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Guideline on the chemistry of active substances

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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).

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

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Guideline on the chemistry of active substances

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Executive summary

Guideline concerning the application of Directive 2001/83/EC with a view to the granting of a marketing authorisation for a medicinal product. 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 guideline 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. For the purposes of this guideline, an existing active substance is one that has been used in a finished product authorised previously within the European Union. This approach is consistent with the definition of new active substance in the Notice to Applicants, Volume 2A, Chapter 1, Annex I: a chemical (…) substance not previously authorised as a medicinal product in the European Union. This guideline is not applicable to herbal, biological, biotechnological products, radiopharmaceuticals and radiolabelled products. The guideline does not apply to contents of submissions during the clinical research stages of drug development. Nevertheless, the development principles presented in this guideline are important to consider during the investigational stages.

This guideline is applicable to active substances that have been developed following a "traditional" or an "enhanced" approach, as described in ICH Q8-11 (Refs 1-4), 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 (Ref 4).

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 (Ref 5). The requirements are 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 (Ref 6).

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: BAN, DCF, DCIT, JAN, USAN;
- Company or laboratory code;
- Systematic Chemical Name(s) (IUPAC nomenclature);
- Other Names (e.g. proprietary);
- Other non-proprietary name(s);
- 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 (M_r), the structural formula should display the stereochemistry of the active substance (indicated conventionally). If this information is not available a detailed description of the nature of the substance should be given. If appropriate, the M_r of the therapeutically active moiety should also be included.

4.1.3. General Properties 3.2.S.1.3

The appearance of the material should 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, acid dissociation constant (pKa), polymorphism, isomerism, partition coefficient (logP), permeability, hygroscopicity and any other relevant properties. (Ref 7).

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 should be provided for the production steps after introduction of the starting material(s).

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, alternative processes and reprocessing with associated controls that may be completed by the intermediate or active substance manufacturer, 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).

Schematic representation of the manufacturing process

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

Sequential procedural narrative

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

The narrative should describe each step in the manufacturing process, and identify critical steps, critical process parameters, process controls employed, and ranges for process parameters (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.

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

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 by providing sufficient evidence that the final quality of the material (i.e. active substance or isolated intermediate) obtained remains unchanged if the submission of data is *via* a CEP and/or an ASMF.

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

Reprocessing

The cases where routine 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 should be 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 (Ref 8) or EU GMP Part II (Ref 9). It should be clearly indicated within the reaction scheme, process description and/or the block flow diagram, where recovered materials are introduced into the process. The impact of the use of recovered materials should form part of the overall risk assessment, and include, in particular, a discussion regarding impurities (with a focus on potential impurities of concern, e.g. mutagenic impurities). It is recommended that recovered materials are used only in the same process and preferably in the same step, and their use should be avoided in the final manufacturing step (e.g., chemical transformation / precipitation / washing), unless otherwise justified.

Re-working

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

4.2.3. Control of Materials 3.2.S.2.3

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

Active Substance (AS) Starting Material(s)

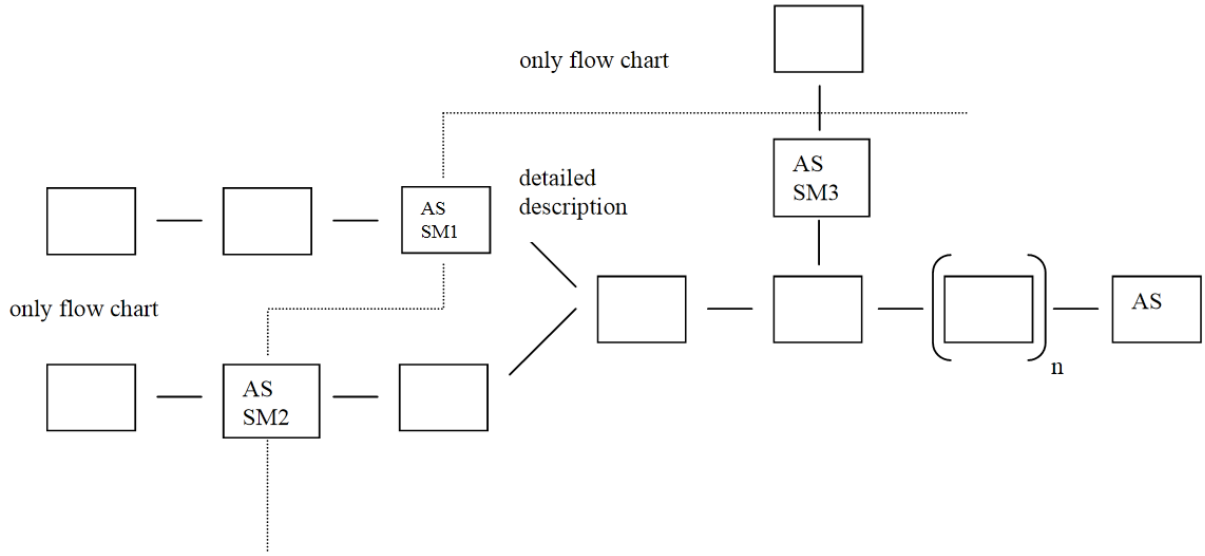
The requirements of ICH Q11 and related Q&A (Ref 4) in relation to the selection of starting materials are relevant to all active substances, regardless of the type of development approach.

