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4 Guideline on the chemistry of active substances

5 Draft

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

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

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13 Guideline on the chemistry of active substances

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51 **Executive summary**

52 This guideline replaces the 'Note for guidance on chemistry of new active substances'
53 (CPMP/QWP/130/96, Rev 1) and 'Chemistry of active substances' (3AQ5a). It has been revised to
54 cover new and existing active substances in one guideline.

55 **1. Introduction (background)**

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

58 **2. Scope**

59 The purpose of this Note for Guidance is to set out the type of information required for the
60 manufacture and control of active substances (existing or new chemical entities) used in a medicinal
61 product. The differences in requirements for new or existing active substances are clarified in the
62 relevant paragraphs of the guideline where applicable. This guideline is not applicable to herbal,
63 biological, biotechnological products, radiopharmaceuticals and radiolabelled products.

64 This guideline is applicable to active substances that have been developed following a "traditional" or
65 an "enhanced" approach or a combination of these. However, when an "enhanced" approach is used or
66 a design space claimed, the information provided in sections 3.2.S.2.2 to 3.2.S.2.6., should be
67 prepared and organised according to ICH Q11¹.

68 **ASMFs and CEPs:**

69 As an acceptable alternative to submission of detailed active substance information in the application
70 for marketing authorisation, the Active Substance Master File (ASMF) or the Certification of Suitability
71 to the Monographs of the European Pharmacopoeia (CEP) procedures may be used as described in
72 'Guideline on the Summary of Requirements for the Active substance in the Quality Part of the Dossier,
73 CHMP/QWP/297/97'². The requirements should be the same regardless of the route of submission of
74 data on the active substance. For procedural aspects and format of the ASMF, please refer to the
75 Guideline on Active Substance Master File procedure CHMP/QWP/227/02³.

76 **3. Legal basis**

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

80 **4. Body of Data**

81 **4.1. General Information 3.2.S.1**

82 This section deals with the identity, nomenclature and chemical structure of the active substance which
83 is the subject of the application for marketing authorisation. Only brief information of physical

84 characteristics should be listed, as full details and proof of structure are required in a separate section
85 (see 3.2.S.3.1).

86 **4.1.1. Nomenclature 3.2.S.1.1**

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

- 88 • International Nonproprietary Name (INN);
- 89 • Compendial (e.g. European Pharmacopoeia) name;
- 90 • National Approved Names: British Approved Name (BAN), Japanese Accepted Name (JAN), United
91 States Adopted Name (USAN), company or laboratory code:
- 92 • Systematic Chemical Name(s) (IUPAC nomenclature);
- 93 • Other Names (e.g. proprietary);
- 94 • Other non-proprietary name(s); and
- 95 • Chemical Abstracts Service (CAS) registry number (RN).

96 **4.1.2. Structure 3.2.S.1.2**

97 The structural formula, including relative and absolute stereochemistry, the molecular formula, and the
98 relative molecular mass should be provided. Along with the stoichiometric formula and relative
99 molecular mass, the structural formula should display the stereochemistry (indicated conventionally) of
100 the active substance. If this information is not available a detailed description of the nature of the
101 substance should be given. If appropriate, the Mr of the therapeutically active moiety should also be
102 included.

103 **4.1.3. General Properties 3.2.S.1.3**

104 The appearance of the material is to be described briefly. A list of physicochemical and other relevant
105 properties of the active substance should be provided, in particular physico-chemical properties that
106 affect pharmacological efficacy and toxicological safety such as solubilities, pKa, polymorphism,
107 isomerism, logP, permeability, hygroscopicity, etc.⁴

108 **4.2. Manufacture 3.2.S.2**

109 **4.2.1. Manufacturer(s) 3.2.S.2.1**

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

113 **4.2.2. Description of Manufacturing Process and Process Controls 3.2.S.2.2**

114 The description of the active substance manufacturing process represents the applicant's commitment
115 for the manufacture of the active substance. Information should be provided to adequately describe
116 the manufacturing process, including special unit operations and process controls. Optional processes
117 and controls that may be completed by the active substance manufacturer, for instance size reduction,

118 should also be described. Particular emphasis should be placed on steps of the process having an
119 impact on the quality of the active substance or intermediates and which are classified as 'critical', (see
120 also under 3.2.S.2.4).

