#">1278</a>	Test methods of non-pharmacopoeial excipients	<ul style="list-style-type: none"> <li>• <a href="#">New test method (e.g. NIR instead of HPLC)</a></li> </ul>		<ul style="list-style-type: none"> <li>• <a href="#">Minor changes of the analytical method already covered by the IMPD</a></li> <li>• <a href="#">Update of the test procedure to comply with revised PhEur, USP, or JP monograph</a></li> </ul>



<a href="#">1279</a>	Specification (release or shelf-life) of medicinal product	<ul style="list-style-type: none"> <li>• <u>Extension of acceptance criteria with clinical relevance, e.g. change in the hardness with influence on the disintegration time and/or the in vitro-dissolution, <a href="#">or widening of acceptance criteria for impurities</a></u></li> <li>• <u>Deletion of tests</u></li> </ul>		<ul style="list-style-type: none"> <li>• Tightening of acceptance criteria (no safety reason)</li> <li>• <u>Addition of test(s) (no safety reason, <a href="#">control of mutagenic impurities excluded</a>)</u></li> </ul>
<a href="#">1280</a>	Container closure system	<ul style="list-style-type: none"> <li>• <u>New container closure system is introduced (e.g., less protective material, different container/material for diluted product)</u></li> </ul>	<ul style="list-style-type: none"> <li>• <u><a href="#">Change or new container closure system for solid oral dosage forms which provides equivalent or better protection (e.g. blister to blister)</a></u></li> </ul>	
<a href="#">1281</a>	<a href="#">Medical devices registered in the IMPD</a>	<ul style="list-style-type: none"> <li>• <u><a href="#">Change to use a different medical device.</a></u></li> <li>• <u><a href="#">Changes to a medical device registered in the IMPD if potentially impacting on the quality, safety and/or efficacy.</a></u></li> </ul>		<ul style="list-style-type: none"> <li>• <u><a href="#">changes to a medical device registered in the IMPD which is not considered to impact on the quality, safety and/or efficacy.</a></u></li> </ul>
<a href="#">1282</a>	Shelf-life of medicinal product including shelf-life after first opening and reconstitution/dilution	<ul style="list-style-type: none"> <li>• Reduction of shelf-life and/or restriction of the storage conditions</li> <li>• Extension of shelf life - proposal for shelf-life extension, defining the criteria based on which the sponsor will extend the shelf-life during an ongoing clinical trial has not been submitted /approved with the initial filing of the IMPD</li> <li>• <u><a href="#">Extension of stability protocol duration through</a></u></li> </ul>		<ul style="list-style-type: none"> <li>• <u><a href="#">Extension of shelf-life and/or <del>extension change of</del> the storage conditions on the basis of additional data <del>with unchanged shelf life specifications, provided a proposal for shelf-life extension, defining the criteria based on which the sponsor will extend the shelf-life during an ongoing clinical trial, has been submitted with the initial or a previous substantial</del></a></u></li> </ul>

		<a href="#">additional timepoints to extend shelf-life</a>		<del>modification filing of the IMPD and has not been questioned by the competent authority within the approved shelf-life extension plan (see 2.2.1.P.8 and similar sections)</del>
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