IPRP
International Pharmaceutical Regulators Programme

GUIDANCE FOR QUALITY ASSESSORS – DRUG SUBSTANCE

IPRP Quality Working Group for Generics (QWGG)

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Foreword

In order to achieve the QWGG's objective to promote collaboration and convergence in the area of generic drug regulation, the QWGG has developed a series of reference documents covering a number of technical and procedural aspects of assessment.

These documents were developed among participating QWGG members and observers as model documents. These QWGG documents have been made available for use by any interested party.

The implementation of these documents by a given QWGG member or observer, either as a whole or in part, is not mandatory. Each QWGG member or observer works within their own specific regulatory setting and some or all aspects of a document may, for a variety of reasons, not be applicable. Equally, a given QWGG member or observer may for practical reasons choose to revise the format or written language of a model document.

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G GENERAL

G.1 Purpose

The purpose of this document is to provide guidance and assistance to new and existing Quality Assessors in the assessment of the technical information contained in Quality Module (Module 3) of Active Substance Master Files (ASMFs)/Drug Master Files (DMFs) and in marketing authorisation applications (MAAs) and to facilitate the preparation of *Quality Assessment Reports (QARs)*.

This *Guidance for Quality Assessors* was initially drafted by the ACSS Consortium - Generic Medicines Working Group which is an international initiative involving the regulatory authorities of Australia, Canada, Singapore and Switzerland to advance collaboration and work sharing initiatives taking place in review and regulation of generic medicines. The Guidance for Assessors has since been developed and finalized as an initiative under the broader IGDRP, now IPRP (which includes the four regulatory authorities of the ACSS Consortium).

G.2 Scope

The guidance document applies to new MAAs as well as ASMFs/DMFs. This guidance document only reflects information on the assessment of chemical entities; it does not include guidance for the assessment of biologicals / biotech products.

G.3 Background Information

This Guidance for Quality Assessors was initially drafted by the ACSS Consortium - Generic Medicines Working Group, which is an international initiative involving the regulatory authorities of Australia, Canada, Singapore and Switzerland to advance collaboration and work sharing initiatives taking place in review and regulation of generic medicines. The Guidance for Assessors has since been developed and finalized as an initiative under the broader IGDRP, now IPRP (which includes the four regulatory authorities of the ACSS Consortium).

This *Guidance for Quality Assessors* follows the format and terminology recommended in ICH's CTD-Q guideline. This guidance is structured to provide recommendations on the preparation of the *Quality Assessment Report (QAR)*, as indicated by "Information to be stated in the QAR", followed by further guidance to assist Quality Assessors in the assessment of the technical information, as indicated by "Points to be considered during assessment".

It should be noted that this document outlines the recommended components of an evaluation of the Quality Module (Module 3) of the ASMF/DMF or application (as applicable). It is acknowledged that there may be additional components to be considered by each regulatory agency during the assessment of the Quality Module beyond this document, depending on each regulatory agencies' legislative/regulatory/policy requirements and review practices.

G.4 Notes on the Preparation of the Quality Assessment Report (QAR)

In general, the following aspects should be considered in conducting the technical assessment of the Quality Module and in the generation of the QAR:

- The QAR should be clear, concise and sufficiently detailed to allow for secondary assessment and finalisation of the recommendations.

- The QAR should include summaries of the critical assessments by the assessor of the data provided in the ASMF/DMF or application (as applicable), scientific discussions reflecting the assessor's views on the information and salient findings. This should include justification for the assessor's recommendations and conclusions (e.g., both positive and negative) and identification of any noted deficiencies in the ASMF/DMF or application that need to be addressed by the ASMF/DMF Holder or applicant. The QAR will document the considerations and findings reached during the assessment to allow for evidence-based decisions on the acceptability of the proposed drug substance and drug product.
- The text in the ASMF/DMF QAR template in blue font is instructional and is intended to be modified or deleted (as appropriate).
- Information generated by the ASMF/DMF Holder or applicant (e.g., copied from the dossier) should be clearly distinguishable from assessor's comments and conclusions.
- The QAR should include discussions on the Quality-related information that needs to be accurately reflected in the product labelling (e.g., Product Monograph, Product Information, Package Insert, container labels).
- Cross-references may be used to clearly indicate the origin of certain information used in the QAR, such as the specific parts of the dossier (e.g., overview, summary, study reports), references to the literature and guidelines or other sources.
- The use of tables is encouraged; examples are given in the QAR template and are to be used as appropriate. Tables copied from the Quality Overall Summary (QOS) as provided by the ASMF/DMF Holder or applicant may be inserted in lieu of that given in the QAR template provided that the inserted table contains the same information recommended in the template.
- Selected information from an ASMF/DMF or application (e.g., diagrams, flowcharts) may be inserted into the QAR provided that the image is clearly legible.
- Prompts within the QAR template may be removed when deemed appropriate by the assessor (e.g., not applicable for the ASMF/DMF or application under review).
- When available, ICH terminology and the terminology in the IPRP QWGG ASMF/DMF Lexicon of Quality Terms should be used.
- Acronyms should be spelled out the first time they are used in the QAR (and in the deficiency comments to the ASMF/DMF Holder or applicant), unless they are well-established industrial terms (e.g., HPLC, IR). The acronym should be then be subsequently used in the QAR.
- If an application refers to an ASMF/DMF for the drug substance information, then the assessment and discussion of the Restricted Part of the ASMF/DMF is to be documented in the *Restricted Part* section of the QAR for the ASMF/DMF.
- If an application does not refer to an ASMF/DMF for drug substance information, assessment and discussion should be documented in the respective CTD sections.
- The deficiencies identified during the assessment of the ASMF/DMF or application (as applicable) should be collated in the section "List of Questions". The deficiency comments should be:
    - Worded in a manner intended to be directed to the ASMF/DMF Holder or applicant (as applicable);
    - Clear, concise and sufficient detail describing the noted deficiency;
    - Risk-based, science-based questions and supported by existing guidelines and regulatory requirements.

