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## 4 Guideline on the chemistry of active substances 5 Draft

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7 This guideline replaces "Note for guidance on chemistry of new active substances"  
8 (CPMP/QWP/130/96, Rev 1) and "Chemistry of active substances" (3AQ5a).

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Keywords	Active Substance, Chemistry, Guideline
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13 **Guideline on the chemistry of active substances**

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## 49 **Executive summary**

50 Guideline concerning the application of Directive 2001/83/EC with a view to the granting of a  
51 marketing authorisation for a medicinal product. This guideline replaces the 'Note for guidance on  
52 chemistry of new active substances' (CPMP/QWP/130/96, Rev 1) and 'Chemistry of active substances'  
53 (3AQ5a). It has been revised to cover new and existing active substances in one guideline.

### 54 **1. Introduction (background)**

55 This guideline has been prepared in accordance with the structure agreed for the quality part of the  
56 dossier (Format ICH-CTD). The subheadings have been included for the sake of clarity.

### 57 **2. Scope**

58 The purpose of this guideline is to set out the type of information required for the manufacture and  
59 control of active substances (existing or new chemical entities) used in a medicinal product. The  
60 differences in requirements for new or existing active substances are clarified in the relevant  
61 paragraphs of the guideline where applicable. For the purposes of this guideline, an existing active  
62 substance is one that has been used in a finished product authorised previously within the European  
63 Union. This approach is consistent with the definition of new active substance in the Notice to  
64 Applicants, Volume 2A, Chapter 1, Annex I: a chemical (...) substance not previously authorised as a  
65 medicinal product in the European Union. This guideline is not applicable to herbal, biological,  
66 biotechnological products, radiopharmaceuticals and radiolabelled products. The guideline does not  
67 apply to contents of submissions during the clinical research stages of drug development.  
68 Nevertheless, the development principles presented in this guideline are important to consider during  
69 the investigational stages.

70 This guideline is applicable to active substances that have been developed following a "traditional" or  
71 an "enhanced" approach, as described in ICH Q8-11 (Refs 1-4), or a combination of these. However,  
72 when an "enhanced" approach is used or a design space claimed, the information provided in sections  
73 3.2.S.2.2 to 3.2.S.2.6., should be prepared and organised according to ICH Q11 (Ref 4).

#### 74 **ASMFs and CEPs:**

75 As an acceptable alternative to submission of detailed active substance information in the application  
76 for marketing authorisation, the Active Substance Master File (ASMF) or the Certification of Suitability  
77 to the Monographs of the European Pharmacopoeia (CEP) procedures may be used as described in  
78 'Guideline on the Summary of Requirements for the Active substance in the Quality Part of the Dossier,  
79 CHMP/QWP/297/97 (Ref 5). The requirements are the same regardless of the route of submission of  
80 data on the active substance. For procedural aspects and format of the ASMF, please refer to the  
81 Guideline on Active Substance Master File procedure CHMP/QWP/227/02 (Ref 6).

### 82 **3. Legal basis**

83 This guideline has to be read in conjunction with the introduction and general principles section (4) of  
84 Annex I to Directive 2001/83/EC and the introduction and general principles section (2) of Annex I to  
85 Directive 2001/82/EC.

## 86 **4. Body of Data**

### 87 **4.1. General Information 3.2.S.1**

88 This section deals with the identity, nomenclature and chemical structure of the active substance which  
89 is the subject of the application for marketing authorisation. Only brief information of physical  
90 characteristics should be listed, as full details and proof of structure are required in a separate section  
91 (see 3.2.S.3.1).

#### 92 **4.1.1. Nomenclature 3.2.S.1.1**

93 Information on the nomenclature of the active substance should be provided, if relevant:

- 94 • International Nonproprietary Name (INN);
- 95 • Compendial (e.g. European Pharmacopoeia) name;
- 96 • National Approved Names: BAN, DCF, DCIT, JAN, USAN;
- 97 • Company or laboratory code;
- 98 • Systematic Chemical Name(s) (IUPAC nomenclature);
- 99 • Other Names (e.g. proprietary);
- 100 • Other non-proprietary name(s);
- 101 • Chemical Abstracts Service (CAS) registry number (RN).

#### 102 **4.1.2. Structure 3.2.S.1.2**

103 The structural formula, including relative and absolute stereochemistry, the molecular formula and the  
104 relative molecular mass should be provided. Along with the stoichiometric formula and relative  
105 molecular mass ( $M_r$ ), the structural formula should display the stereochemistry of the active substance  
106 (indicated conventionally). If this information is not available a detailed description of the nature of the  
107 substance should be given. If appropriate, the  $M_r$  of the therapeutically active moiety should also be  
108 included.

#### 109 **4.1.3. General Properties 3.2.S.1.3**

110 The appearance of the material should be described briefly. A list of physicochemical and other  
111 relevant properties of the active substance should be provided, in particular physico-chemical  
112 properties that affect pharmacological efficacy and toxicological safety such as solubilities, acid  
113 dissociation constant (pKa), polymorphism, isomerism, partition coefficient (logP), permeability,  
114 hygroscopicity and any other relevant properties. (Ref 7).