121 **Flow diagram of the manufacturing process**

122 A flow diagram of the synthetic process(es) should be provided that includes molecular formula,
123 weights, yield ranges, chemical structures of starting materials, intermediates, reagents and active
124 substance reflecting stereochemistry, and identifies operating conditions, unit operations, catalysts and
125 solvents.

126 **Sequential procedural narrative**

127 A sequential procedural narrative of the manufacturing process should be submitted. This narrative
128 should include the quantities (or ranges) of raw materials, starting materials and intermediates,
129 solvents, catalysts and reagents used in manufacture of a representative scale commercial batch. The
130 narrative should describe each step in the manufacturing process, and identify critical steps, process
131 controls employed, and ranges for equipment operating conditions (e.g.: temperature, pressure, pH,
132 time, flow-rate, etc.).

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

134 **Scale of Manufacture, Range, Yield**

135 The description of the process should indicate the scale of manufacture and the range for which the
136 considered process may be used. It may be helpful to indicate the yield or yield range produced at
137 each stage.

138 **Alternative processes**

139 Alternative processes should be explained and described with the same level of detail as the primary
140 process. The process description should fully define the method of synthesis. However, if alternative
141 steps or solvents are proposed they should be justified providing sufficient evidence that the final
142 quality of the material (i.e.: active substance or isolated intermediate) obtained remains unchanged.

143 **Reprocessing**

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

147 **Recovery**

148 Recovery (e.g. from mother liquors or filtrates) of solvents, reactants, intermediates or the active
149 substance is considered acceptable according to ICH Q7⁵ or EU GMP Part II⁶, provided that approved
150 procedures exist for the recovery and the recovered materials meet specifications suitable for their
151 intended use.

152 **4.2.3. Control of Materials 3.2.S.2.3**

153 Materials used in the manufacture of the active substance (e.g., raw materials, starting materials,
154 solvents, reagents, catalysts, process aids, etc.) should be listed identifying where each material is
155 used in the process. Adequate specifications including information on the identification of these
156 materials should be provided. Information demonstrating that materials meet standards appropriate

157 for their intended use should be provided. If the quality of a specific input material is critical for the
158 quality of the active substance, and non-compendial test methods are used to control that material,
159 suitable validation data for control tests carried out should be submitted.

160 **Biologically-sourced materials**

161 Information on the source, processing, characterization and control of all materials of biological origin
162 must be provided, including viral and/or TSE safety data.

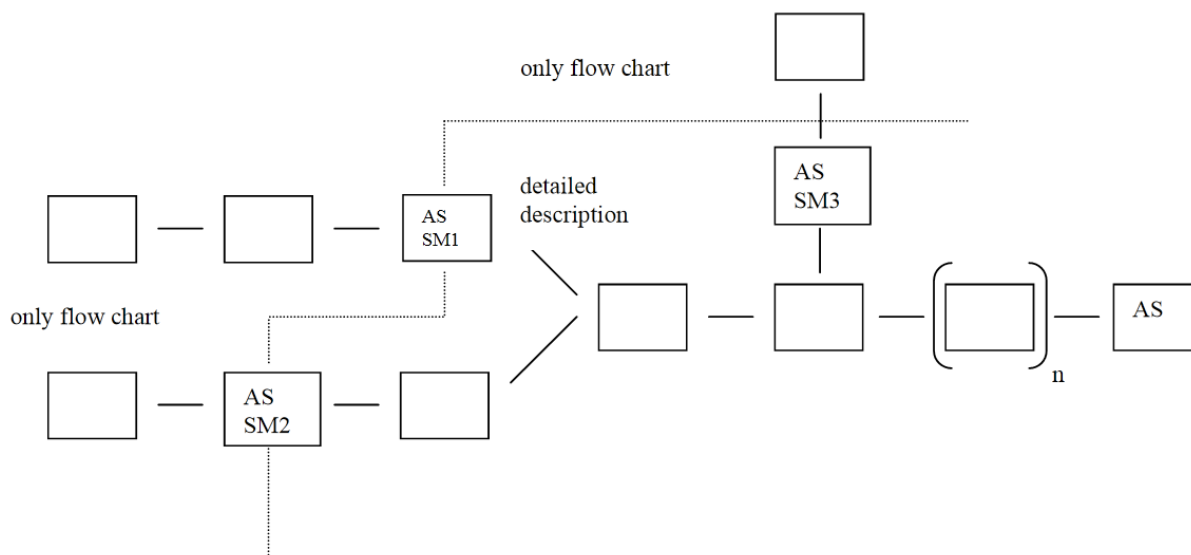
163 **Active Substance (AS) Starting Material(s)**