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. The 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. The addition of manufacturers for the starting materials needs to be approved by a variation

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

Schematic description (illustrative only):



Starting materials should be substances with defined chemical properties and structures. Structure elucidation of starting materials should be performed using state of the art techniques, except for European pharmacopoeial active substances. Complete specifications should be provided, including limits for impurities. The possibility that any kind of impurity, for example isomeric impurities or mutagenic impurities (including those from the 'cohort of concern', Ref 10), present in a starting material may be carried through the synthetic process unchanged or as derivatives should be discussed. Such impurities should, 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.

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

Starting materials of animal or human origin

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

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

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

Starting materials of herbal origin

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

Information on the scientific name (genus, species, variety and author), chemotype (where applicable) and plant part used should be specified. If the starting material is an extract, the primary extraction solvent and concentration used in the first step of extraction should be specified as well. 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 and adulterants, pesticides, microbiological contamination, heavy metals, mycotoxins (aflatoxins, ochratoxin A, etc.), radioactive contamination, residual solvents, and other relevant impurities/contaminants (e.g. pyrrolizidine alkaloids) should be discussed, taking into account the production of the herbal drug, and the subsequent extraction and purification processes.

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

Semi-synthetic active substances

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

Solvents, Reagents and other materials

Specifications for all materials (solvents, reagents, catalysts, depletion agents, processing aids etc.) used in synthesis should be submitted. Materials used in the final stages of the active substance synthesis may require greater control (i.e. tighter specifications) than those used in earlier stages. Possible contamination of raw materials (e.g., reagents, catalysts and solvents including water / disinfected water, processing aids) with nitrosating agents (e. g. $NaNO_2$) or amines, which may be carried over from steps used to prepare them, should be considered, as the presence of those contaminants could cause nitrosamine formation in the active substance process (Ref 11, 14). Adequate acceptance criteria should be defined and justified.

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

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

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

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

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

Critical Steps: Tests and acceptance criteria performed at critical steps identified in 3.2.S.2.2 of the manufacturing process should be described and justified based on relevant experimental data. 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;
- 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;
- The final purification step.

Steps which have an impact on solid-state properties and homogeneity of the active substance are generally 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. Proper justification should be provided when these properties do not impact performance of the finished product.

Intermediates:

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

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

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

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

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. Process validation data and/or evaluation studies for aseptic processing and sterilisation should be provided (Refs 4, 8, 9).

4.2.6. Manufacturing Process Development 3.2.S.2.6

A description and discussion 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, should be provided.

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 may not be necessary in these cases but will often add to the understanding of the control strategy.

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

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

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

4.3. Characterisation 3.2.S.3

4.3.1. Elucidation of Structure and other Characteristics 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 may 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. Relevant 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 (Ref 21). 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 spectra with interpretation and discussion of results;
- Discussion of the synthetic route as evidence of structure;
- Evidence or structure of key intermediates (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;
- Evidence of the indicated relative molecular mass determined by mass spectrometry or other analytical techniques.

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

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 active substance. Information on the proposed commercial solid state form should be provided in 3.2.S.3.1. This information should be related to the in vivo performance of the finished product in 3.2.P.2.1.

Polymorphism

Polymorphism is the property of a solid state chemical substance to exist in the solid state in different crystalline forms. 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;
- Solid state NMR spectroscopy.

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 if not otherwise justified (Ref 7).