### 115 **4.2. Manufacture 3.2.S.2**

#### 116 **4.2.1. Manufacturer(s) 3.2.S.2.1**

117 The name, address, and responsibility of each manufacturer, including contractors, and each proposed  
118 production site or facility involved in manufacturing and testing should be provided for the production  
119 steps after introduction of the starting material(s).

## 120 **4.2.2. Description of Manufacturing Process and Process Controls 3.2.S.2.2**

121 The description of the active substance manufacturing process represents the applicant's commitment  
122 for the manufacture of the active substance. Information should be provided to adequately describe  
123 the manufacturing process, including special unit operations and process controls. Optional processes,  
124 alternative processes and reprocessing with associated controls that may be completed by the  
125 intermediate or active substance manufacturer, should also be described. Particular emphasis should  
126 be placed on steps of the process having an impact on the quality of the active substance or  
127 intermediates and which are classified as 'critical' (see also under 3.2.S.2.4).

### 128 **Schematic representation of the manufacturing process**

129 Graphical representations of the synthetic process(es) should be provided, covering the entire process  
130 for the active substance and each intermediary process stage/step. These should comprise of reaction  
131 schemes that include chemical structures, molecular formulae and molecular weight of starting  
132 materials, intermediates and the active substance, as well as all reagents (including depletion agents  
133 such as nitrites for azides), catalysts and solvents used. Each non-isolated intermediate should be  
134 identified by presenting the chemical structure in brackets. The structures should reflect the  
135 stereochemistry of the molecules in question. A block flow diagram that identifies in-process controls,  
136 operating conditions, unit operations, weights, yield ranges etc. should preferably also be provided.  
137 Uncommon or non-standard abbreviations for reagents and solvents should be avoided.

### 138 **Sequential procedural narrative**

139 A sequential procedural narrative of the manufacturing process should be submitted. All used materials  
140 (starting materials, solvents, reagents, depletion agents, recovered materials, catalysts, processing  
141 aids, gases and materials used for quenching or work-up) and their quantities (or ranges) should be  
142 clearly disclosed, and attributed to the corresponding step or sub-step. For each manufacturing step,  
143 quantities of all reagents (including depletion agents) and catalysts should also be expressed in molar  
144 equivalents relative to the starting material / intermediate, identifying in particular materials used in  
145 molar excess.

146 The narrative should describe each step in the manufacturing process, and identify critical steps,  
147 critical process parameters, process controls employed, and ranges for process parameters (e.g.:  
148 temperature, pressure, pH, time, flow-rate, etc.).

149 The control of critical steps and intermediates should be described in 3.2.S.2.4.

150 The description of the process should indicate the scale of manufacture and the range for which the  
151 considered process may be used. Yields or yield ranges for each stage should be provided.

### 152 **Alternative processes**

153 Alternative processes should be explained and described with the same level of detail as the primary  
154 process. The process description should fully define the method of synthesis. However, if alternative  
155 steps or solvents are proposed they should be justified by providing sufficient evidence that the final  
156 quality of the material (i.e. active substance or isolated intermediate) obtained remains unchanged if  
157 the submission of data is *via* a CEP and/or an ASMF.

158 Regarding new active substances, if differences in impurity profiles are encountered, they should be  
159 analysed with validated methods and shown to be toxicologically acceptable.

### 160 **Reprocessing**

161 The cases where routine reprocessing is carried out should be identified and justified. Any data to  
162 support this justification should be either referenced or presented in 3.2.S.2.5. The reprocessing  
163 method should be clearly described and the criteria for deciding when re-processing can be performed  
164 should be provided.

#### 165 **Recovery**

166 Recovery (e.g. from mother liquors or filtrates) of solvents, reactants, intermediates or the active  
167 substance is considered acceptable according to ICH Q7 (Ref 8) or EU GMP Part II (Ref 9). It should be  
168 clearly indicated within the reaction scheme, process description and/or the block flow diagram, where  
169 recovered materials are introduced into the process. The impact of the use of recovered materials  
170 should form part of the overall risk assessment, and include, in particular, a discussion regarding  
171 impurities (with a focus on potential impurities of concern, e.g. mutagenic impurities). It is  
172 recommended that recovered materials are used only in the same process and preferably in the same  
173 step, and their use should be avoided in the final manufacturing step (e.g., chemical transformation /  
174 precipitation / washing), unless otherwise justified.

#### 175 **Re-working**

176 Re-working procedures should not be included in the dossier and should be carried out according to  
177 ICH Q7 (Ref 8) or EU GMP Part II (Ref 9).