164 The requirements of ICH Q11 in relation to the selection of starting materials are relevant to all active
165 substances, regardless of the type of development approach. Reflection paper⁷ should also be
166 consulted.

167 Generally, the description of the process and the synthesis schematic should include all the steps of
168 the process, proceeding from the starting material(s) to the intermediates, and ultimately to the active
169 substance. Use of starting materials marks the beginning of the description of the process and
170 manufacture under GMP. Typically, multiple chemical transformation steps should separate the starting
171 material from the final active substance. The full description of the process should cover all the
172 synthetic steps critical to the quality of the active substance.

173 The marketing authorisation applicant should propose and justify which substance should be
174 considered as the AS starting material (SM), e.g. incorporated as a significant structural fragment into
175 the structure of the active substance. Non-isolated compounds are not considered appropriate to be
176 selected as starting materials. The name and address of the starting material manufacturers should be
177 provided. Information, in the form of a flow chart, indicating the synthetic process prior to the
178 introduction of the starting material (including reagents, solvents and catalysts), is necessary to
179 evaluate the suitability of the proposed starting material and its specifications.

180 Schematic description (illustrative only):



181

182 When the proposed starting material is itself an active substance covered by a monograph of the
183 European Pharmacopoeia (Ph. Eur.), and when the active substance manufacturer has demonstrated
184 the suitability of the Ph. Eur. monograph as evident by a valid Certificate of Suitability to the

185 monographs of the European Pharmacopoeia (CEP) for the proposed starting material, this would be
186 accepted. Alternatively, such a starting material may already be the active substance in a marketing
187 authorisation in the EU. However, clear evidence that the marketing authorisation is still valid and that
188 the starting material is manufactured under GMP to the same quality standard as the active substance
189 in the already-authorized product, (manufacturer, site, process, impurity profile and specifications),
190 should be provided in the dossier.

191 In both above cases, although defined as starting materials in the dossier, these compounds are
192 actually considered to be synthetic intermediates since their acceptance is contingent on being
193 manufactured under GMP in line with another dossier (CEP, ASMF or standalone dossier). For the
194 purposes of GMP and traceability, the sites of manufacture for these starting materials should be
195 registered as intermediate manufacturing sites in the marketing authorisation application and be the
196 subject of a QP declaration²².

197 Starting materials should be fully characterized to ascertain suitability for intended use and complete
198 specifications should be provided, including an impurity profile. The possibility that any kind of
199 impurity, for example isomeric impurities, present in a starting material may be carried through the
200 synthetic process unchanged or as derivatives should be discussed and should therefore, if relevant, be
201 controlled in the starting material by appropriate acceptance criteria with suitably validated methods.
202 Acceptance criteria should be established by the applicant based on evaluation of the fate of impurities
203 present in the starting material, when subjected to the normal processing conditions. Relevant viral
204 safety and / or TSE data must be provided if any animal-derived material is used during the active
205 substance manufacturing process (e.g. arising from fermentation, enzymes, amino acids, etc.).

206 **Materials of plant origin**

207 Information on the source, processing, characterization and control of all materials of plant origin must
208 be provided to ascertain suitability and a contaminant profile should be established and submitted.
209 Information on the scientific name (genus, species, variety and author) of the plant and plant part
210 used should be specified as should the solvents in the extraction process. The specification of the
211 starting material of herbal origin should follow the principles set out in the European Pharmacopoeia
212 monographs and the potential presence of foreign matter, pesticides, microbiological contamination,
213 total ash, heavy metals, mycotoxins, radioactive contamination, residual solvents, and other relevant
214 impurities should be discussed. Information on the geographical origin, collection or cultivation,
215 harvesting, and post-harvest treatments (possible pesticides and fumigants used and possible
216 radioactive contamination) may be appropriate depending on the subsequent synthetic steps.

