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

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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)  
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Keywords	Guideline, Clinical Trial, Quality
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15 **pharmaceutical quality documentation concerning**  
16 **investigational medicinal products in clinical trials**

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## 197 **1. Introduction**

### 198 **1.1. Objectives of the guideline**

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

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

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

### 213 **1.2. Scope of the guideline**

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

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

### 231 **1.3. General points concerning all IMPs**

232 IMPs should be produced in accordance with the principles and the detailed guidelines of Good  
233 Manufacturing Practices for Medicinal Products (The Rules Governing Medicinal Products in The  
234 European Community, Volume IV).

235 **1.4. Submission of data**

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

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

241 **1.5. General considerations**

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

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

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

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

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

262 **2.2.1.S Drug substance**

263 Reference to an Active Substance Master File or a Certificate of Suitability of the European Directorate  
264 for the Quality of Medicines is acceptable. The procedure as described in the "Guideline on Active  
265 Substance Master File Procedure – CPMP/QWP/227/02 Rev 3 corr" and the "Guideline on Summary of  
266 Requirements for Active Substances in the Quality Part of the Dossier – CHMP/QWP/297/97 Rev 1" in  
267 their current version should be followed.

268 For reference to pharmacopoeial monographs, see section 1.5 General Considerations.

269 If the Active substance used is already authorised in a drug product within the EU/EEA, in one of the  
270 ICH-regions or one of the Mutual Recognition Agreement (MRA)-partner countries, reference can be



271 made to the valid marketing authorisation. A statement should be provided that the active substance  
272 has the same quality as in the approved product.

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

### 275 **2.2.1.S.1 General information**

#### 276 **2.2.1.S.1.1 Nomenclature**

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

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

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

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

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

#### 292 **2.2.1.S.1.2 Structure**

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

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

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

#### 303 **2.2.1.S.1.3 General properties**

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

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

## 309 **2.2.1.S.2 Manufacture**

### 310 **2.2.1.S.2.1 Manufacturer(s)**

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

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

### 318 **2.2.1.S.2.2 Description of manufacturing process and process controls**

319 For chemical substances: A brief summary of the synthesis process, a flow chart of the successive  
320 steps including, for each step, the starting materials, intermediates, solvents, catalysts and critical  
321 reagents used should be provided. . Any relevant process controls should be indicated. Where critical  
322 steps in the synthesis have been identified, a more detailed description may be appropriate. The  
323 stereo-chemical properties of starting materials should be discussed, where applicable. For substances  
324 which comply to the European Pharmacopoeia (Ph. Eur.), the Pharmacopoeia of an EU Member State,  
325 the United States Pharmacopoeia (USP) or the Japanese Pharmacopoeia (JP) reference to the  
326 monographs is acceptable, but suitability of the referenced monograph to adequately control the  
327 quality of the active substance (impurity profile) should be discussed by submission of sufficient  
328 information on the manufacturing process of the active substance (see section 1.5).

329 For radio-nuclides, the manufacturing process, as well as nuclear reactions should be described,  
330 including possible undesired nuclear reactions. The conditions for irradiation should be given. The  
331 cleaning and segregation processes for the radiopharmaceutical preparation and the organic-chemical  
332 precursors should be stated.

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

337 The production scale or range of batch sizes to be used in the clinical trial should be stated.

### 338 **2.2.1.S.2.3 Control of materials**

339 Materials used in the manufacture of the drug substance (e.g. raw materials, starting materials,  
340 solvents, reagents, catalysts) should be listed together with a brief summary on the quality and control  
341 of any attributes anticipated to be critical, for example, where control is required to limit an impurity in  
342 the drug substance, e.g. chiral control, metal catalyst control or control of a precursor to a potential  
343 genotoxic impurity. Brief information on synthesis or flow chart of the starting material(s) should be  
344 provided unless otherwise justified. For radio-nuclides, details on the target material should be given.

### 345 **2.2.1.S.2.4 Control of critical steps and intermediates**

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

348 **2.2.1.S.2.5 Process validation and/or evaluation**

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

350 **2.2.1.S.2.6. Manufacturing process development**

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

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

357 **2.1.2.S.3 Characterisation**

358 **2.1.2.S.3.1 Elucidation of structure and other characteristics**

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

361 For radiopharmaceutical substances, the analogous non-radioactive substances should be used to  
362 determine the structure. For radiopharmaceutical kits the structure of the radiolabelled compound  
363 should be described where possible.

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

368 **2.1.2.S.3.2 Impurities**

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

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

375 Discussion on (potential) mutagenic impurities should be provided (structure, origin, limit justification).  
376 The level of detail necessary depends on the phase of the clinical trial.

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

378 In the case of radio-nuclides or radio-labelled substances which are used in phase I studies in humans  
379 to develop a non-radioactive medicinal product, the radiochemical purity and the chemical purity  
380 should be indicated describing any assumptions made, e.g. as a consequence of the determination  
381 being made prior to dilution with cold material. For radiopharmaceutical substances, the radio-nuclidic  
382 purity, the radiochemical purity and the chemical purity should be stated and discussed.