### 178 **4.2.3. Control of Materials 3.2.S.2.3**

179 All materials used in the manufacture of the active substance (starting materials, solvents, reagents,  
180 catalysts, depletion agents, process aids, gases and materials used for quenching and work-up, etc.)  
181 should be listed and attributed unequivocally to the corresponding step or sub-step, stating also their  
182 intended function. Adequate specifications for these materials should be provided and should include a  
183 suitably specific identification test and purity limits, unless otherwise justified (see also Ref 8). The  
184 specifications should address the characteristics of the material and its suitability for the intended use  
185 and the step it is used in. For example, particular attention should be paid to materials used in later  
186 steps due to the higher probability of an impact on the quality of the active substance. Submission of  
187 validation data is generally not expected for analytical procedures. However, if the test in question is  
188 essential for the control strategy of the active substance (e.g. removal of a mutagenic impurity), a  
189 tabulated summary of the results of the validation carried out is generally sufficient.

#### 190 **Active Substance (AS) Starting Material(s)**

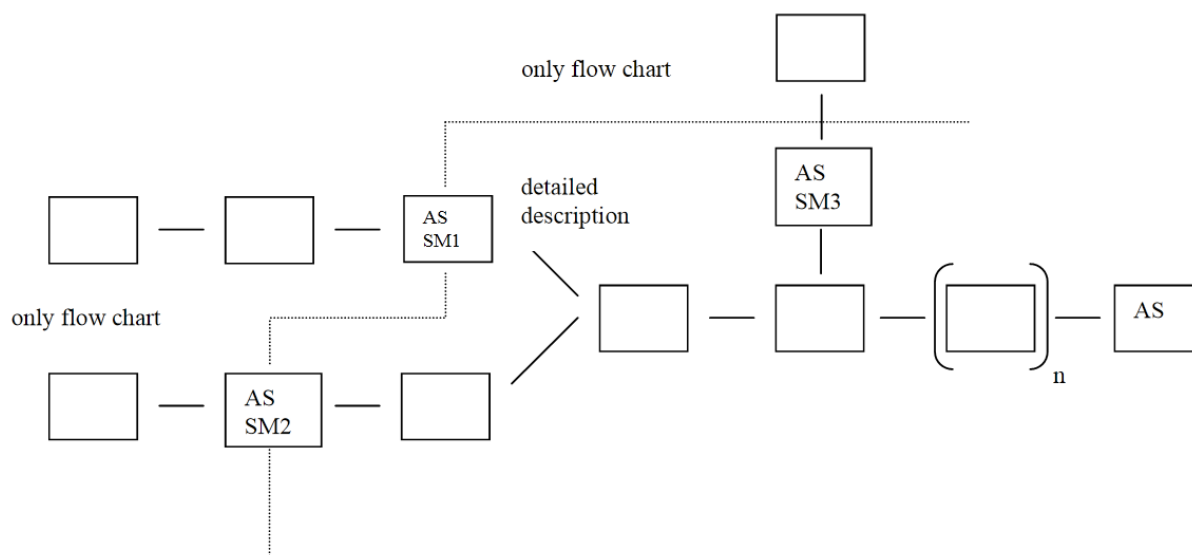
191 The requirements of ICH Q11 and related Q&A (Ref 4) in relation to the selection of starting materials  
192 are relevant to all active substances, regardless of the type of development approach.

193 Generally, the description of the process and the synthesis schematic should include all the steps of  
194 the process, proceeding from the starting material(s) to the intermediates, and ultimately to the active  
195 substance. The use of starting materials marks the beginning of the description of the process and  
196 manufacture under GMP. Typically, multiple chemical transformation steps should separate the starting  
197 material from the final active substance. The full description of the process should cover all the  
198 synthetic steps critical to the quality of the active substance.

199 The marketing authorisation applicant should propose and justify which substance should be  
200 considered as the AS starting material (SM), e.g. incorporated as a significant structural fragment into  
201 the structure of the active substance. Non-isolated compounds are not considered appropriate to be  
202 selected as starting materials. The name and address of the starting material manufacturers should be  
203 provided. The addition of manufacturers for the starting materials needs to be approved by a variation

204 according to European legislation. Information, in the form of a flow chart, indicating the synthetic  
205 process prior to the introduction of the starting material (including details of reagents, solvents and  
206 catalysts used), is necessary to evaluate the suitability of the proposed starting material and its  
207 specifications.

208 Schematic description (illustrative only):



209

210 Starting materials should be substances with defined chemical properties and structures. Structure  
211 elucidation of starting materials should be performed using state of the art techniques, except for  
212 European pharmacopoeial active substances. Complete specifications should be provided, including  
213 limits for impurities. The possibility that any kind of impurity, for example isomeric impurities or  
214 mutagenic impurities (including those from the 'cohort of concern', Ref 10), present in a starting  
215 material may be carried through the synthetic process unchanged or as derivatives should be  
216 discussed. Such impurities should, if relevant, be controlled in the starting material by appropriate  
217 acceptance criteria with suitably validated methods. Acceptance criteria should be established by the  
218 applicant based on evaluation of the fate of impurities present in the starting material, when subjected  
219 to the normal processing conditions.

