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# Guideline on the chemistry of active substances

## Draft

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

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# Guideline on the chemistry of active substances

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# Executive summary

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

# 1. Introduction (background)

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

# 2. Scope

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

This guideline is applicable to active substances that have been developed following a "traditional" or an "enhanced" approach or a combination of these. However, when an "enhanced" approach is used or a design space claimed, the information provided in sections 3.2.S.2.2 to 3.2.S.2.6., should be prepared and organised according to ICH Q11[1].

**ASMFs and CEPs:**

As an acceptable alternative to submission of detailed active substance information in the application for marketing authorisation, the Active Substance Master File (ASMF) or the Certification of Suitability to the Monographs of the European Pharmacopoeia (CEP) procedures may be used as described in 'Guideline on the Summary of Requirements for the Active substance in the Quality Part of the Dossier, CHMP/QWP/297/97'[2]. The requirements should be the same regardless of the route of submission of data on the active substance. For procedural aspects and format of the ASMF, please refer to the Guideline on Active Substance Master File procedure CHMP/QWP/227/02[3].

# 3. Legal basis

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

# 4. Body of Data

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

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

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

### 4.1.1. Nomenclature 3.2.S.1.1

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

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

### 4.1.2. Structure 3.2.S.1.2

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

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

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

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

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

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

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

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

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

**Flow diagram of the manufacturing process**

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

**Sequential procedural narrative**

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

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

**Scale of Manufacture, Range, Yield**

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

**Alternative processes**

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

**Reprocessing**

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

**Recovery**

Recovery (e.g. from mother liquors or filtrates) of solvents, reactants, intermediates or the active substance is considered acceptable according to ICH Q7[5] or EU GMP Part II[6], provided that approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use.

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

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

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

**Biologically-sourced materials**

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

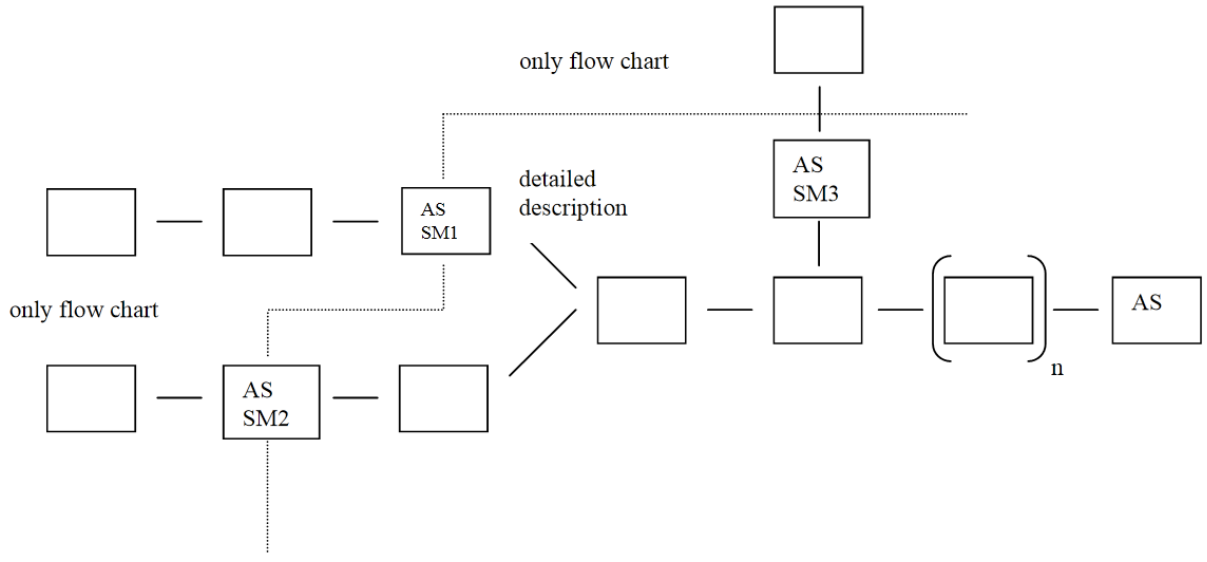
**Active Substance (AS) Starting Material(s)**

The requirements of ICH Q11 in relation to the selection of starting materials are relevant to all active substances, regardless of the type of development approach. Reflection paper[7] should also be consulted.

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

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

Schematic description (illustrative only):




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

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

In both above cases, although defined as starting materials in the dossier, these compounds are actually considered to be synthetic intermediates since their acceptance is contingent on being manufactured under GMP in line with another dossier (CEP, ASMF or standalone dossier). For the purposes of GMP and traceability, the sites of manufacture for these starting materials should be registered as intermediate manufacturing sites in the marketing authorisation application and be the subject of a QP declaration[22].