217 **Solvents, Reagents and other materials**

218 Specifications for all materials (solvents, reagents, processing aids) used in synthesis should be
219 submitted. Materials used in the final stages of the synthesis may require greater control (i.e.: tighter
220 specifications) than those used in earlier stages.

221 If water is used as solvent in the last purification/crystallisation step the water quality required
222 depends on pharmaceutical form of the Drug Product in which the active substance will be used^{4,7-10}.

223 **4.2.4. Control of Critical Steps and Intermediates 3.2.S.2.4**

224 **Critical Steps:** Tests and acceptance criteria (with justification based on experimental data)
225 performed at critical steps identified in 3.2.S.2.2 of the manufacturing process should be provided. A
226 critical step is defined as one where the process conditions, test requirements or other relevant

227 parameters must be controlled within predetermined limits to ensure that the AS meets its
228 specification.

229 Critical steps could be for instance:

230 • Mixing of multiple components;

231 • Phase change and phase separation steps;

232 • Steps where control of temperature and pH are critical; and

233 • Steps which introduce an essential molecular structural element or result in a major chemical;

234 **Transformation:**

- 235 • Steps which introduce (or remove) significant impurities to (or from) the active substance. For
236 those impurities not controlled in the active substance, suitable in-process controls should be
237 carried out with justified ranges and documented; and
- 238 • The final purification step.

239 Steps which have an impact on solid-state properties and homogeneity of the active substance are
240 always considered as critical, particularly, if the active substance is used within a solid dosage form,
241 since they may adversely affect dissolution of the active substance from the dosage form and thereby
242 affect bioavailability.

243 **Intermediates:**

244 Information on the quality and control of intermediates isolated during the process should be provided.
245 For intermediates which are those which influence final quality of the active substance, the analytical
246 methods used to control them, should be suitably validated if they are non-compendial. Information on
247 the characterisation of these intermediates should be provided⁴.

248 **4.2.5. Process Validation and/or Evaluation 3.2.S.2.5**

249 Even if no process validation data is provided in the application, the active substance manufacturing
250 process must be validated before commercial distribution and a commitment to do so should be
251 provided. Process validation data and/or evaluation studies for aseptic processing and sterilisation
252 should be provided.

253 **4.2.6. Manufacturing Process Description 3.2.S.2.6**

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

257 Reference should be made to the active substance data provided in section 3.2.S.4.4.

258 For existing active substances, all provided data might be obtained on production scale batches
259 manufactured according to the presented manufacturing description. A description of the
260 manufacturing process development is not necessary in these cases but will often add to the
261 understanding of the control strategy¹¹.

262 **4.3. Characterisation 3.2.S.3**

263 **4.3.1. Elucidation of Structure and other Characterisation 3.2.S.3.1**

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

267 This section should include the research and development program performed to verify the structure
268 and the chemical and physico-chemical properties of the active substance. The results described in this
269 section should be reflected in the control tests on the active substance to check batch-to-batch
270 uniformity.

271 **Evidence of chemical structure**

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

275 A scientific discussion of the chemistry of the active substance should be provided, including
276 unequivocal proof of structure, configuration and potential isomerism. This should include a
277 presentation of the stereochemical properties of the molecule (see reference 10). It is important that
278 the evidence of structure should be related to the actual material to be used in the marketed product,
279 especially for highly complex molecular structures.

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

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

286 The information will normally include such evidence as:

- 287 • Elemental analysis with theoretical values;
- 288 • Infra-red spectra with interpretation;
- 289 • Nuclear magnetic resonance spectra with interpretation;
- 290 • Discussion on UV characteristics including pH dependent shifts;
- 291 • Mass spectrum with interpretation and discussion of results;
- 292 • Discussion of the synthetic route as evidence of structure;
- 293 • Evidence or structure of key intermediates or synthesis (e.g. using IR, NMR, etc.);
- 294 • Characteristic chemical reactions which are diagnostic of the structure of the molecule;
- 295 • X-ray crystallography with interpretation and discussion of results (refer to S.2.3.);
- 296 • Optical rotation (Absence of optical rotation should be reported if it serves to demonstrate the
297 racemic nature of a chiral molecule); and
- 298 • Evidence of the indicated relative molecular mass.