ADMINISTRATIVE INFORMATION AND QUALITY ASSESSOR'S INTRODUCTION

Information to be stated on drug substance in the QAR:

- A summary of the Administrative Information should be provided (e.g., information relating to the ASMF/DMF, if applicable). For an ASMF/DMF QAR, details should be described on the characteristics for the drug product application (e.g., maximum daily dose as >2 g/day or <2g/day for the drug product, dosage form, route(s) of administration, target patient population(s), and if the API is manufactured as sterile or non-sterile).

- Tabulate the available literature references (e.g., pharmacopoeia) on the drug substance.
- Other noteworthy information (e.g., salient points of the MAA, other MAs for similar products, filing & marketing status in other markets, patent status), reference product, cytotoxic drug and other relevant information that affects quality, safety and efficacy of the drug.
- State the approach used by the applicant for providing information on the drug substance, i.e.,
    - Full details in the dossier,
    - Reference to an ASMF/DMF or
    - Reference to a Certificate of Suitability to the Monograph of the European Pharmacopoeia (CEP) issued by EDQM.
- If multiple drug substance manufacturers are proposed, provide a summary of the manufacturers and which approach is used for each (i.e., full dossier, ASMF/DMF or CEP).

Points to be considered during assessment on drug substance:

- Summary of available literature references on the drug substance (e.g., if present in pharmacopeia).

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Information to be stated in the QAR:

- In case of a reference to an ASMF/DMF, state its reference number, the ASMF/DMF version for both the Applicant's and Restricted Parts and state if the ASMF/DMF assessment is provided in a separate QAR for the ASMF/DMF.
- In case of a reference to an CEP, state the CEP number, validity date and any/all pertinent information stated in the CEP including, but not limited to, testing of additional impurity(ies)/residual solvent(s) and the acceptance limit, particle size limits, container closure system, re-test period and the submission of any annexes.

Points to be considered during assessment:

- In case of reference to an ASMF/DMF, check if the same version of the Applicant's Part (AP) of the ASMF/DMF, which was submitted by the ASMF/DMF holder, has been provided by the applicant.
- In case of reference to a CEP, ensure that the current version of the CEP is provided and that the Declaration of Access box is duly signed, grants proper authorisation for its use and the appropriate product name and all annexes have been provided (if applicable). The current version of the CEP can be verified by checking against the version listed on EDQM's website. If the version of the submitted CEP has been superseded, then the latest version as listed in EDQM's website should be requested.
    - Assess any points not covered by the CEP, such as particle size, polymorphic form or re-test period of the drug substance.
    - Assessment of section S.4 Specification of the Quality Module should ensure that any additional appropriate tests and acceptance criteria are included in the specifications of the facility responsible for releasing the drug substance (e.g., the drug product manufacturer).
    - Assessment of section S.7 Stability may be required if a re-test period is not stated on the CEP or if the applicant is proposing a longer re-test period than that listed on the CEP.

S.1 General Information

S.1.1 Nomenclature

Information to be stated in the QAR:

- International Non-proprietary Name (INN)

- Compendial name and other relevant names or codes (e.g., company code)
- Chemical Abstracts Service (CAS) number

Points to be considered during assessment:

- The chemical names listed in the dossier should be consistent with those appearing in scientific literature (e.g., pharmacopoeia) and those appearing on the product labelling (e.g., Product Monograph, Product Information, Package Insert, container labels).
- Where several names exist, the preferred name should be indicated in the dossier.

S.1.2 Structure

Information to be stated in the QAR:

- Structural formula (including relative and absolute stereochemistry, salt form and solvate moieties)
- Molecular formula
- Molecular mass

Points to be considered during assessment:

- The structural formula should be a diagram that shows the stereochemistry of the drug substance.
- This information should be consistent with that provided in section S.1.1 and in the product labelling.
- For drug substances existing as salts and/or hydrates/solvates, the molecular formula and molecular mass of the free base or free acid or unsolvated moiety should also be provided in the dossier.

S.1.3 General Properties

Information to be stated in the QAR:

- Physical characteristics (appearance, colour, physical state)
- Solubility over the physiological pH range (pH 1.2 to 6.8) in mg/ml
- Solubilities in relevant solvents (e.g., including those used in the manufacturing process, analytical methods or for cleaning)
- Hygroscopicity
- Polymorphism
- Other properties as appropriate, e.g., stereochemistry, pKa, pH, partition coefficient, melting point, particle size distribution (PSD)

Points to be considered during assessment:

- Aqueous solubility over the physiological pH range should be provided in the dossier as in mg/ml either from literature data or experimental data. If general terms are used and reference is made to a pharmacopeia, the specific pharmacopeia should be identified (e.g., “sparingly soluble” as per USP).

S.2 Manufacture

S.2.1 Manufacturer(s)

Information to be stated in the QAR:

- Name, address (including unit/plot/block), and responsibility of each manufacturing facility(ies) (including manufacturer(s) of the intermediates, if sourced from a third party)

Points to be considered during assessment:

- Manufacturing, milling, micronisation, sterilisation, packaging, labelling, testing and storage facilities of the drug substance or key intermediates should be included in the dossier.
- The actual address, including the unit, plot or block (if any), where the relevant operation(s) is (are) performed should be stated in the dossier, rather than the administrative office address(es).