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

**Materials of plant origin**

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

**Solvents, Reagents and other materials**

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

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

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

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

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

Critical steps could be for instance:

- Mixing of multiple components;
- Phase change and phase separation steps;
- Steps where control of temperature and pH are critical; and
- Steps which introduce an essential molecular structural element or result in a major chemical;

**Transformation:**

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

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

**Intermediates:**

Information on the quality and control of intermediates isolated during the process should be provided. For intermediates which are those which influence final quality of the active substance, the analytical methods used to control them, should be suitably validated if they are non-compendial. Information on the characterisation of these intermediates should be provided[4].

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

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

### 4.2.6. Manufacturing Process Description 3.2.S.2.6

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

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

For existing active substances, all provided data might be obtained on production scale batches manufactured according to the presented manufacturing description. A description of the manufacturing process development is not necessary in these cases but will often add to the understanding of the control strategy[11].

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

### 4.3.1. Elucidation of Structure and other Characterisation 3.2.S.3.1

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

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

**Evidence of chemical structure**

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

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

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

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

The information will normally include such evidence as:

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

The relevance of the eventual or possible isomers regarding biological/pharmacological activity should be discussed[10].

**Physico-chemical Characteristics**

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

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

Polymorphism

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

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

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

The presence of polymorphic forms and solvates and the methods of detection and control should be discussed. Similarly, amorphous forms should be characterised and detection and control methods described[4].

Solubility

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

Physical characteristics

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

pKa and pH values

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

Other characteristics

Information is to be provided concerning the following:

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

### 4.3.2. Impurities 3.2.S.3.2

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

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

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

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

### 4.4.1. Specification 3.2.S.4.1

The active substance specification should be provided.

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

- Description;
- Identification;
- Impurities; and
- Assay and/or potency.

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

## 4.4.2. Analytical Procedures 3.2.S.4.2

Details of the analytical procedures used for testing the active substance should be provided. They should be described in such a way that they can be repeated by an Official Medicines Control Laboratory[9].

**Analytical Development**

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

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

Analytical validation data, including experimental results for the analytical procedures used for the control of the active substance, should be provided. Validation of analytical tests concerning the active substance should be performed according to the requirements of the current Guidelines[9].

## 4.4.4. Batch Analyses 3.2.S.4.4

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

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

The results should include:

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

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

brief explanatory note should be included. Any apparently inconsistent or anomalous results in the batch analyses should be explained[4,11,12,18].

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

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

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

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

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

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

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

Compliance of the primary packaging with any current applicable regulatory requirements (e.g. food grade materials) should be provided[20].

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

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

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

For active substances described in an official pharmacopoeial monograph (European

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

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

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

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

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

## Definitions

May be added later.

# References


1. ICH guideline Q11 on development and manufacture of drug substances (chemical entities and biotechnological/ biological entities) CHMP/ICH/425213/2011;

2. Guideline on the Summary of Requirements for the Active substance in the Quality Part of the Dossier, CHMP/QWP/297/97 Rev 1 corr.;

3. Guideline on Active Substance Master File procedure CHMP/QWP/227/02 Rev 3/ Corr.;

4. Specifications – Test Procedure and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances CPMP/ICH/367/96;

5. ICH guideline Q7 on good manufacturing practice for active pharmaceutical ingredients CPMP/ICH/4106/00;

6. EU GMP Part II: Basic Requirements for Active Substances used as Starting Materials;

7. Requirements for selection and justification of starting materials for the manufacture of chemical active substances EMA/448443/2014;

8. Note for guidance on quality of water for pharmaceutical use CPMP/QWP/158/01;

9. Validation of analytical procedures: text and methodology CPMP/ICH/381/95;

10. Investigation of Chiral Active Substances 3CC29a;

11. Impurities testing guideline: impurities in new drug substances CPMP/ICH/2737/99;

12. Impurities: residual solvents CPMP/ICH/283/95;

13. Stability Testing of New Drug Substances and Products CPMP/ICH/2736/99;

14. Stability Testing of Existing Active Ingredients and Related Finished Products CPMP/QWP/122/02;

15. Guideline on the limits of genotoxic impurities CPMP/SWP/5199/02;

16. Guideline on the specification limits for residues of metal catalysts or metal reagents CPMP/SWP/QWP/4446/00;

17. Stability testing: photostability testing of new drug substances and products CPMP/ICH/279/95;

18. Guideline on control of impurities of pharmacopoeial substances: compliance with the European Pharmacopoeia General Monograph “Substances for pharmaceutical use” and General Chapter “Control of impurities in substances for pharmaceutical use” CPMP/QWP/1529/04;

19. Guideline on setting specifications for related impurities in antibiotics EMA/CHMP/CVMP/QWP/199250/2009;

20. Guideline on plastic immediate packaging materials CPMP/QWP/4359/03;

21. ICH M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk;

22. The QP declaration template EMA/334808/2014.

# Annex

May be added later.