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

#### 386 **2.2.1.S.4 Control of the Drug Substance**

##### 387 **2.2.1.S.4.1 Specification(s)**

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

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

396 The microbiological quality for drug substances used in aseptically manufactured products should be  
397 specified.

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

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

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

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

##### 408 **2.2.1.S.4.2 Analytical procedures**

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

413 For radiopharmaceutical substances, the method used for the measurement of radioactivity should be  
414 described.

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

417 **2.2.1.S.4.3 Validation of analytical procedures**

418 **Information for phase I clinical trials**

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

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

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

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

431 In case of major changes in analytical methods, cross-validation data should be presented especially  
432 for specified unknown impurities identified by their relative retention time (RRT). A re-analysis of  
433 preclinical batch with the new method should also be performed.

434 **2.2.1.S.4.4 Batch analyses**

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

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

443 **2.2.1.S.4.5 Justification of specification(s)**

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

449 **2.2.1.S.5 Reference standards or materials**

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

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

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

#### 458 **2.2.1.S.6 Container closure system**

459 The immediate packaging material used for the drug substance should be stated.

#### 460 **2.2.1.S.7 Stability**

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

469 The retest period should be defined based on the available stability data and should be clearly stated.  
470 In case no retest period is defined, statement should be included that the drug substance is tested  
471 immediately before the drug product manufacture.

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

### 473 **2.2.1.P Investigational medicinal product under test**

#### 474 **2.2.1.P.1 Description and composition of the investigational medicinal** 475 **product**

476 The complete qualitative and quantitative composition of the IMP should be stated. This includes also  
477 prefabricated components (e.g. capsule shells) and excipient mixtures (e.g. film-coating mixtures). A  
478 short statement or a tabulation of the dosage form and the function of each excipient should be  
479 included.

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

#### 483 **2.2.1.P.2 Pharmaceutical development**

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

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

487 For paediatric studies, the medicinal product components, the dosage form and the administration  
488 device if any should be safe and suitable for the paediatric population.

489 Where applicable, the compatibility with solvents used for reconstitution, diluents and admixtures  
490 should be demonstrated. For extemporaneously prepared medicinal products, e.g. products to be

491 reconstituted or diluted prior to their use, the method of preparation should be summarised and  
492 reference made to a full description in the clinical protocol.

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

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

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

### 502 **2.2.1.P.2.1 Manufacturing process development**

503 Changes in the current manufacturing process compared to the one used in phase I and phase II  
504 clinical trials, respectively, are to be explained. Special consideration should be given to dosage form  
505 specific changes in quality parameters with potential clinical relevance, e.g. in vitro dissolution rate.

### 506 **2.2.1.P.3 Manufacture**

#### 507 **2.2.1.P.3.1 Manufacturer(s)**

508 The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and  
509 each proposed production site involved in manufacture, packaging/assembly and testing should be  
510 provided. In case that multiple manufacturers contribute to the manufacture of the IMP, their  
511 respective responsibilities need to be clearly stated.

512 When packaging and or labelling is carried out at a hospital, health centre or clinic where the  
513 investigational medicinal product is to be used for the trial exclusively at that institution, and where an  
514 exemption from the need to hold a manufacturing authorisation, as provided for in article 61 (5) of  
515 the regulation 536/2014 applies, it is not necessary to provide the names and addresses of those  
516 institutions in this section. If relevant, it is sufficient to indicate that these activities will take place.

#### 517 **2.2.1.P.3.2 Batch formula**

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

#### 520 **2.2.1.P.3.3 Description of manufacturing process and process controls**

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

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

527 **2.2.1.P.3.4 Controls of critical steps and intermediates**

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

- 529 • Non-standard manufacturing processes; and  
530 • Manufacturing processes for sterile products.

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

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

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

536 **2.2.1.P.3.5 Process validation and/or evaluation**

537 Data are not required during the development phases, i.e. clinical phases I to III, except for non-  
538 standard sterilisation processes not described in the Ph. Eur., USP or JP and non-standard  
539 manufacturing processes. In these cases, the critical manufacturing steps, the validation of the  
540 manufacturing process as well as the applied in process controls should be described.

541 **2.2.1.P.4 Control of excipients**

542 **2.2.1.P.4.1 Specifications**

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

549 **2.2.1.P.4.2 Analytical procedures**

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

552 **2.2.1.P.4.3 Validation of the analytical procedures**

553 Not applicable.

554 **2.2.1.p.4.4 Justification of specifications**

555 Not applicable.

556 **2.2.1.P.4.5 Excipients of animal or human origin**

557 Cf. section 7.2.1.A.2.



558 **2.2.1.P.4.6 Novel excipients**

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

563 **2.2.1.P.5 Control of the investigational medicinal product**

564 **2.2.1.P.5.1 Specifications**

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

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

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

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

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

579 For extemporaneously prepared medicinal products, the acceptable quality standard after preparation  
580 should be stated and documented by development testing.