S.2.2 Description of Manufacturing Process and Process Controls

Information to be stated in the QAR:

- Flow diagram of the synthetic process(es).
- A short summary of the sequential procedural narrative of the manufacturing process and process controls, including the raw material, starting material, reagents, solvents and catalysts used. The narrative summary should not repeat information that is already reflected in the flow diagram. The narrative should also include additional processing steps after the final drug substance has been produced, e.g., milling, micronisation. A comment should be made in the QAR as to whether the description of the process is sufficiently detailed or not.
- The batch size(s) or range of typical commercial production batches.
- Describe alternative processes (if any) and state if they are described with the same level of details than the main process. Comment if the same impurity profile is obtained.
- Briefly describe reprocessing steps (if any) and note if they are justified.
- Briefly describe the recovery of materials or solvents (if any), including how the materials or solvents are recovered.
- Blending of production batches of the final drug substance to obtain a larger batch size, if applicable. It should be stated whether the batches are tested prior to blending according to the final specifications.

Points to be considered during assessment:

- The flow diagram of the synthetic process should include the chemical structures of starting materials, intermediates, reagents and the drug substance reflecting stereochemistry. The flow diagram should identify reagents, catalysts and solvents used in each step.
- In order to conclude that sufficient detail of the manufacturing process has been provided, the narrative of the synthetic process provided in the dossier should include, for example, quantities (mass or molar equivalents) of starting materials, raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, process controls, equipment and operating conditions (e.g., temperature, pressure, pH, time).
- Catalysts and solvents used should be disclosed in the Applicant's Part of the ASMF/DMF.
- The proposed batch size should be supported by batch data filed in section S.4.4.
- Alternative processes should be explained and described with the same level of detail as the primary process. It should be demonstrated that batches obtained by the alternate process(es) have the same impurity profile as the primary process.
- Reprocessing steps (i.e., re-application of previously-described processing steps) should be identified and justified. Any data to support this justification should be either referenced or filed in S.2.5.
- Although reworking (i.e., application of steps different from those of the described process) is generally not acceptable, each regulatory agency may assess the proposal for reworking procedure and conclude on the acceptability (e.g., in accordance with recommendation by ICH Q7).
- Blending of batches of the final drug substance to obtain a larger size is acceptable provided each batch incorporated into the blend is individually tested and found to meet specifications set for the final drug substance prior to blending.

- Information on the route of synthesis and purification of the drug substance should be provided (e.g., in S.2.6) in a manner that allows the assessment of the fate and purging of all potential impurities, including regioisomeric and stereoisomeric impurities, toxic (including mutagenic) impurities, residual solvents and residues of catalysts in the starting material, intermediate and the drug substance.
- Where particle size is considered a critical attribute of the drug substance, the milling/micronisation equipment, process parameters and procedures should be described.
- If more than one manufacturing site is responsible for the last few stages of production, purification and/or micronisation (if applicable) of the drug substance, alternative processes undertaken at the different site(s) should be described and any significant differences should be assessed.
- If the drug substance is prepared as sterile, a complete description should be provided for the method used in the sterilisation. The controls used to maintain the sterility of the drug substance during storage and transportation should be provided. Results of process validation studies of the sterilisation process should be included in S.2.5.
- For a drug substance of plant (botanical) origin, a description of the botanical species and the part of plant used, the geographical origin, potential source of contamination and the time of year harvested (if relevant) should be part of the dossier. All processing steps after harvesting should be documented (e.g., drying equipment and time, treatment of plant material (e.g., solvent extraction, pesticides)). It may be necessary to include limits for residues resulting from such treatment in the drug substance specification. Discussion, which may include supporting data, should be provided to demonstrate absence of toxic metals and radioactivity.
- For a drug substance manufactured by fermentation process, the source and type of micro-organism used, procedures and controls for preparation of master and working cell banks, composition of media, control of microbial bioburden in the fermentation process, precursors or metabolic substrates if applicable, additional details on how the reaction conditions are controlled (e.g., times, temperatures, rates of aeration), name and composition of preservatives, potential for the presence of adventitious agents based on the type of micro-organism used (e.g., mycotoxins, enzymes) should be provided in dossier.
- The manufacturing process for the batch(es) used in the clinical and/or comparative bioavailability studies should be representative of the process for commercial purposes (i.e., laboratory scale batches are not considered acceptable).

References:

- ICH Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)

S.2.3 Control of Materials

Information to be stated in the QAR:

- State the following for the proposed API starting material(s): name, chemical structure, name and address of manufacturer(s), flow diagram of the syntheticic route of the API starting material (including reagents, solvents and catalysts (if applicable)), and specification.
- State if a justification of the proposed starting material(s) according to ICH Q11 has been provided and if the proposed API starting material(s) is/are acceptable or not. State if details of the analytical methods for the starting material specifications have been provided. The specification for the API starting material should be justified (e.g. based on the general principles described in ICH Q11).
- State if specifications have been provided for all other materials used in the preparation of the drug substance (i.e., raw materials, solvents, reagents, catalysts, recovered materials, seed crystals) and comment on their acceptability.
- State if potential contaminating ICH Class 1 solvents are controlled in any solvent where this is known to be possible (e.g., contaminating benzene in toluene, acetone).

- State the presence of adventitious agents, including viral/bacterial agents, residual proteins and TSE agents, if applicable. Otherwise, state if a letter of attestation which confirms that the drug substance and all materials used to manufacture the drug substance is without risk of transmitting agents of animal spongiform encephalopathies.