220 Risk of formation and carry-over of nitrosamines during the starting materials synthesis should be  
221 evaluated (e.g., use of nitrosating agents, secondary or tertiary amines, etc.) (Ref 11). If a risk is  
222 identified, adequate control strategies (in the specification of the starting material or further  
223 downstream in the active substance process) should be established, or other starting material sources  
224 using a different manufacturing process may be explored.

### 225 **Starting materials of animal or human origin**

226 Information on the source, processing, characterisation and control of all materials of animal or human  
227 origin must be provided, including viral and/or TSE safety data in the relevant part of the dossier. A  
228 contaminant/impurity profile should be established and submitted. Information on the scientific name  
229 (species) of the animal and animal part used should be specified, as should the solvents, reagents and  
230 catalysts used in the process. The specification of the starting material of animal origin should follow  
231 the principles set out in the European Pharmacopoeia monographs and the potential presence of  
232 foreign matter, microbiological contamination, total ash, heavy metals, environmental pollutants,  
233 radioactive contamination, residual solvents, and other relevant impurities should be discussed.

234 Information on the geographical origin and extraction process may be appropriate depending on the  
235 subsequent synthetic steps.

236 Relevant viral safety and/or TSE data must be provided if any material of animal or human origin is  
237 used during the starting material manufacturing process (e.g. arising from fermentation, enzymes,  
238 amino acids, etc.).

### 239 **Starting materials of herbal origin**

240 Information on the source, processing, characterisation and control of starting materials of plant origin  
241 must be provided to ascertain suitability. A contaminant profile should be established and submitted,  
242 taking into consideration the number of chemical steps between the starting material and the semi-  
243 synthetic active substance.

244 Information on the scientific name (genus, species, variety and author), chemotype (where applicable)  
245 and plant part used should be specified. If the starting material is an extract, the primary extraction  
246 solvent and concentration used in the first step of extraction should be specified as well. The  
247 specification of the starting material of herbal origin should follow the principles set out in the  
248 European Pharmacopoeia monographs and the potential presence of foreign matter and adulterants,  
249 pesticides, microbiological contamination, heavy metals, mycotoxins (aflatoxins, ochratoxin A, etc.),  
250 radioactive contamination, residual solvents, and other relevant impurities/contaminants (e.g.  
251 pyrrolizidine alkaloids) should be discussed, taking into account the production of the herbal drug, and  
252 the subsequent extraction and purification processes.

253 Information on the geographical origin, site of collection or cultivation, harvesting, and post-harvest  
254 treatments (e.g. fumigants used) may be appropriate depending on the subsequent synthetic steps  
255 (Ref 12). Reference to the Ph. Eur. monograph on Herbal Drugs (1433) should be considered as  
256 needed.

### 257 **Semi-synthetic active substances**

258 For semi-synthetic active substances (where a starting material is obtained from fermentation (Ref 13)  
259 or by extraction from biological material), the impurity profile of the fermented or extracted starting  
260 material should be sufficiently understood and appropriately discussed. Regarding fermented starting  
261 materials, in addition to the discussion on typical impurities, the possible carryover of specific  
262 impurities from the fermentation process (e.g. DNA, proteins etc.) to the final substance should be  
263 discussed.

### 264 **Solvents, Reagents and other materials**

265 Specifications for all materials (solvents, reagents, catalysts, depletion agents, processing aids etc.)  
266 used in synthesis should be submitted. Materials used in the final stages of the active substance  
267 synthesis may require greater control (i.e. tighter specifications) than those used in earlier stages.  
268 Possible contamination of raw materials (e.g., reagents, catalysts and solvents including water /  
269 disinfected water, processing aids) with nitrosating agents (e. g. NaNO<sub>2</sub>) or amines, which may be  
270 carried over from steps used to prepare them, should be considered, as the presence of those  
271 contaminants could cause nitrosamine formation in the active substance process (Ref 11, 14).  
272 Adequate acceptance criteria should be defined and justified.

273 For enzymes used in the process, the origin (recombinant, animal or herbal origin) should be indicated  
274 and the possibility of specific impurities from the reaction to the final substance should be discussed.  
275 Peptone is considered a critical raw material, whose origin (animal or vegetal) and source (supplier  
276 name and address) should be specified (Ref 15).



277 In addition, for any material of animal or human origin, TSE and viral safety aspects should be  
278 addressed.

279 The grade of water used during the manufacture of active substances will depend on the stage at  
280 which it is used, the subsequent processing steps and the nature of the final product, according to a  
281 risk based approach to be applied as part of an overall control strategy (Ref 16).

282 Recovered materials should be controlled by their own specifications with special emphasis on the  
283 possibility of contamination with impurities (e.g. nitrosamines) during recovery processes and their  
284 accumulation in case of repeated recovery.

#### 285 **4.2.4. Control of Critical Steps and Intermediates 3.2.S.2.4**

286 **Critical Steps:** Tests and acceptance criteria performed at critical steps identified in 3.2.S.2.2 of the  
287 manufacturing process should be described and justified based on relevant experimental data. A  
288 critical step is defined as one where the process conditions, test requirements or other relevant  
289 parameters must be controlled within predetermined limits to ensure that the AS meets its  
290 specification.