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

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

584 **2.2.1.P.5.2 Analytical procedures**

585 The analytical methods should be described for all tests included in the specification (e.g. dissolution  
586 test method).

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

588 **2.2.1.P.5.3 Validation of analytical procedures**

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

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

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

599 **2.2.1.P.5.4 Batch analyses**

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

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

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

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

612 **2.2.1.P.5.5 Characterisation of impurities**

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

615 **2.2.1.P.5.6 Justification of specification(s)**

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

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

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

622 **2.2.1.P.6 Reference standards or materials**

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

627 **2.2.1.P.7 Container closure system**

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

636 **2.2.1.P.8 Stability**

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

- 642 • Results at long-term as well as at accelerated storage conditions are available;
- 643 • No trends in stability behaviour are observed. If any observed, justification should be provided;
- 644 • Stability protocol covering the proposed extrapolated shelf life should be provided;
- 645 • Criteria used to extrapolate data should be clearly defined; and
- 646 • Depending on the data available an fourfold extrapolation of real time data may be acceptable up  
647 to a shelf life of 12 months and an extrapolation of x+12 months for a shelf life of more than 12  
648 months. Other schemes may be possible but should be justified.

649 Furthermore, bracketing and matrixing designs of appropriate IMPs may be acceptable, where justified.  
650 The batches of drug product must meet specification requirements throughout the period of use. If  
651 issues arise, then the Competent Authorities should be informed of the situation, including any  
652 corrective action proposed.

653 In case the drug product is stored in a bulk for a significant time period, relevant stability data should  
654 be provided as well as shelf life, storage conditions and packaging material for the bulk. In case the  
655 final drug product shelf life is calculated not from the first mixing of the drug substance with excipients  
656 but from the time of packaging into the primary package, this should be clearly stated and justified.

657 Any proposal for a future shelf life extension without substantial modification submission should be  
658 stated in the IMPD. Stability protocol, shelf life extension plan and a statement that in case of any  
659 significant negative trend the Sponsor will inform the competent authority should be provided. The  
660 stability protocol should cover the maximum planned shelf life.

661 For preparations intended for applications after reconstitution, dilution or mixing, and products in  
662 multi-dose containers, excluding oral solid dosage forms, in-use stability data should be presented. In-  
663 use stability studies should cover the practice described in the clinical protocol. Relevant parameters  
664 should be monitored within the in-use stability studies (e.g. appearance, assay, impurities, visible and  
665 sub-visible particles, microbial contamination/sterility). Shelf life and storage conditions after first  
666 opening and/or after reconstitution and/or dilution should be defined. These studies are not required if

667 the preparation is to be used immediately after opening or reconstitution and if it can be justified that  
668 no negative influence on the quality of the preparation through instabilities is to be expected.

669 For radiopharmaceuticals, the time of calibration should be specified, since the stability also depends  
670 on the half-life of the radioactive isotope.

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

672 For phase I clinical trials, it should be confirmed that an ongoing stability program will be carried out  
673 with the relevant batch(es) and that, prior to the start of the clinical trial, at least studies under  
674 accelerated and long-term storage conditions will have been initiated. Where available, the results  
675 from these studies should be summarised in a tabulated form. Supportive data from development  
676 studies should be summarised in a tabular overview. An evaluation of the available data and  
677 justification of the proposed shelf-life to be assigned to the IMP in the clinical study should be  
678 provided.

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

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

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

## 688 **3. Information on the chemical and pharmaceutical quality of** 689 **authorised, non-modified test and comparator products in** 690 **clinical trials**

691 For test and comparator products to be used in clinical trials which have already been authorised in the  
692 EU/EEA, in one of the ICH-regions or one of the Mutual Recognition Agreement (MRA)-partner  
693 countries, it will be sufficient to provide the name of the MA-holder and the MA-number as proof for  
694 the existence of a MA, incl. copy of the SmPC/Summary of Product Characteristics or its equivalent e.g.  
695 Prescribing information. For repackaged/modified comparator products, see following chapter.

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

699 For IMPs sourced from outside of the EU/EEA, MRA- partner countries or ICH regions, a full  
700 documentation, according to the requirements stated in chapter 2 of this guideline, should be  
701 submitted.

702 **4. Information on the chemical and pharmaceutical quality of**  
703 **modified authorised comparator products in clinical trials**

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

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

710 **4.2.1.P Modified comparator product**

711 **4.2.1.P.1 Description and composition**

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

717 **4.2.1.P.2 Pharmaceutical development**

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

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

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

732 **4.2.1.P.3 Manufacture**

733 **4.2.1.P.3.1 Manufacturer(s) related to the modification**

734 The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and  
735 each proposed production site involved in the modification, packaging/assembly and testing of the  
736 modified product should be provided. In case that multiple manufacturers contribute to the  
737 manufacture of the IMP, their respective responsibilities need to be clearly stated.