Points to be considered during assessment:

- Definition of the starting material should be assessed in line with the general principles outlined in ICH Q11 (i.e., a significant structural fragment, defined chemical properties and structure, an isolated substance, typically multiple chemical transformation steps separate the starting material from the drug substance, manufacturing steps that impact the impurity profile of the drug substance should normally be included in the manufacturing process described in section S.2.2, satisfactory studies on fate and purge of starting material impurities and their derivatives in subsequent processing steps, a commercially available chemical). If the proposed starting material(s) is/are unacceptable, then a re-definition should be requested.
- The specification of a starting material should include tests for identity and purity (e.g., controls on impurities) and, where applicable, could include acceptance criteria for assay, specified, unspecified and total impurities, residual solvents, reagents, elemental impurities and mutagenic impurities. Special consideration should be given to potential isomeric impurities and mutagenic impurities, particularly those that could be carried through the synthesis to the drug substance.
- Where there is more than one starting material manufacturer/supplier declared in the dossier, batch analysis results of the final drug substance obtained from all declared suppliers should be provided to confirm that the impurity profiles are similar.
- Specifications for all materials used in the preparation of the drug substance should be provided.
- Specifications should be checked for an appropriate assay/purity test relevant for the type of starting material. Solvents which may be contaminated with benzene (e.g., acetone, toluene) should be checked for a test for benzene or for a justification for the absence of the testing for benzene.
- The quality of the water should be in line with any applicable guidance and/or pharmacopoeia.
- If recovered materials (e.g., solvents, intermediates) are used, the details of purification and the specifications (including justification of the suitability of these specifications) for the recovered materials should be provided or confirmation that the specifications are identical to those used for the fresh material should be provided. Batch analysis data of batches manufactured with recovered materials should be provided to demonstrate that the impurity profile is comparable quality to that of the API manufactured with un-recovered materials
- The potential for the presence of adventitious agents, including viral and bacterial agents, residual proteins and TSE/BSE agents should be discussed, if applicable. Otherwise, a letter of attestation should be provided confirming that the drug substance and all materials used to manufacture the drug substance are without risk of transmitting agents of animal spongiform encephalopathies.
- Semi-synthetic drug substance: Semi-synthetic products are obtained from a plant extract or from a fermented starting material by a process involving at least cleavage and formation of covalent bonds followed by extraction/purification steps. For semi-synthetic products derived from a fermented starting material, compliance with the Ph. Eur. General Monograph *Products of Fermentation* is not applicable, though the fermented starting material should be characterised (specifying the purity, the impurity profile and discussing the possibility of carrying impurities from the fermentation process to the drug substance).
- The quality of the starting material of herbal origin should follow the principles set out in the pharmacopoeiap monographs on herbal drugs, herbal drug preparations, extracts and essential oils, as applicable: the potential presence of foreign matter, pesticides, microbiological contamination, total ash, heavy metals, aflatoxins, ochratoxin A, radioactive contamination, residual solvents, and other relevant impurities should be discussed as far as relevant for the material. A risk assessment about contaminants however can be considered and justified in the QAR (see EMA Q&A on starting materials of herbal origin).
- The specification for the starting material of herbal origin should be fully justified by the ASMF/DMF Holder or applicant and should include suitable tests for identity, assay, impurities

and potential contaminants when applicable. The starting material should be characterised and the impurity profile, together with the extraction solvents, should be discussed in the dossier. Assessment should take into consideration the number of chemical steps between the starting material and the drug substance.

References:

- ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
- ICH Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)
- ICH Q11 Question & Answers: Selection and Justification of Starting Materials for the Manufacture of Drug Substances

S.2.4 Controls of Critical Steps and Intermediates

Information to be stated in the QAR:

- List critical process steps and critical process parameters, isolated intermediate specifications, and in-process control acceptance criteria
- For the isolated intermediates and in process controls, state whether analytical methods have been provided.
- Comment on the adequacy of the controls of the critical steps and isolated intermediates, including the reaction conditions, completion of individual reaction steps and the identity and purity of the isolated intermediates.
- State the information of the supplier for the intermediate. For multiple suppliers of intermediate, comment on the acceptability of different specifications.

Points to be considered during assessment:

- Critical process parameters (e.g., temperature, equipment controls during micronisation) should be listed in the dossier and scientifically justified.
- Specifications of isolated intermediates should include tests and acceptance criteria at minimum for identity, assay and related substances. Purity profile instead of assay can be accepted if appropriate. Special consideration should be given to potential isomeric impurities and mutagenic impurities, particularly those that could be carried through the synthesis to the drug substance.
- Analytical methods should be described in the dossier.
- If an intermediate is not isolated, an in-process control to test for completeness of reaction should be included before advancing to the next step, unless otherwise justified (e.g., in a case when a reaction resulting in a non-isolated intermediate is consistently rapid and complete).

S.2.5 Process Validation and/or Evaluation

Information to be stated in the QAR:

- Summary of process validation and/or evaluation studies in case of aseptic processing and sterilisation.
- State the justification for the choice of sterilisation method and comment on its acceptability.
- The following should be stated for sterile filtration: type of filter and its pore size (≤0.22micron), pre-filtration bioburden (NMT 10 CFU/100 ml), integrity test of the filter before and after use, validation of the sterile filter (physical and chemical compatibility, adsorption, extractables, viability and bacterial challenge test), validation of the process by media fills.

Points to be considered during assessment:

- For non-sterile drug substances, evaluation of process validation studies is not normally required.

S.2.6 Manufacturing Process Development

Information to be stated in the QAR:

- Comment on any significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in bioavailability or biowaiver, clinical, scale up and production batches.
- State the fate and purging of all potential impurities including regioisomeric and stereoisomeric impurities, toxic (including mutagenic) impurities, residual solvents and residues of catalysts in the starting material, key intermediate and drug substance.
- Discussion of manufacturing process development to support a design space and/or real time release (if proposed).