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 (distribution), solvation, melting point, hygroscopicity and 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:

- Partition properties (oil/water partition coefficient, octanol/water partition coefficient, log P, etc.);
- 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, reagents and those derived from reagents. The related substances considered as potential impurities arising from the synthesis and degradation products should be discussed and described briefly including an indication of their origin. As part of the overall discussion on impurities, a specific discussion should be provided with regard to potential mutagenic impurities (Ref 10). If a mutagenic impurity is liable to be present in the substance, then the control strategy should be demonstrated to be in compliance with control options outlined in ICH M7 and the related Q&A, and the risk of presence of compounds of the "cohort of concern" (according to ICH M7) or other potent toxins should also be discussed. Regarding nitrosamine impurities, reference is made to the identified risk factors (Ref 11).

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

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.

To adequately detect and quantify impurities, the applied analytical method should be suitably sensitive. For nitrosamines, the LOQ should be minimum at or sufficiently below the toxicologically required limit, taking into account the purpose of testing (e.g., routine testing, justifying skip testing or omission of specification). See (Ref 11). 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 (Refs 7, 10 and 22-26).

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;
- 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. (Refs 7, 10, 23-26).

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 (Ref 27).

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, (methods using different principles and providing different selectivities), should be developed in cases where a lack in specificity and/or selectivity leads to an inadequate control strategy for the affected impurities. 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 unless methods of the respective drug substance monograph in Ph. Eur. are referred to and the tests of the monograph have been demonstrated suitable to control the substance. Validation of analytical tests concerning the active substance should be performed according to the requirements of the current Guidelines (Ref 27). For nitrosamines, additional requirements are stated in the nitrosamine Q&A (Ref 11).

4.4.4. Batch Analyses 3.2.S.4.4

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

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

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;

- 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. 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 (Refs 7, 22, 23, 25).

4.4.5. Justification of Specification 3.2.S.4.5

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

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 qualification thresholds are subject to further justification, e. g. safety qualification data or reference to published literature data (Refs 7, 10, 22-26).

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

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. Chemical reference substances (Ph. Eur. CRS) are qualified as primary reference standards and do not need to be further qualified, provided they are used for their intended purpose. The criteria for establishing the primary reference substances should be given with full analytical profiles. The procedure for establishing secondary reference standards or materials normally used for routine analysis should be stated (Ref 7).

4.6. Container Closure System 3.2.S.6

A brief description of the storage container closure system(s), including specifications with suitable identity test(s) and details of materials of construction should be provided. If the storage container closure system is critical for assuring the quality of the active substance, its suitability should be justified. Depending on nature of the active substance, aspects that may need justification include choice of the primary packaging 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 (Ref 28).

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 stability-indicating parameters, compliance with the established specification limits should be verified during stability studies and this should include any "cohort of concern" compounds or other highly potent toxins which may potentially form or increase during storage.

For active substances described in an official pharmacopoeial monograph (Ph. Eur. or the Pharmacopoeia of an EU 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. For existing active substances, the Guideline on Stability testing of existing active substances and related finished products should be consulted (Refs 5, 29-31).

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 for production scale batches covering the full proposed re-test period or expiry date is not available (Refs 5, 29-31).

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 tabular or graphical format. 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 should be discussed. The storage conditions and the retest period should be defined (Refs 5, 21, 29-31).

References

1. ICH guideline Q8 (R2) on pharmaceutical development CHMP/ICH/167068/04
2. ICH guideline Q9 on quality risk management INS/GMP/79766/2011
3. ICH guideline Q10 on pharmaceutical quality system INS/GMP/79818/2011
4. ICH guideline Q11 on development and manufacture of drug substances (chemical entities and biotechnological/ biological entities) CHMP/ICH/425213/2011 and related Q&A EMA/CHMP/ICH/809509/2016
5. Guideline on the Summary of Requirements for the Active substance in the Quality Part of the Dossier, CHMP/QWP/297/97 Rev 1 corr
6. Guideline on Active Substance Master File procedure CHMP/QWP/227/02 Rev 4/ Corr.
7. Specifications – Test Procedure and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances CPMP/ICH/367/96
8. ICH guideline Q7 on good manufacturing practice for active pharmaceutical ingredients CPMP/ICH/4106/00
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10. ICH guideline M7 (R2) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk EMA/CHMP/ICH/83812/2013 and the related Q&A EMA/CHMP/ICH/321999/2020
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22. Impurities testing guideline: impurities in new drug substances CPMP/ICH/2737/99

23. Impurities: residual solvents CPMP/ICH/283/95

24. ICH guideline Q3D on elemental impurities CHMP/ICH/353369/2013

25. 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/152904

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

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

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

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

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

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