738 When packaging is carried out at a hospital, health centre or clinic where the investigational medicinal  
739 product is to be used for the trial exclusively at that institution, and where an exemption from the need  
740 to hold a manufacturing authorisation, as provided for in article 61 (5) of the regulation 536/2014  
741 applies, it is not necessary to provide the names and addresses of those institutions in this section. If  
742 relevant, it is sufficient to indicate that these activities will take place.

#### 743 **4.2.1.P.3.2 Batch formula**

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

#### 746 **4.2.1.P.3.3 Description of manufacturing process and process controls**

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

#### 749 **4.2.1.P.4 Control of excipients**

##### 750 **4.2.1.P.4.1 Specifications**

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

##### 757 **4.2.1.P.4.2 Analytical procedures**

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

##### 760 **4.2.1.P.4.3 Validation of analytical procedures**

761 Not applicable.

##### 762 **4.2.1.P.4.4 Justification of specifications**

763 Not applicable.

##### 764 **4.2.1.P.4.5 Excipients of animal or human origin**

765 Cf. Appendix 7.2.1.A.2.

#### 766 **4.2.1.P.5 Control of the modified comparator product**

##### 767 **4.2.1.P.5.1 Specifications**

768 The chosen release and shelf-life specifications of the modified comparator product should be  
769 submitted, including test methods and acceptance criteria. Generally, they should include description

770 and identification of the drug substance as well as the control of important pharmaceutical and  
771 technological properties, such as dissolution. Where an intact solid oral dosage form that is easily  
772 identifiable by its colour, shape and marking is encapsulated, identification of the active substance may  
773 not be necessary, and visual examination may suffice for identification. Depending on the degree of  
774 modification of the authorised product, additional quality criteria, e.g. determination of the drug  
775 substance(s) and impurities/degradants, may need to be specified and tested.

#### 776 **4.2.1.P.5.2 Analytical procedures**

777 For parameters relevant to the performance of the comparator product, e.g. dissolution, the methods  
778 should be described.

#### 779 **4.2.1.P.5.3 Validation of analytical procedures**

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

#### 784 **4.2.1.P.5.4 Batch analyses**

785 Results or certificates of analysis for the batch of modified comparator product to be used in the clinical  
786 trial or of a representative batch should be provided.

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

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

#### 793 **4.2.1.P.5.5 Characterisation of impurities**

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

#### 804 **4.2.1.P.5.6 Justification of specification(s)**

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

807 **4.2.1.P.7 Container closure system**

808 The type of immediate packaging, material and package size(s) should be specified. If materials other  
809 than those authorised are used, a description and specifications should be provided. Where  
810 appropriate, reference should be made to the relevant pharmacopoeial monograph.

811 **4.2.1.P.8 Stability**

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

814 In the case of any modification with a likely significant impact on product stability, a minimum of  
815 stability data on the modified comparator product should be available, depending on the length of the  
816 planned clinical trial, prior to the start of the clinical trial in order to allow an assessment of the impact  
817 of the modifications on product safety and stability. The available stability data should be presented in  
818 a tabulated form. An evaluation of the available data and justification of the proposed shelf-life to be  
819 assigned to the IMP in the clinical study should be provided. Any degree of extrapolation may not  
820 exceed the shelf-life originally assigned to the specific batch of authorised product by its MAH.

821 In the case of only minor modifications, a justification of the stability over the intended study period  
822 may be acceptable.

823 In-use stability studies should be performed in case of use of the comparator product in different  
824 conditions as those described in the SPC (according to the clinical protocol), if not otherwise justified.

825 **5. Information on the chemical and pharmaceutical quality of**  
826 **investigational medicinal products containing existing active**  
827 **substances used in bio-equivalence studies, e.g. generics**  
828 **(chemical substances)**

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

832 **5.2.1.S Drug substance**

833 Reference to an Active Substance Master File or a Certificate of Suitability of the European Directorate  
834 for the Quality of Medicines is acceptable. The procedure as described in the "Guideline on Active  
835 Substance Master File Procedure – CPMP/QWP/227/02 Rev 3 corr" and the "Guideline on Summary of  
836 Requirements for Active Substances in the Quality Part of the Dossier – CHMP/QWP/297/97 Rev 1" in  
837 their current version should be followed.

838 For reference to pharmacopoeial monographs, see section 1.5 General Considerations.

839 If the Active substance used is already authorised in a drug product within the EU/EEA , in one of the  
840 ICH-regions or one of the Mutual Recognition Agreement (MRA)-partner countries, reference can be  
841 made to the valid marketing authorisation. A statement should be provided that the active substance  
842 has the same quality as in the approved product.