Points to be considered during assessment:

- Where a Quality by Design (QbD) approach has been used for development of the drug substance synthesis and a design space is being proposed,
    - Summarize the process development studies that provide the basis for the design space(s) which are used to justify specifications, manufacturing parameters, etc.
    - Use terminology in a manner that is consistent with ICH definitions (e.g., PARs vs. design space).
    - Be clear about claims and proposed flexibility supported by enhanced development (e.g., design space(s), PARs, Real Time Release Testing, omission of drug substance specification test for impurity(ies)).
    - Discuss the role of QbD in the overall control strategy (e.g., describe purging studies to demonstrate removal of impurities from synthetic process).
    - Where PARs or a design space have been claimed in S.2.2, studies which support the proposed ranges should be described in S.2.6. Studies conducted to assess criticality of process parameters or material attributes identified in S.2.3 and/or S.2.4 should also be described in S.2.6.

S.3 Characterisation

S.3.1 Elucidation of Structure and other Characteristics

Information to be stated in the QAR:

- Studies performed to elucidate the structure (e.g., IR, UV, NMR, MS, elemental analysis), including a brief summary of results and a conclusion (e.g., if the results support the proposed structure).
- The potential for isomerism, identification of stereochemistry, polymorphism and/or particle size distribution (PSD).

Points to be considered during assessment:

- The studies carried out to elucidate and/or confirm the chemical structure of non-compendial drug substances normally include elemental analysis, Infrared (IR), Ultraviolet (UV), Nuclear Magnetic Resonance (NMR), and Mass Spectra (MS) studies. Other tests could include X-ray diffraction (XRD), solid state studies or Molecular weight distribution where relevant.
- For drug substances with a compendial reference standard, it is sufficient to ensure that IR and UV spectra of the drug substance from the proposed manufacturers match the spectra of the compendial reference standard.
- Isomerism & stereochemistry: When a drug substance contains one or more asymmetric centres, structural elucidation studies should confirm whether the drug substance is a specific stereoisomer, a mixture of stereoisomers, a mesoisomer or a racemate. The potential for

interconversion of the isomers or enantiomers should be discussed.

- Polymorphism: If applicable, results from an investigation of several drug substance batches should be provided to determine if the drug substance exists in more than one crystalline form (e.g., X-ray Diffraction (XRD), Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR)). The absence of the potential for polymorphism can further be confirmed by providing the results of a literature search. For NCE a scientifically sound polymorph screening is expected. If controls for polymorphism are critical, then data should be provided to confirm the consistency of manufacture and the stability of the polymorph on several batches. Polymorphism can also include solvation or hydration products (also known as pseudopolymorphs), which should be appropriately characterised using solid state studies.
- Particle size distribution (PSD): If controls for PSD are critical (e.g., part of the drug substance specifications), then results from several batches of the drug substance should be provided and the acceptance criteria should be justified (e.g., particle size limits for d10, d50 and d90). Information on PSD may also be found in section S.1.3, S.4.1 or S.4.5.
- During the assessment of the application, the discussion on the control of polymorph and PSD should take into consideration the results of the batches used in the clinical and/or comparative bioavailability studies (e.g., as further discussed in P.2).

References:

- ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

S.3.2 Impurities

Information to be stated in the QAR:

- Actual and potential drug-related impurities (e.g., starting materials, by-products, intermediates, chiral impurities and degradation products), e.g. descriptor, origin and chemical structure of each impurity.
    - State the maximum observed levels (actual numerical results) from batch analysis (S.4.4) and stability (S.7.3) batches and, if applicable, the limit of quantitation (LOQ) (S.4.2, S.4.3) and proposed limits (S.4.1, S.4.5).
    - If an impurity matches an identified impurity in a pharmacopoeial monograph, then it should be clearly stated (e.g., “Ph.Eur. Impurity A”).
- Process-related impurities (e.g., residual solvents, reagents, elemental impurities).
    - Residual solvents: all solvent(s) used, their classification as per ICH Q3C, the synthetic step(s) in which they are used, the observed levels from batch analysis data and, if applicable, the LOQ and proposed limits should be stated.
    - Elemental Impurities (e.g., metal catalysts, reagents): the metal(s) used, their classification as per ICH Q3D and the synthetic step(s) in which they are used, the observed levels from batch analysis data and, if applicable, the LOQ and proposed limits should be stated.
- Discussion of the potential mutagenic impurities and if they are suitably controlled/qualified as per ICH M7.

Points to be considered during assessment:

- The possible carryover of impurities that may arise during synthesis and of impurities from the preparation of the starting material(s) and intermediates to the final drug substance should be discussed.
- The origin of potential and actual impurities comprises starting material impurities, starting materials, synthetic by-product, intermediates, degradation product, isomer, metabolite, etc.
- If a drug substance pharmacopoeial monograph exists: The discussion of a pharmacopoeial drug substance should not be limited to the impurities specified in the monograph, i.e., all potential organic impurities should be discussed.
- If there are identified impurities specified in the pharmacopoeial monograph (e.g., as in the Ph.

Eur. transparency section) that are not monitored by the proposed in-house method, justification should be provided for their exclusion (e.g., the impurities are not formed by the synthetic route) or it should be demonstrated that the in-house method is capable of controlling theses impurities as unspecified impurities.

- Potential mutagenic impurities: identified impurities should be examined to ensure that no structural alerts are present in the structure. If a structural alert is identified, then the impurity should be investigated and controlled in accordance with ICH M7.

References:

- ICH Q3A(R2) Impurities in New Drug Substances
- ICH Q3C(R5) Impurities: Guideline for Residual Solvents
- ICH Q3D Guideline for Elemental Impurities
- ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
- ICH M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk
- USP General Chapters (General Notice 5.60.10)
- Ph. Eur. General Monographs Substances for Pharmaceutical Use (2034)

S.4 Control of the Drug Substance

S.4.1 Specification

Information to be stated in the QAR:

- Summary of the proposed specification (including test parameters, analytical procedures and acceptance criteria)
- State the standard claimed by the ASMF/DMF Holder or applicant (e.g., Ph. Eur./BP/USP/In-house).
- Specification reference number and/or version.
- Indicate if there is reduced testing proposed for certain parameters.
- Include a discussion on the acceptability of the proposed specification and claimed standard.