291 Critical steps could be, for instance:

- 292 • Mixing of multiple components;
- 293 • Phase change and phase separation steps;
- 294 • Steps where control of temperature and pH are critical;
- 295 • Steps which introduce an essential molecular structural element or result in a major chemical  
296 transformation;
- 297 • Steps which introduce (or remove) significant impurities to (or from) the active substance. For  
298 those impurities not controlled in the active substance, suitable in-process controls should be  
299 carried out with justified ranges and documented;
- 300 • The final purification step.

301 Steps which have an impact on solid-state properties and homogeneity of the active substance are  
302 generally considered as critical, particularly, if the active substance is used within a solid dosage form,  
303 since they may adversely affect dissolution of the active substance from the dosage form and thereby  
304 affect bioavailability. Proper justification should be provided when these properties do not impact  
305 performance of the finished product.

#### 306 **Intermediates:**

307 Information on the quality and control of intermediates isolated during the process should be provided.  
308 Identity of isolated intermediates should be confirmed by appropriate state-of-the-art techniques,  
309 except for European pharmacopoeial substances. If non-compendial methods are used to control the  
310 intermediate, they should be suitably validated. Submission of validation data is generally not expected  
311 for analytical procedures. However, it may be required if the test in question is essential for the control  
312 strategy of the active substance (e.g. removal of a mutagenic impurity). In the latter case a tabulated  
313 summary of the results of the validation carried out is generally sufficient. Information on the  
314 characterisation of these intermediates should be provided (Ref 7).

315 If an intermediate in the proposed synthesis of the active substance is itself an active substance  
316 described in a monograph of the European Pharmacopoeia (Ph. Eur.) and covered by a valid CEP, then  
317 the CEP can be submitted as an alternative to submitting its process description. Documentation on the

318 additional chemical transformation steps from the intermediate to the active substance should be  
319 provided in 3.2.S.2.2. The manufacturers involved in the process covered by the CEP should be listed  
320 in module 3.2.S.2.1 and in the QP declaration (Ref 17). See also (Ref 18, section 3.3).

321 If an intermediate in the proposed synthesis of the active substance is itself an active substance  
322 already included in a finished product authorised in the EU and documented in an accepted workshared  
323 (WS) ASMF, then this can be referenced. Complete information on the manufacturing process  
324 (3.2.S.2), starting with the starting materials will still need to be submitted, either as part of a new  
325 ASMF or in the dossier and conclusion of the related WS assessment can be considered. See also (Ref  
326 19).

#### 327 **4.2.5. Process Validation and/or Evaluation 3.2.S.2.5**

328 Even if no process validation data is provided in the application, the active substance manufacturing  
329 process must be validated before commercial distribution. Process validation data and/or evaluation  
330 studies for aseptic processing and sterilisation should be provided (Refs 4, 8, 9).

#### 331 **4.2.6. Manufacturing Process Development 3.2.S.2.6**

332 A description and discussion of any significant changes made to the manufacturing process and/or  
333 manufacturing sites of the active substance used in producing non-clinical, clinical, scale-up, pilot, and,  
334 if available, production scale batches, should be provided.

335 For existing active substances, all provided data might be obtained on production scale batches  
336 manufactured according to the presented manufacturing description. A description of the  
337 manufacturing process development may not be necessary in these cases but will often add to the  
338 understanding of the control strategy.

339 Reference should be made to the active substance data provided in section 3.2.S.4.4. The information  
340 provided should include detailed descriptions of the individual elements of the control strategy plus,  
341 when appropriate, a summary of the overall active substance control strategy as detailed in ICH Q11  
342 (for example in tabular or in a diagrammatic format).

343 The justification for the selected process and its parameters, where necessary should be presented in  
344 tabular format for each manufacturing step and for each sub-step in telescoped processes with non-  
345 isolated intermediate(s). The rationale should include a discussion on the presence of potentially  
346 mutagenic impurities, particularly 'cohort of concern' compounds, and other potent toxins originating  
347 from intermediates and intentionally introduced materials. The impact of the use of reagents and  
348 depletion agents (particularly in molar excess) on the active substance impurity profile should be  
349 considered. The selected process should also be justified by discussing the potential for formation of  
350 by-products and side products of toxicological relevance considering critical compound combinations  
351 (for example, Ref 20).

352 In particular, efforts to minimise the risk of nitrosamine formation in the process should be guided by  
353 the Q&A document (Ref 11), in which the risk factors are listed, together with the measures for risk  
354 mitigation and principles of control strategies. If the use of nitrosating agents is unavoidable within the  
355 synthetic process, then combination with nitrosatable compounds under conditions amenable to  
356 nitrosamine formation should be mitigated. If potential for formation of nitrosamines is unavoidable, a  
357 control strategy at an appropriate control point should be implemented and justified based on  
358 adequate process knowledge using a suitable analytical procedure where needed (Ref 11 and 14).