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



845 **5.2.1.S.1 General information**

846 **5.2.1.S.1.1 Nomenclature**

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

849 **5.2.1.S.1.2 Structure**

850 The structural formula should be presented.

851 **5.2.1.S.1.3 General Properties**

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

853 **5.2.1.S.2 Manufacture**

854 **5.2.1.S.2.1 Manufacturer(s)**

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

857 **5.2.1.S.2.2 Description of manufacturing process and process controls**

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

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

867 **5.2.1.S.3 Characterisation**

868 **5.2.1.S.3.2 Impurities**

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

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

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

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

878 **5.2.1.S.4 Control of the drug substance**

879 **5.2.1.S.4.1 Specifications**

880 The microbiological quality of drug substances used in aseptically manufactured products should be  
881 specified.

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

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

892 **5.2.1.S.4.2 Analytical procedures**

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

898 **5.2.1.S.4.3 Validation of analytical procedures**

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

904 **5.2.1.S.4.4 Batch analyses**

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

909 **5.2.1.S.4.5 Justification of specifications**

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

915 **5.2.1.S.5 Reference Standards or materials**

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

919 **5.2.1.S.6 Container closure system**

920 The immediate packaging material used for the drug substance should be stated.

921 **5.2.1.S.7 Stability**

922 The available stability data should be provided in a tabulated form. The retest period should be defined  
923 based on the available stability data and should be clearly stated. In case no retest period is defined,  
924 statement should be included that the drug substance is tested immediately before the drug product  
925 manufacture.

926 **5.2.1.P Investigational medicinal product under test**

927 **5.2.1.P.1 Description and composition**

928 The complete qualitative and quantitative composition of the IMP should be stated. This includes also  
929 prefabricated components (e.g. capsule shells) and excipient mixtures (e.g. film-coating mixtures).

930 **5.2.1.P.2 Pharmaceutical development**

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

932 **5.2.1.P.3 Manufacture**

933 **5.2.1.P.3.1 Manufacturer(s)**

934 The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and  
935 each proposed production site involved in manufacture, packaging/assembly and testing should be  
936 provided. In case multiple manufacturers contribute to the manufacture of the IMP, their respective  
937 responsibilities in the manufacturing chain should be clearly indicated.

938 When packaging and or labelling is carried out at a hospital, health centre or clinic where the  
939 investigational medicinal product is to be used for the trial exclusively at that institution, and where an  
940 exemption from the need to hold a manufacturing authorisation, as provided for in article 61 (5) of the  
941 regulation 536/2014, it is not necessary to provide the names and addresses of those institutions in  
942 this section. If relevant, it is sufficient to indicate that these activities will take place.

943 **5.2.1.P.3.2 Batch formula**

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

946 **5.2.1.P.3.3 Description of manufacturing process and process controls**

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

950 **5.2.1.P.3.4 Control of critical steps and intermediates**

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

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

955 **5.2.1.P.3.5 Process validation and/or evaluation**

956 Data are not required, except for non-standard sterilisation processes not described in the Ph. Eur.,  
957 USP or JP and non-standard manufacturing processes. In these cases, the critical manufacturing steps,  
958 the validation of the manufacturing process as well as the applied in process controls should be  
959 described (c.f. Annex II to Note for Guidance on Process Validation: Non-Standard Processes  
960 (CPMP/QWP/2054/03).

961 **5.2.1.P.4 Control of excipients**

962 **5.2.1.P.4.1 Specifications**

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

969 **5.2.1.P.4.2 Analytical procedures**

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

972 **5.2.1.P.4.3 Validation of analytical procedures**

973 Not applicable.

974 **5.2.1.P.4.4 Justification of specifications**

975 Not applicable.

976 **5.2.1.P.4.5 Excipients of animal or human origin**

977 Cf. Appendix 7.2.1.A.2.

978 **5.2.1.P.4.6 Novel excipients**

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

983 **5.2.1.P.5 Control of the investigational medicinal product**

984 **5.2.1.P.5.1 Specifications**

985 The chosen release and shelf-life specifications should be submitted, including test methods and  
986 acceptance criteria. At least, tests on identity, assay and degradation products should be included for  
987 any pharmaceutical form. Drug product specific tests and acceptance criteria should be included in the  
988 specifications in line with the pharmaceutical form used (e.g. dissolution/disintegration for oral solid  
989 dosage forms; uniformity of dosage units; or pH, bacterial endotoxins and sterility for parenteral  
990 dosage forms).

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

992 **5.2.1.P.5.2 Analytical procedures**

993 The analytical methods should be described for all tests included in the specification (e.g. dissolution  
994 test method).

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

996 **5.2.1.P.5.3 Validation of analytical procedures**

997 The suitability of the analytical methods used should be demonstrated. A tabulated summary of the  
998 validation results should be provided (e.g. results or values found for specificity, linearity, range,  
999 accuracy, precision, quantification and detection limit, as appropriate). It is not necessary to provide a  
1000 full validation report.

1001 **5.2.1.P.5.4 Batch analyses**

1002 Certificates of analysis or batch analysis data for the batch(es) intended to be used in the planned bio-  
1003 equivalence study or, in their absence, representative batches, should be provided.

1004 The batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance  
1005 criteria and the test results should be listed.

1006 **5.2.1.P.5.5 Characterisation of impurities**

1007 Additional impurities/degradants observed in the IMP, but not covered by section 5.2.1.S.3.2, should  
1008 be stated.