Points to be considered during assessment:

- If a drug substance monograph exists: specifications must comply, if required by national law.
- If no monograph exists: drug substance may be controlled by a related monograph (i.e., related salt / hydrate) or appropriate in-house specifications.
- For sterile drug substances, additional controls such as sterility and bacterial endotoxin are required.

Note: Drug substance specification controlled by the drug product manufacturer should be captured in the QAR and it should be clearly separated from the specification controlled by the drug substance manufacturer.

References:

- ICH Q3A(R2) Impurities in New Drug Substances
- ICH Q3C(R5) Impurities: Guideline for Residual Solvents
- ICH Q3D Impurities: Guideline for Elemental Impurities
- ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
- ICH M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to

Limit Potential Carcinogenic Risk
- Ph. Eur. Chapter 5.10 Control of Impurities in Substances for Pharmaceutical Use
- EMA Q&A part 1, June 2012: Impurities - Harmonisation of policies on setting specifications for potentially mutagenic impurities, heavy-metal-catalyst residues and class-1 solvent residues
- CPMP/QWP/450/03-Rev 1: Annexes to CPMP/ICH/283/95 Impurities: Guideline for Residual Solvents
- Ph. Eur. General Monographs Substances for Pharmaceutical Use (2034)

S.4.2 Analytical Procedures

Information to be stated in the QAR:
- State if the analytical procedures used are those specified in the monograph or in-house.
- Short description of all in-house analytical procedures, which may include analytical conditions, system suitability, relative response factors, method of quantification (external standard, normalisation).

Points to be considered during assessment:
- A clear description of all analytical procedures used must be in the dossier.
- System suitability tests (SSTs) are an integral part of chromatographic analytical procedures. System suitability tests should follow ICH Q2 and pharmacopoeial requirements, as appropriate.

References:
- ICH Q2(R1) Validation of Analytical Procedures: Text and Methodology

S.4.3 Validation of Analytical Procedures

Information to be stated in the QAR:
- State if the validation is in accordance with ICH or not, and mention any deviation.
- State if the purity methods are stability indicating and a brief description of the evidence that was provided to support the claim (e.g., peak purity of active, observance of mass balance).
- The summary table (validation parameters, method type) listed in the QAR template or a brief description of the data presented (no values typically except for limit of detection and/or limit of quantification) should be included.

Points to be considered during assessment:
- Full validation of in-house methods in line with ICH Q2(R1), the purity method should be stability indicating. Typical chromatograms should be included in the dossier.
- If an in-house method is used instead of the pharmacopoeial method: cross-validation data should demonstrate equivalence of the methods. This could be accomplished by performing replicate analyses of two samples by both methods and providing comparative results from the study. Alternate approaches to demonstrating equivalency of analytical procedures may be considered acceptable, if scientifically justified.
- If the target impurity limit validated is not the proposed specification limit then ensure that validation parameters, e.g. range, recovery either cover that limit or are sufficient close to the limit to be acceptable.
- If the pharmacopoeial method is unsuitable to control additional in-house impurities, the in-house method needs to be validated.
- If the pharmacopoeial method is suitable to control additional in-house impurities, then the method needs to be validated for the additional in-house impurities.

References:
- ICH Q2(R1) Validation of Analytical Procedures: Text and Methodology

S.4.4 Batch Analyses

Information to be stated in the QAR:

- Briefly describe the data: batch numbers, batch size, manufacturing site, manufacturing date, use of batch.
- Indicate typical results (e.g., impurities, assay).
- Do the analysis results of all batches comply with the proposed specifications and demonstrate the consistent quality of the material? Do they indicate that the process is under control?
- The discussion of the results should focus on observations noted for the various tests, rather than reporting as "All tests meet specifications". This should include ranges of analytical results and any trends that were observed. A discussion and justification should be provided for any incomplete analyses (e.g., batches not tested according to the proposed specification).

Points to be considered during assessment:

- Batches used in nonclinical, clinical, comparative bioavailability, comparative in vitro, and stability studies should be provided, If the scale of the batch is less than $1/10^{th}$ commercial scale, a justification of why the smaller scale is representative should be provided
- Batch analyses data on several batches should be included.
- Numeric values for the data where possible ('complies' should be avoided).
- Where there is more than one starting material manufacturer/supplier declared in the dossier, batch analysis results of the final drug substance obtained from all declared suppliers should be provided to confirm that the impurity profiles are similar.

References:

- ICH Q3A(R2) Impurities in New Drug Substances
- ICH Q3C(R5) Impurities: Guideline for Residual Solvents
- ICH Q3D Impurities: Guideline for Elemental Impurities
- ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

S.4.5 Justification of Specification

Information to be stated in the QAR:

- State if the drug substance specifications are in line with requirements of the pharmacopoeia and ICH guidelines.
- Drug substances without monograph: brief summary of the data and assessment of the proposed specification limits may be necessary.

Points to be considered during assessment:

- In line with batch and stability data, monograph and guideline requirements.
- Maximum daily dose of the drug substance (route of administration: e.g., inhalation, oral).
- Justification of omitted tests. Examples suitable justification for omitted test could include demonstration of suitable fate and purge controls for drug-related and process-related impurities.
- The control of impurities should be scientifically justified (e.g., for not controlling certain impurities and for the proposed acceptance criteria for those impurities that are to be controlled). Toxicological studies or other scientifically acceptable justification such as confirmation of a metabolite should be provided if limit for an impurity or degradation product exceeds the applicable ICH Q3A/B(R2) qualification thresholds.
- General limits in a compendial monograph for unspecified impurities that exceed the applicable ICH Identification Threshold are not considered acceptable (e.g., a general compendial limit of NMT 0.2% for unspecified impurities would not be considered acceptable when the applicable

ICH Identification Threshold is NMT 0.10%). Furthermore, a general limit for unspecified impurities would not be considered acceptable as qualification for a new identified impurity if it exceeds the applicable ICH Qualification Threshold.