299 The relevance of the eventual or possible isomers regarding biological/pharmacological activity should
300 be discussed¹⁰.

301 **Physico-chemical Characteristics**

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

305 There are many ways of modifying the solid state physico-chemical properties of an active substance
306 such as making salts, solvates, cocrystals, or selecting for a given polymorphic form, which can
307 influence biologically-relevant properties of said API. Information on the proposed commercial solid
308 state form should be provided and related to the in vivo performance of the finished product.

309 Polymorphism

310 Polymorphism is the property of a chemical substance to exist in the solid state in different crystalline
311 forms having the same chemical composition. Some active substances exist in different polymorphs
312 possessing different physico-chemical properties. These forms may affect processability, stability,
313 dissolution and bioavailability of the drug product.

314 Examples of analytical methods commonly used to determine the existence of multiple polymorphic
315 forms are:

- 316 • Melting point (including hot-stage microscopy);
- 317 • Solid state IR and NIRS;
- 318 • X-ray powder diffraction;
- 319 • Thermal analysis procedures such as differential scanning calorimetry (DSC), thermogravimetric
320 analysis (TGA) and differential thermal analysis (DTA);
- 321 • Raman spectroscopy;
- 322 • Scanning electron microscopy; and
- 323 • Solid state NMR.

324 The presence of polymorphic forms and solvates and the methods of detection and control should be
325 discussed. Similarly, amorphous forms should be characterised and detection and control methods
326 described⁴.

327 Solubility

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

332 Physical characteristics

333 Physical properties should be stated here and, if significant, information on particle size (complete
334 particle size profile), solvation, melting point, hygroscopicity, boiling point should be added.

335

336 pKa and pH values

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

339 Other characteristics

340 Information is to be provided concerning the following:

- 341 • Physico-chemical characteristics (oil/water partition coefficient, octanol/water partition coefficient,
342 log P, etc.); and
- 343 • Physical properties of significance may be stated.

344 **4.3.2. Impurities 3.2.S.3.2**

345 Information on impurities and their carry-over should be provided. This includes related substances,
346 residual solvents, elemental impurities and those derived from reagents. The related substances
347 considered as potential impurities arising from the synthesis should be discussed and described briefly
348 together with an indication of their origin. The genotoxic potential of impurities should be addressed.
349 In each case, it should be stated whether actual samples of impurities have been synthesized for test
350 purposes. Characterisation data for identified impurities should be provided.

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

352 The analytical methods (with limits of detection (LOD) and limits of quantitation (LOQ) used to detect
353 each of the likely impurities considered above or other related impurities, the exact identities of which
354 may be unknown, should be described. Copies of relevant chromatograms should be provided. A
355 summary should be given on the nature and levels of the actual impurities detected in the batch
356 samples of the material. Justification should be provided for selecting the limits based on safety and
357 toxicity data, as well as on the methods used for the control of impurities (see 3.2.S.4.4.). For
358 qualification of impurities, refer to 3.2.S.4.5^{4,10-18}.

359 **4.4. Control of the Active Substance 3.2.S.4**

360 **4.4.1. Specification 3.2.S.4.1**

361 The active substance specification should be provided.

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

- 364 • Description;
- 365 • Identification;
- 366 • Impurities; and
- 367 • Assay and/or potency.

368 Additional tests may be required depending on the nature of the active substance or its subsequent
369 use (e.g. polymorphic form, enantiomeric purity, particle size, microbiological purity, bacterial
370 endotoxins, etc.^{4,12,15,16,18,19}).

371 **4.4.2. Analytical Procedures 3.2.S.4.2**

372 Details of the analytical procedures used for testing the active substance should be provided. They
373 should be described in such a way that they can be repeated by an Official Medicines Control
374 Laboratory⁹.