1009 **5.2.1.P.5.6 Justification of specification(s)**

1010 It will be sufficient to briefly justify the specifications and acceptance criteria for degradation products  
1011 and any other parameters that may be relevant to the performance of the drug product. Toxicological  
1012 justification should be given, where appropriate.

1013 **5.2.1.P.6 Reference standards or materials**

1014 The parameters for characterisation of the reference standard should be submitted, if no compendial  
1015 reference standard is available.

1016 Section 5.2.1.S.5 - Reference Standards or Materials - may be referred to, where applicable.

1017 **5.2.1.P.7 Container closure system**

1018 The intended immediate packaging and additionally, where relevant for the quality of the drug product,  
1019 the outer packaging to be used for the IMP in the clinical trial, should be stated. Where appropriate,  
1020 reference should be made to the relevant pharmacopoeial monograph. If the product is packed in a  
1021 non-standard administration device, or if non-compendial materials are used, a description and  
1022 specifications should be provided. For dosage forms that have a higher potential for interaction  
1023 between filling and container closure system (e.g. parenterals, ophthalmic products, oral solutions),  
1024 more details may be needed. For dosage forms where an interaction is unlikely, e.g. solid oral dosage  
1025 forms, a justification for not providing any information may suffice.

1026 **5.2.1.P.8 Stability**

1027 For bioequivalence studies, it should be confirmed that an ongoing stability program will be carried out  
1028 with the relevant batch(es) and that, prior to the start of the clinical trial, at least studies under  
1029 accelerated and long-term storage conditions will have been initiated. The results from at least one  
1030 month accelerated studies or the results of the initial phase of studies under long-term storage  
1031 conditions should be summarised in a tabulated form. Supporting data from development studies  
1032 should also be summarised in a tabular overview. An evaluation of the available data and justification  
1033 of the proposed shelf-life and storage conditions to be assigned to the IMP in the bio-equivalence study  
1034 should be provided. Extrapolation may be used, provided a commitment is included to perform an  
1035 ongoing stability study in parallel to the bioequivalence study.

1036 **6. Information on the chemical and pharmaceutical quality**  
1037 **concerning placebo products in clinical trials**

1038 The quality documentation to be submitted for placebos is limited to the following sections of the  
1039 product part.

1040 **6.2.1.P Placebo product in clinical trials**

1041 **6.2.1.P.1 Description and composition**

1042 The complete qualitative and quantitative composition of the placebo should be stated. This includes  
1043 also prefabricated components (e.g. capsule shells) and excipient mixtures (e.g. film-coating

1044 mixtures). A short statement or a tabulation of the dosage form and the function of each excipient  
1045 should be included.

#### 1046 **6.2.1.P.2 Pharmaceutical development**

1047 It should be described how possible differences of the placebo preparation in relation to the  
1048 investigational medicinal product regarding taste, appearance and smell are masked, where applicable.

#### 1049 **6.2.1.P.3 Manufacture**

##### 1050 **6.2.1.P.3.1 Manufacturer(s)**

1051 The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and  
1052 each proposed production site and facility involved in manufacture, packaging/assembly and testing  
1053 should be provided. In case that multiple manufacturers contribute to the manufacture of the placebo,  
1054 their respective responsibilities need to be clearly stated.

1055 When packaging and or labelling is carried out at a hospital, health centre or clinic where the  
1056 investigational medicinal product is to be used for the trial exclusively at that institution, and where an  
1057 exemption from the need to hold a manufacturing authorisation, as provided for in article 61 (5) of the  
1058 regulation 536/2014, it is not necessary to provide the names and addresses of those institutions in  
1059 this section. If relevant, it is sufficient to indicate that these activities will take place.

##### 1060 **6.2.1.P.3.2 Batch formula**

1061 The batch formula for the batch to be used for the clinical trial should be presented. Where relevant,  
1062 an appropriate range of batch sizes may be given.

##### 1063 **6.2.1.P.3.3 Description of manufacturing process and process controls**

1064 A flow chart of the successive steps, indicating the components used for each step and including in-  
1065 process controls should be provided. In addition, a brief narrative description of the manufacturing  
1066 process should be included.

##### 1067 **6.2.1.P.3.4 Control of critical steps and intermediates**

1068 Information is not required with the exception of manufacturing processes for sterile products.

##### 1069 **6.2.1.P.3.5 Process validation and/or evaluation**

1070 Data are not required, except for non-standard sterilisation processes not described in the Ph. Eur.,  
1071 USP or JP. In these cases, the critical manufacturing steps, the validation of the manufacturing process  
1072 as well as the applied in process controls should be described.