- Qualification of impurities: the qualification of an identified impurity can be based on toxicological data or actual test results of impurities/degradation products determined in one or more batches of appropriately stored sample of the Reference Product (e.g., the innovator product), if justified by the manufacturer. A limit equivalent to the level found in the Reference Product would be considered supportive provided there are no other reasons that would indicate otherwise (e.g., no mutagenic structural alerts).
- The acceptance criteria are also set taking into consideration the actual levels of impurities found in several batches of the drug substance from each manufacturer, including the levels found in the batches used for the nonclinical, clinical, and bioequivalence studies.
- Specifications should cover all of the relevant quality parameters such as identity, organoleptic, physical, chemical and stereochemical properties, impurities, assay and microbiological quality. Organoleptic properties may include appearance, colour and clarity of solution. Physical properties may include crystalline/polymorphic form, PSD, specific optical rotation, solubility, melting point, molecular weight (ICH Q6A).
- When there is no qualified limit (e.g., for water content), the specification limits should take into consideration batch analyses results and stability data and the precision of the analytical method used.
- Assay limits of 98.0-102.0% for specific (e.g., HPLC) methods and 98.5-101.5% for non-specific (e.g., titration) methods are normally acceptable with little justification. Wider limits need to be justified.
- Related substances should be in line with ICH Q3A(R2) for specified and unspecified impurities (identification / qualification thresholds, maximum daily dose), ICH Q6A Decision Tree #1 (Establishing acceptance criterion for a specified impurity in a new drug substance).
- Residual solvents should be in line with ICH Q3C(R5), EMA guideline Annex I: Specifications for Class 1 and Class 2 Residual Solvents in Active Substances (CPMP/QWP/450/03-Rev 1) (2013) and USP <467> Residual solvents.
- Potentially mutagenic impurities, Class 1 metals and Class 1 solvents should be in line ICH Q3D and M7.
- Particle Size Distribution (PSD): limits should be based on ICH Q6A Decision Tree #3 (Setting acceptance criteria for drug substance PSD), if drug product performance is affected.
- Polymorphism: limits should be based on ICH Q6A Decision Tree #4 (Investigating the need to set acceptance criteria for polymorphism in drug substances).
- Chiral drug substance: limits should be based on ICH Q6A Decision Tree #5 (Establishing identity, assay and enantiomeric impurity procedures for chiral new drug substances).
- Microbiology: limits should be based on ICH Q6A Decision Tree #6 (Microbiological quality attributes of drug substance),Ph. Eur. 5.1.4. Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use and USP <61> Microbial examination of non-sterile products
- Any proposal for periodic test schedules or alternate testing frequencies should be fully justified and based on sufficient supporting data, scientific rationale and a suitable risk assessment.

References:

- ICH Q3A(R2) Impurities in New Drug Substances
- ICH Q3C(R5) Impurities: Guideline for Residual Solvents
- ICH Q3D Impurities: Guideline for Elemental Impurities
- ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
- ICH M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk
- Ph. Eur. General Monographs Substances for Pharmaceutical Use (2034)
- USP <467> Residual solvents

- USP <61> Microbial examination of non-sterile products

S.5 Reference Standards or Materials

Information to be stated in the QAR:

- Description and source of reference standards or reference materials for drug substance and impurity(ies).
- State the primary reference standard used: a compendial reference standard or an in-house reference standard and batch number.
- If a primary in-house reference standard is used, state if it is fully characterised (e.g., IR, UV, NMR, MS). State if a certificate of analysis has been submitted with purity assigned based on mass balance or a determination of absolute purity.
- State if a secondary reference standard (e.g., working standard) is standardised against the compendial reference standard or primary reference standard.

Points to be considered during assessment:

- The source(s) of the reference standards or materials (e.g., in-house, Ph. Eur., USP) used in the testing of the drug substance (e.g., for the identification, purity, potency tests). If a Ph. Eur. reference standard is used for quantitative analysis, the reference standard should be for content (not for identity only).
- Primary standard (preparation, characterisation (e.g., IR, UV, NMR, MS), determination of purity), batch number. Ph. Eur. or USP primary reference standards do not need further structural elucidation.
- Secondary standard (identification, assigned purity), batch number.
- Impurity standard (characterisation, purity), if applicable.

References:

- Ph. Eur. Chapter 5.12. Reference Standards

S.6 Container Closure System

Information to be stated in the QAR:

- State the container closure system (CCS) used for storage of the drug substance and the identity of the material used for each component.
- State if the specifications for the CCS are sufficient and include an appropriate identification test for the primary packaging in contact with the drug substance.
- For liquid drug substances: depending on the CCS material used, state results of compatibility studies, e.g., extractable and/or leachable studies.
- Compliance with appropriate guidelines should be stated.

Points to be considered during assessment:

- Is the choice of the CCS justified, bearing in mind the physical/chemical properties of the drug substance?
- Does it provide adequate protection from microbial contamination, if this is considered to be necessary?
- When applicable (e.g., liquids), suitability of the primary packaging material for its intended purpose should be demonstrated by the ASMF/DMF Holder or applicant or the supplier of the material (migration studies).
- Compliance with appropriate guidelines, e.g., food contact EC/10/2011, Ph. Eur. Chapter 3, USP.

References:

- USP General Chapters (e.g. USP <661> Containers Plastics)

- Ph. Eur. General Chapters (e.g. Chapter 3 Materials for the Production of Containers)
- Commission regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food (EC/10/2011) CPMP/QWP/4359/03, Appendix I: Guideline on plastic immediate packaging materials.
- EMA Q&A part 2 on packaging, January 2009: acceptable quality standards for plastic materials to be used for containers for solid oral dosage forms and solid drug substances.