375 **Analytical Development**

376 Any critical aspects of significance concerning analytical development in regard to the active substance
377 specification should be mentioned. The discussion here should highlight any unusual aspects
378 concerning the tests dealing with the specification of the active substance. Tests for purity and
379 impurity levels can be discussed under the section on impurities. Orthogonal analytical methods should
380 be developed in the case that a lack in specificity and/or selectivity is observed for a purity method. If
381 biological control procedures are necessary, then particular emphasis should be placed on the
382 discussion of the test precision and accuracy.

383 **4.4.3. Validation of Analytical Procedures 3.2.S.4.3**

384 Analytical validation data, including experimental results for the analytical procedures used for the
385 control of the active substance, should be provided. Validation of analytical tests concerning the active
386 substance should be performed according to the requirements of the current Guidelines⁹.

387 **4.4.4. Batch Analyses 3.2.S.4.4**

388 Description of batches and results of batch analyses should be provided.

- 389 • Batches of material used in the pre-clinical tests and clinical studies reported in support of the
390 application; and
- 391 • Data illustrating the actual results obtained from routine quality control of the active substance.
392 Recent consecutive batches (at least 3) which are representative (not-less-than 10% of maximum
393 commercial batch size at the time of the approval) of the active substance which will be supplied
394 for the purpose covered by the marketing authorisation to show that the proposed methods will
395 give routine production material which falls within the specification limits cited. Information on
396 production size batches should be provided, if necessary on an on-going basis, after approval.

397 The results should include:

- 398 • Date of manufacture;
- 399 • Batch size and number;
- 400 • Place of manufacture (data from all manufacturing sites must be provided);
- 401 • Results of analytical determination; and
- 402 • Use of batches.

403 Presentation of this information in tabular form is recommended for improved clarity. Test results
404 should be expressed numerically e.g. impurity levels. Results which merely state that the material
405 “complies” with the test are insufficient, especially if a relatively wide limit is allowed in the
406 specification. The batch analyses should include all the tests in the specification. There may, however,
407 be cases where previous batches were tested using a slightly different specification. In these cases, a

408 brief explanatory note should be included. Any apparently inconsistent or anomalous results in the
409 batch analyses should be explained^{4,11,12,18}.

410 **4.4.5. Justification of Specification 3.2.S.4.5**

411 Justification for the active substance specification should be provided. The specification should be
412 based on results from preclinical, clinical and, where applicable, production scale batches and taking
413 into account the qualification of impurities.

414 The requirements of the general monograph of the European Pharmacopoeia *Substances for*
415 *Pharmaceutical Use (2034)* should be met, where applicable. For existing active substances, the
416 respective monograph of Ph. Eur. or in default of this the respective monograph of the pharmacopoeia
417 of an EU-Member-State should be the basis of the active substance specification. Supplementation by
418 additional tests, e.g., impurity tests might be necessary. For existing active substances not covered by
419 Ph. Eur or a pharmacopoeia of an EU-Member-State, impurity levels above the ICH Q3A thresholds are
420 subject to toxicological evaluation^{4,11,12,15,16,18,19}.

421 **4.5. Reference Standards or Materials 3.2.S.5**

422 Information on the reference standards or reference materials used for testing of the active substance
423 should be provided: Specifications, full analytical and physico-chemical characterizations, impurities
424 profile, etc. The criteria for establishing the reference substances (primary and secondary) for routine
425 analysis should be given with full analytical profiles. Aliquotation, storage, handling and the strategy to
426 establish an expiration date should be described. The source of future secondary reference standards
427 or materials should be stated^{4,10}.

428 **4.6. Container Closure System 3.2.S.6**

429 A brief description of the bulk storage container closure system (s), including specifications with
430 suitable identity test (s) and details of materials of construction should be provided. If the bulk storage
431 container closure system is critical for assuring the quality of the active substance, its suitability should
432 be justified with respect to choice of materials, protection from light and/or moisture, compatibility
433 with the active substance including sorption to material and leaching and/ or any safety aspects.
434 Reference to stability data can be additional supportive information to justify suitability of the proposed
435 container closure system. The information should cover the whole packaging including the primary
436 packaging material (e.g.: polyethylene bag) and secondary packaging (e.g. fibre or metal drum).

437 Compliance of the primary packaging with any current applicable regulatory requirements (e.g. food
438 grade materials) should be provided²⁰.