#### 1073 **6.2.1.P.4 Control of excipients**

##### 1074 **6.2.1.P.4.1 Specifications**

1075 References to the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP should be indicated.  
1076 For excipients not described in one on of the mentioned pharmacopoeias, reference to the relevant

1077 food-chemical regulations (e.g. FCC) can be made. For excipient mixtures composed of  
1078 pharmacopoeial substances, e.g. pre -fabricated dry mix for film-coating, a general specification of the  
1079 mixture will suffice. For excipients not covered by any of the afore-mentioned standards, an in-house  
1080 monograph should be provided. Specification for capsule shells should be provided.

#### 1081 **6.2.1.P.4.2 Analytical procedures**

1082 In cases where reference to a pharmacopoeial monograph listed under 6.2.1.P.4.1 cannot be made,  
1083 the analytical methods used should be indicated.

#### 1084 **6.2.1.P.4.3 Validation of analytical procedures**

1085 Not applicable.

#### 1086 **6.2.1.P.4.4 Justification of specifications**

1087 Not applicable.

#### 1088 **6.2.1.P.4.5 Excipients of animal or human origin**

1089 Cf. Appendix 7.2.1. A.2.

#### 1090 **6.2.1.P.4.6 Novel excipients**

1091 For novel excipients, details are to be given on their manufacturing process, characterisation and  
1092 control in relevance to product safety. Information as indicated in section 3.2.S of the CTD should be  
1093 provided in annex 2.1.A.3 (c.f. section 7.2.1.A.3) consistent with the respective clinical phase, details  
1094 are to be included on e.g. their manufacturing process, characterisation and stability. If the same novel  
1095 excipient is already described in the IMPD for the respective test product, cross-reference to the  
1096 relevant section will suffice.

#### 1097 **6.2.1.P.5 Control of the placebo product**

##### 1098 **6.2.1.P.5.1 Specifications**

1099 The chosen release and shelf-life specifications should be submitted, including test methods and  
1100 acceptance criteria. The specifications should at minimum include a test which enables to clearly  
1101 differentiate between the respective investigational medicinal product and the placebo.

##### 1102 **6.2.1.P.5.2 Analytical procedures**

1103 The analytical methods should be described for all tests included in the specification.

##### 1104 **6.2.1.P.7 Container closure system**

1105 The intended immediate packaging and additionally, where relevant for the quality of the drug product,  
1106 the outer packaging to be used for the placebo in the clinical trial, should be stated.



1107 **6.2.1.P.8 Stability**

1108 The shelf-life and storage conditions of the placebo should be defined. The shelf life of the placebo  
1109 product should preferably cover the anticipated duration of the clinical trial. Stability studies are only  
1110 required in cases where there is reason to suspect that the placebo product will undergo changes in its  
1111 physical characteristics or degradation, respectively, e.g. microbial purity of multi-dose containers,  
1112 hardness or appearance. In all other cases, a short justification of the assigned shelf-life will suffice.

1113 **7. Appendices**

1114 **7.2.1.A.1 Facilities and equipment**

1115 Not applicable.

1116 **7.2.1.A.2 Adventitious agents safety evaluation**

1117 All materials of human or animal origin used in the manufacturing process of both drug substance and  
1118 drug product, or such materials coming into contact with drug substance or drug product during the  
1119 manufacturing process, should be identified. Information assessing the risk with respect to potential  
1120 contamination with adventitious agents of human or animal origin should be provided in this section.

1121 ***TSE agents***

1122 Detailed information should be provided on the avoidance and control of transmissible spongiform  
1123 encephalopathy agents. This information can include, for example, certification and control of the  
1124 production process, as appropriate for the material, process and agent.

1125 The "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy  
1126 Agents via Human and Veterinary Medicinal Products, EMEA/410/01" in its current version is to be  
1127 applied.

1128 ***Viral safety***

1129 Where applicable, information assessing the risk with respect to potential viral contamination should be  
1130 provided in this section. The risk of introducing viruses into the product and the capacity of the  
1131 manufacturing process to remove or inactivate viruses should be evaluated.

1132 ***Other adventitious agents***

1133 Detailed information regarding the other adventitious agents, such as bacteria, mycoplasma, and fungi  
1134 should be provided in appropriate sections within the core dossier.

1135 **7.2.1.A.3 Novel excipients**

1136 For novel excipients, information as indicated in section.3.2.S of the CTD should be provided,  
1137 consistent with the respective clinical phase.

#### 1138 **7.2.1.A.4 Solvents for reconstitution and diluents**

1139 For solvents for reconstitution and diluents, the relevant information as indicated in section 3.2.P of the  
1140 CTD should be provided as applicable.

### 1141 **8. Auxiliary medicinal products**

1142 For auxiliary medicinal products the same requirements and principles apply as for investigational  
1143 medicinal products. The requirements depend on the type of the product (authorised / not authorised /  
1144 modified / non-modified medicinal product).

### 1145 **9. Changes to the investigational medicinal product with a** 1146 **need to request a substantial modification to the IMPD**

1147 In accordance with Good Manufacturing Practice, a Product Specification File should be maintained for  
1148 each IMP at the respective site and be continually updated as the development of the product  
1149 proceeds, ensuring appropriate traceability to the previous versions. Guidance given in this section  
1150 relates only to changes that need to be notified to the competent authorities and when they should be  
1151 notified.