### 359 **4.3. Characterisation 3.2.S.3**

#### 360 **4.3.1. Elucidation of Structure and other Characteristics 3.2.S.3.1**

361 Section 3.2.S.3.1 describes the information which is expected for a new chemical entity. For existing  
362 active substances, not all items may be necessary to prove the identity of the material, especially if the  
363 identity can be verified by a specific test in comparison to an official standard.

364 This section should include the research and development program performed to verify the structure  
365 and the chemical and physico-chemical properties of the active substance. Relevant results described  
366 in this section should be reflected in the control tests on the active substance to check batch-to-batch  
367 uniformity.

#### 368 **Evidence of chemical structure**

369 Confirmation of structure based on e.g., synthetic route and spectral analyses, information regarding  
370 the potential for isomerism, identification of stereochemistry, or potential for forming polymorphs  
371 should be included.

372 A scientific discussion of the chemistry of the active substance should be provided, including  
373 unequivocal proof of structure, configuration and potential isomerism. This should include a  
374 presentation of the stereochemical properties of the molecule (Ref 21). It is important that the  
375 evidence of structure should be related to the actual material to be used in the marketed product,  
376 especially for highly complex molecular structures.

377 If the data included in this section originates from a synthetic process other than the one covered by  
378 the application (i.e. different routes), evidence may be required to confirm the structural identity of the  
379 materials from different origin. This is particularly important where toxicological studies have been  
380 carried out on material from different origin.

381 Publication references may be included if the synthetic route and structure of the intermediates are  
382 cited as structural evidence.

383 The information will normally include such evidence as:

- 384 • Elemental analysis with theoretical values;
- 385 • Infra-red spectra with interpretation;
- 386 • Nuclear magnetic resonance spectra with interpretation;
- 387 • Discussion on UV characteristics including pH dependent shifts;
- 388 • Mass spectra with interpretation and discussion of results;
- 389 • Discussion of the synthetic route as evidence of structure;
- 390 • Evidence or structure of key intermediates (e.g. using IR, NMR, etc.);
- 391 • Characteristic chemical reactions which are diagnostic of the structure of the molecule;
- 392 • X-ray crystallography with interpretation and discussion of results;
- 393 • Evidence of the indicated relative molecular mass determined by mass spectrometry or other  
394 analytical techniques.

395 Relevant quality aspects of eventual or possible isomers with biological/pharmacological activity should  
396 be discussed (Ref 21).

## 397 **Physico-chemical Characteristics**

398 Information set out under the relevant headings below should cover aspects of physicochemical  
399 characteristics which have been investigated, whether or not they are included in the specification for  
400 the active substance.

401 There are many ways of modifying the solid state physico-chemical properties of an active substance  
402 such as making salts, solvates, cocrystals, or selecting for a given polymorphic form, which can  
403 influence biologically-relevant properties of said active substance. Information on the proposed  
404 commercial solid state form should be provided in 3.2.S.3.1. This information should be related to the  
405 in vivo performance of the finished product in 3.2.P.2.1.

### 406 Polymorphism

407 Polymorphism is the property of a solid state chemical substance to exist in the solid state in different  
408 crystalline forms. Some active substances exist in different polymorphs possessing different physico-  
409 chemical properties. These forms may affect processability, stability, dissolution and bioavailability of  
410 the drug product.

411 Examples of analytical methods commonly used to determine the existence of multiple polymorphic  
412 forms are:

- 413 • Melting point (including hot-stage microscopy);
- 414 • Solid state IR and NIRS;
- 415 • X-ray powder diffraction;
- 416 • Thermal analysis procedures such as differential scanning calorimetry (DSC), thermogravimetric  
417 analysis (TGA) and differential thermal analysis (DTA);
- 418 • Raman spectroscopy;
- 419 • Scanning electron microscopy;
- 420 • Solid state NMR spectroscopy.

421 The presence of polymorphic forms and solvates and the methods of detection and control should be  
422 discussed. Similarly, amorphous forms should be characterised and detection and control methods  
423 described if not otherwise justified (Ref 7).

### 424 Solubility

425 Numeric solubility values (e.g. mg/ml) for the active substance in water at various temperatures and in  
426 aqueous buffer at physiologically relevant pHs should be provided, as well as the corresponding pH  
427 values for the equilibrium solubility test solutions. Data for solubility in other solvents may also be  
428 provided. The test procedures used for solubilities should be described.

### 429 Physical characteristics

430 Physical properties should be stated here and, if significant, information on particle size (distribution),  
431 solvation, melting point, hygroscopicity and boiling point should be added.

### 432 pKa and pH values

433 The pKa values of the active substance and the pH in solutions of defined concentration should be  
434 stated. In the case of a salt, the corresponding values of the base or acid should be stated.

### 435 Other characteristics

436 Information is to be provided concerning the following:

- 437 • Partition properties (oil/water partition coefficient, octanol/water partition coefficient, log P, etc.);
- 438 • Physical properties of significance may be stated.