439 **4.7. Stability 3.2.S.7**

440 **4.7.1. Stability Summary and Conclusions 3.2.S.7.1**

441 The types of studies conducted, protocols used, and the results of the studies should be summarized.
442 The summary should include results, for example, from forced degradation studies and stress
443 conditions (light stress, higher temperature, etc.), as well as conclusions with respect to storage
444 conditions and retest date or expiry date as appropriate.

445 For active substances described in an official pharmacopoeial monograph (European

446 Pharmacopoeia or the Pharmacopoeia of a European Union Member State), which covers the
447 degradation products and for which suitable limits have been set, stability studies might not be
448 necessary if it is demonstrated that the substance complies with the monograph (and any additional
449 tests in the specification) immediately before manufacture of each batch of the finished product.
450 ^{2,13,14,17}

451 **4.7.2. Post-approval Stability Protocol and Stability Commitment 3.2.S.7.2**

452 A post-approval stability protocol and stability commitment should be provided if data covering the full
453 proposed re-test period is not available^{2,13,14,17}.

454 **4.7.3. Stability Data 3.2.S.7.3**

455 Detailed results of the stability studies including forced degradation studies and stress conditions
456 should be presented in an appropriate format such as tabular or graphical. Information on the
457 analytical procedures used to generate the data and validation of these procedures should be included.
458 The major degradation pathways of the active substance, the storage conditions and the retest period
459 should be defined^{2,9,13,14,17}.

460 **Definitions**

461 May be added later.

462

463 **References**

- 464 1. ICH guideline Q11 on development and manufacture of drug substances (chemical entities and
465 biotechnological/ biological entities) CHMP/ICH/425213/2011;
- 466 2. Guideline on the Summary of Requirements for the Active substance in the Quality Part of the
467 Dossier, CHMP/QWP/297/97 Rev 1 corr.;
- 468 3. Guideline on Active Substance Master File procedure CHMP/QWP/227/02 Rev 3/ Corr.;
- 469 4. Specifications – Test Procedure and Acceptance Criteria for New Drug Substances and New Drug
470 Products – Chemical Substances CPMP/ICH/367/96;
- 471 5. ICH guideline Q7 on good manufacturing practice for active pharmaceutical ingredients
472 CPMP/ICH/4106/00;
- 473 6. EU GMP Part II: Basic Requirements for Active Substances used as Starting Materials;
- 474 7. Requirements for selection and justification of starting materials for the manufacture of chemical
475 active substances EMA/448443/2014;
- 476 8. Note for guidance on quality of water for pharmaceutical use CPMP/QWP/158/01;
- 477 9. Validation of analytical procedures: text and methodology CPMP/ICH/381/95;
- 478 10. Investigation of Chiral Active Substances 3CC29a;
- 479 11. Impurities testing guideline: impurities in new drug substances CPMP/ICH/2737/99;
- 480 12. Impurities: residual solvents CPMP/ICH/283/95;
- 481 13. Stability Testing of New Drug Substances and Products CPMP/ICH/2736/99;
- 482 14. Stability Testing of Existing Active Ingredients and Related Finished Products CPMP/QWP/122/02;
- 483 15. Guideline on the limits of genotoxic impurities CPMP/SWP/5199/02;
- 484 16. Guideline on the specification limits for residues of metal catalysts or metal reagents
485 CPMP/SWP/QWP/4446/00;
- 486 17. Stability testing: photostability testing of new drug substances and products CPMP/ICH/279/95;
- 487 18. Guideline on control of impurities of pharmacopoeial substances: compliance with the European
488 Pharmacopoeia General Monograph “Substances for pharmaceutical use” and General Chapter “Control
489 of impurities in substances for pharmaceutical use” CPMP/QWP/1529/04;
- 490 19. Guideline on setting specifications for related impurities in antibiotics
491 EMA/CHMP/CVMP/QWP/199250/2009;
- 492 20. Guideline on plastic immediate packaging materials CPMP/QWP/4359/03;
- 493 21. ICH M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to
494 Limit Potential Carcinogenic Risk;
- 495 22. The QP declaration template EMA/334808/2014.

496 **Annex**

497 May be added later.