1152 The following examples of changes to IMP quality data concerning:

- 1153 • Importation of the medicinal product;
- 1154 • Change of name or code of IMPs;
- 1155 • Immediate packaging material;
- 1156
- 1157 • Manufacturer(s) of drug substance;
- 1158
- 1159 • Manufacturing process of the drug substance;
- 1160
- 1161 • Specifications of active substance;
- 1162 • Manufacture of the medicinal product;
- 1163
- 1164 • Specification (release or shelf-life) of the medicinal product;
- 1165
- 1166 • Specification of excipients where these may affect product performance;
- 1167
- 1168 • Shelf-life including after first opening and reconstitution;
- 1169
- 1170 • Major change to the formulation;
- 1171
- 1172 • Storage conditions;
- 1173
- 1174 • Test procedures of active substance;
- 1175
- 1176 • Test procedures of the medicinal product; and

- 1177 • Test procedures of non-pharmacopoeial excipients are only to be regarded as “substantial” where  
1178 they are likely to have a significant impact on:
- 1179 – The safety or physical or mental integrity of the patients;
  - 1180 – The scientific values of the trial;
  - 1181 – The conduct or management of the trial;
  - 1182 – The quality or safety of any IMP used in the trial.

**Table 1**

Changes in the quality	Relevance for		Example	
	quality / safety?			
	Yes	Possible	Notification of a substantial modification	Notification of a substantial modification
			<b>not required</b>	<b>required</b>
Importation of the medicinal product		✓		Change of the importing site
Change of name or code of IMPs		✓		Change from company code to INN or trade name during ongoing study (exchange of the label)
Immediate packaging material		✓	Change to a packaging material which is given as an alternative in the IMPD (e.g. blister -> HDPE- bottle)	Immediate packaging material

Table 2

Changes in the quality	Relevance for		Example	
	quality / safety?			
	Yes	Possible	Notification of a substantial modification	Notification of a substantial modification
			<b>not required</b>	<b>required</b>
Manufacturer(s) of drug substance.	✓		Alternate sites of manufacture within one company with unchanged specifications.	Change to a completely new manufacturer.
Manufacturing process of the drug substance.		✓	Change in the synthesis of an early step (prior to GMP Starting Material).	Different route of synthesis (final steps). Additional or new impurity <sup>1</sup> .
			Modifications of the process parameters (same process, same reagents).	Extension of the acceptance criteria. Changes in the physicochemical properties with influence on the quality of the IMP (e.g. particle size distribution, polymorphism etc.).
			Scale-Up.	Change in the manufacturing process of a herbal substance or herbal preparation.
Specifications of drug substance.		✓		Extension of the acceptance criteria. Deletion of tests.
Manufacturer(s) of the medicinal product.		✓	Deletion of manufacturing, packaging or testing site (no safety reason).	
Manufacture of the medicinal product.		✓	Modifications of the process parameters (same process).	Significant changes to the manufacturing process (e.g. dry compacting vs. wet granulation, conventional granulation vs. fluid-bed-granulation).
			Scale-Up.	
Specification (release or shelf-life) of the medicinal product.		✓	Tightening of specifications (no safety reason).	Extension of acceptance criteria with clinical relevance, e.g. change in the hardness with influence on the disintegration time and/or the <i>in vitro</i> -dissolution. Deletion of tests.

<sup>1</sup> Extensions in the limits of single impurities should be toxicologically justified.

**Table 3**

Changes in the quality	Relevance for quality / safety?		Example	
	Yes	Possible	Notification of a substantial modification <b>not required</b>	Notification of a substantial modification <b>required</b>
Specification of excipients, where these may affect product performance.	✓			E.g. changes in the particle size distribution with influence on the <i>in vitro</i> -dissolution.
Shelf-life including after first opening and reconstitution/dilution.		✓	Extension of shelf-life and/or extension of the storage conditions on the basis of additional data 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 study, has been submitted with the initial filing of the IMPD and has not been questioned by the competent authority (see 2.2.1.P.8 and similar sections).	Reduction of shelf-life, restriction of the storage conditions.
			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 study has not been submitted /approved with the initial filing of the IMPD.	
Major change to the formulation.	✓		Qualitatively identical but quantitatively different composition of non-functional tablet coating.	Change in the composition (including exchange of excipients to excipients with same functional characteristics, e.g. disintegrant).
			Different form in an IR-tablet, e.g. round to capsule-shaped, with no clinical impact (e.g. the dissolution profile of the new form is comparable to the old one).	
Test methods of drug substance / drug product		✓	Variation of the method already covered by the IMPD.	New test methods (e.g. NIR instead of HPLC).
			The new test conditions are validated and lead to comparable or better validation results.	
Test methods of non-pharmacopoeial excipients.		✓	See above.	See above.
CoA for new batch of the medicinal product.		✓	New batch was manufactured using the approved process and manufacturing sites.	