#### 439 **4.3.2. Impurities 3.2.S.3.2**

440 Information on impurities and their carry-over should be provided. This includes related substances,  
441 residual solvents, elemental impurities, reagents and those derived from reagents. The related  
442 substances considered as potential impurities arising from the synthesis and degradation products  
443 should be discussed and described briefly including an indication of their origin. As part of the overall  
444 discussion on impurities, a specific discussion should be provided with regard to potential mutagenic  
445 impurities (Ref 10). If a mutagenic impurity is liable to be present in the substance, then the control  
446 strategy should be demonstrated to be in compliance with control options outlined in ICH M7 and the  
447 related Q&A, and the risk of presence of compounds of the “cohort of concern” (according to ICH M7)  
448 or other potent toxins should also be discussed. Regarding nitrosamine impurities, reference is made  
449 to the identified risk factors (Ref 11).

450 In each case, it should be stated whether actual samples of impurities have been synthesised or  
451 isolated for test purposes. Structural analysis data for identified impurities should be provided unless  
452 identity is proved by other means.

453 Possible routes of degradation should also be discussed - please see section 3.2.S.7.1.

454 The analytical methods (with limits of detection (LOD) and limits of quantitation (LOQ)) used to detect  
455 each of the likely impurities considered above or other related impurities, the exact identities of which  
456 may be unknown, should be described. Copies of relevant chromatograms should be provided.

457 To adequately detect and quantify impurities, the applied analytical method should be suitably  
458 sensitive. For nitrosamines, the LOQ should be minimum at or sufficiently below the toxicologically  
459 required limit, taking into account the purpose of testing (e.g., routine testing, justifying skip testing or  
460 omission of specification). See (Ref 11). A summary should be given on the nature and levels of the  
461 actual impurities detected in the batch samples of the material. Justification should be provided for  
462 selecting the limits based on safety and toxicity data, as well as on the methods used for the control of  
463 impurities (see 3.2.S.4.4.). For qualification of impurities, refer to 3.2.S.4.5 (Refs 7, 10 and 22-26).

#### 464 **4.4. Control of the Active Substance 3.2.S.4**

##### 465 **4.4.1. Specification 3.2.S.4.1**

466 The active substance specification should be provided.

467 The following tests should be performed as a minimum required and appropriate acceptance criteria  
468 applied:

- 469 • Description;
- 470 • Identification;
- 471 • Impurities;
- 472 • Assay and/or potency.

473 Additional tests may be required depending on the nature of the active substance or its subsequent  
474 use (e.g. polymorphic form, enantiomeric purity, particle size, microbiological purity, bacterial  
475 endotoxins, etc. (Refs 7, 10, 23-26).

#### 476 **4.4.2. Analytical Procedures 3.2.S.4.2**

477 Details of the analytical procedures used for testing the active substance should be provided. They  
478 should be described in such a way that they can be repeated by an Official Medicines Control  
479 Laboratory (Ref 27).

#### 480 **Analytical Development**

481 Any critical aspects of significance concerning analytical development in regard to the active substance  
482 specification should be mentioned. The discussion here should highlight any unusual aspects  
483 concerning the tests dealing with the specification of the active substance. Tests for purity and  
484 impurity levels can be discussed under the section on impurities. Orthogonal analytical methods,  
485 (methods using different principles and providing different selectivities), should be developed in cases  
486 where a lack in specificity and/or selectivity leads to an inadequate control strategy for the affected  
487 impurities. If biological control procedures are necessary, then particular emphasis should be placed on  
488 the discussion of the test precision and accuracy.

#### 489 **4.4.3. Validation of Analytical Procedures 3.2.S.4.3**

490 Analytical validation data, including experimental results for the analytical procedures used for the  
491 control of the active substance, should be provided unless methods of the respective drug substance  
492 monograph in Ph. Eur. are referred to and the tests of the monograph have been demonstrated  
493 suitable to control the substance. Validation of analytical tests concerning the active substance should  
494 be performed according to the requirements of the current Guidelines (Ref 27). For nitrosamines,  
495 additional requirements are stated in the nitrosamine Q&A (Ref 11).

#### 496 **4.4.4. Batch Analyses 3.2.S.4.4**

497 Description of batches and results of batch analyses should be provided as follows:

- 498
- 499 • Batches of material used in the pre-clinical tests and clinical studies reported in support of the application;
  - 500 • Data illustrating the actual results obtained from routine quality control of the active substance.  
501 Results from at least three recent consecutive batches from each manufacturing site,  
502 manufactured according to the proposed process at not less than 10% of maximum production  
503 scale at the time of submission should be provided. These results should demonstrate that routine  
504 production material falls within the specification limits cited for the purpose covered by the  
505 marketing authorisation.

506 The results should include:

- 507 • Date of manufacture;
- 508 • Batch size and number;
- 509 • Place of manufacture (data from all manufacturing sites must be provided);
- 510 • Results of analytical determination;

511 • Use of batches.

512 Presentation of this information in tabular form is recommended for improved clarity. Test results  
513 should be expressed numerically, e.g. impurity levels. Results which merely state that the material  
514 “complies” with the test are insufficient. The batch analyses should include all the tests in the  
515 specification. There may, however, be cases where previous batches were tested using a slightly  
516 different specification. In these cases, a brief explanatory note should be included. Any apparently  
517 inconsistent or anomalous results in the batch analyses should be explained (Refs 7, 22, 23, 25).

#### 518 **4.4.5. Justification of Specification 3.2.S.4.5**

519 Justification for the control strategy and active substance specification should be provided. The  
520 specification should be based on results from non-clinical, clinical and, where applicable, production  
521 scale batches and taking into account the qualification of impurities and the overall control strategy.

522 The requirements of the general monograph of the European Pharmacopoeia *Substances for*  
523 *Pharmaceutical Use* (2034) should be met, where applicable. For existing active substances, the  
524 respective monograph of Ph. Eur. or, in default of this, the respective monograph of the  
525 pharmacopoeia of an EU Member State should be the basis of the active substance specification.  
526 Supplementation by additional tests, (e.g., impurity tests) might be necessary. For existing active  
527 substances not covered by Ph. Eur. or a pharmacopoeia of an EU member state, impurity levels above  
528 the ICH Q3A qualification thresholds are subject to further justification, e. g. safety qualification data  
529 or reference to published literature data (Refs 7, 10, 22-26).

530 If a risk of presence of compounds of the “cohort of concern” (according to ICH M7) or other potent  
531 toxins has been identified, then appropriate control of these impurities should also be discussed.  
532 Regarding nitrosamine impurities, exceptions from routine testing may be possible, if the root cause is  
533 demonstrated to be well-understood and the requirements outlined in (Ref 11) are fulfilled.

#### 534 **4.5. Reference Standards or Materials 3.2.S.5**

535 Information on the reference standards or reference materials used for testing of the active substance  
536 should be provided: specifications, full analytical and physico-chemical characterizations, impurities  
537 profile, etc. Chemical reference substances (Ph. Eur. CRS) are qualified as primary reference standards  
538 and do not need to be further qualified, provided they are used for their intended purpose. The criteria  
539 for establishing the primary reference substances should be given with full analytical profiles. The  
540 procedure for establishing secondary reference standards or materials normally used for routine  
541 analysis should be stated (Ref 7).

#### 542 **4.6. Container Closure System 3.2.S.6**

543 A brief description of the storage container closure system(s), including specifications with suitable  
544 identity test(s) and details of materials of construction should be provided. If the storage container  
545 closure system is critical for assuring the quality of the active substance, its suitability should be  
546 justified. Depending on nature of the active substance, aspects that may need justification include  
547 choice of the primary packaging materials, protection from light and/or moisture, compatibility with the  
548 active substance including sorption to material and leaching and/or any safety aspects. Reference to  
549 stability data can be additional supportive information to justify suitability of the proposed container  
550 closure system. The information should cover the whole packaging including the primary packaging  
551 material (e.g. polyethylene bag) and secondary packaging (e.g. fibre or metal drum).



552 Compliance of the primary packaging with any current applicable regulatory requirements (e.g. food  
553 grade materials) should be provided (Ref 28).

#### 554 **4.7. Stability 3.2.S.7**

##### 555 **4.7.1. Stability Summary and Conclusions 3.2.S.7.1**

556 The types of studies conducted, protocols used, and the results of the studies should be summarized.  
557 The summary should include results, for example, from forced degradation studies and stress  
558 conditions (light stress, higher temperature, etc.), as well as conclusions with respect to storage  
559 conditions and retest date or expiry date as appropriate. For stability-indicating parameters,  
560 compliance with the established specification limits should be verified during stability studies and this  
561 should include any "cohort of concern" compounds or other highly potent toxins which may potentially  
562 form or increase during storage.

563 For active substances described in an official pharmacopoeial monograph (Ph. Eur. or the  
564 Pharmacopoeia of an EU member state), which covers the degradation products and for which suitable  
565 limits have been set, stability studies might not be necessary if it is demonstrated that the substance  
566 complies with the monograph (and any additional tests in the specification) immediately before  
567 manufacture of each batch of the finished product. For existing active substances, the Guideline on  
568 Stability testing of existing active substances and related finished products should be consulted (Refs  
569 5, 29-31).

##### 570 **4.7.2. Post-approval Stability Protocol and Stability Commitment 3.2.S.7.2**

571 A post-approval stability protocol and stability commitment should be provided if data for production  
572 scale batches covering the full proposed re-test period or expiry date is not available (Refs 5, 29-31).

##### 573 **4.7.3. Stability Data 3.2.S.7.3**

574 Detailed results of the stability studies including forced degradation studies and stress conditions  
575 should be presented in an appropriate tabular or graphical format. Information on the analytical  
576 procedures used to generate the data and validation of these procedures should be included. The  
577 major degradation pathways of the active substance should be discussed. The storage conditions and  
578 the retest period should be defined (Refs 5, 21, 29-31).

579



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