S.7 Stability

S.7.1 Stability Summary and Conclusions

Information to be stated in the QAR:

- Summarise the studies undertaken to support the proposed re-test period/shelf-life. Information to state include: batch numbers and size, manufacturing site, manufacturing date, container closure system(s), storage conditions (long-term, intermediate (if applicable), accelerated) and completed testing intervals.
- Summarise the conditions and results of stress testing studies of the drug substance.
- State the proposed re-test period/shelf-life and storage condition and comment whether or not they are justified.

Points to be considered during assessment:

- Data on three pilot scale batches (at least 10% of commercial scale) or two pilot scale batches and one small scale batch should be submitted. The batches should be manufactured by the same synthetic route as, and using a method of manufacture and procedure that simulates the final process to be used for, production batches.
- Stability results should be provided at the time of filing. Extrapolation of re-test period should be based on ICH Q1E.
- If the route of manufacture or process conditions are different, then results of long term and accelerated (or intermediate, as appropriate) testing on the drug substance should be provided at the time of filing.
- Stress testing:
    - The nature of the stress testing will depend on the individual drug substance and the type of drug product involved. Stress testing (e.g., heat, humidity, oxidation, photolysis, acidic/basic solutions) is normally carried out under more severe conditions than those used for accelerated testing.
    - The objective of the stress testing study is not to completely degrade the drug substance, but to generate sufficient degradation to achieve its intended purpose. This is typically 10-20% loss of active by assay when compared with the non-degraded compound. This target is chosen such that some degradation occurs, but it is not so severe that secondary degradation products (i.e., degradation products of degradation products) are generated. Mass balance and peak purity determinations (e.g., by Diode Array or Mass Spectroscopic Detection) can be used to demonstrate that methods are stability indicating and all degradation products are detected by the methodology and that no chromatographic interferences occur.
    - A summary of the results of the stress testing studies should be provided including the treatment conditions (e.g., concentrations of solutions prepared, storage temperatures and durations) and the observations for the various test parameters (e.g., assay, degradation products) as well as a discussion of the results (e.g., observance of mass balance, potential impact on drug product manufacture, likelihood of formation of impurities under accelerated and long term conditions).
- Proposed storage conditions: The proposed storage conditions should normally include controls for temperature. Based on the results of the stability assessment, additional storage precautions

may be warranted (e.g., "Protect from light", "Protect from moisture"). Precautionary statements should not be a substitute for selecting the appropriate CCS.
- For drug substances known to be labile (e.g., certain antibiotics), it is more appropriate to establish a shelf life than a re-test period.

References:
- ICH Q1A(R2) Stability Testing of New Drug Substances and Products
- ICH Q1B Stability Testing: Photostability Testing of New Drug Substances and Products
- ICH Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products
- ICH Q1E Evaluation of Stability Data
- EMA Guideline on Stability Testing: Stability testing of existing active substances and related finished products CPMP/QWP/122/02, rev 1 corr

S.7.2 Post-approval Stability Protocol and Stability Commitment

Information to be stated in the QAR:
- A summary of the post-approval stability protocol and stability commitment should be provided.
- State whether the stability studies have been completed or are continuing.
- If the studies are being (or need to be) continued or supplemented, summarise and assess the acceptability of the manufacturer's stability protocol and stability commitment, which should include information such as batch number, testing frequency and acceptance criteria.

Points to be considered during assessment:
- When available long term stability data on commercial scale batches do not cover the proposed re-test period or shelf life (as appropriate) granted at the time of market authorisation, a commitment should be made to continue the stability studies post-authorisation in order to firmly establish the shelf life. The long term stability studies for the Commitment Batches should be conducted through the proposed shelf life/re-test period (and the accelerated studies for six months, if relevant) on at least three production batches.
- The stability protocol for commitment batches should include, but is not limited to: number of batches and batch sizes, tests and acceptance criteria, container closure system(s), testing frequency and storage conditions (and tolerances) of samples.
- Stability protocol for the annual stability monitoring programme should be provided (to be further discussed, relates to ICH Q7). At least one batch per year of drug substance manufactured at each commercial site (unless none is produced that year) should be added to the continuing stability monitoring program and tested at least annually to confirm the stability.
- Any differences in the stability protocols used for the primary batches and those proposed for the Commitment batches should be scientifically justified.

References:
- ICH Q1A(R2) Stability Testing of New Drug Substances and Products
- ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

S.7.3 Stability Data

Information to be stated in the QAR:
- A discussion of key stability data and trends (supported by numeric examples).
- Stability specification as described in section S.4.1.

Method validation should be discussed if the analytical method used is different from that as described in section S.4.2.

Points to be considered during assessment:

- The discussion of results in the dossier should focus on observations noted for the various tests, rather than reporting comments such as "All tests meet specifications". This should include ranges of analytical results and any trends that were observed. For quantitative tests (e.g., individual and total degradation product, water content and assay), it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms". Where trends in the data are noted, these should be highlighted and discussed. Statistical analysis of the data should be used as necessary to justify conclusions.

References:

- ICH Q1A(R2) Stability Testing of New Drug Substances and Products
- ICH Q1E Evaluation for Stability Data
- ICH Q2(R1) Validation of Analytical Procedures: Text and Methodology

OVERALL CONCLUSIONS AND LIST OF QUESTIONS

A brief summary of the main conclusions should be described.

The proposed List of Questions should be collated and should be:

- worded in a manner intended to be directed to the ASMF/DMF Holder or applicant (as applicable);
- clear, concise and sufficient detail describing the noted deficiency;
- risk-based, science-based questions and supported by existing guidelines and regulatory requirements.

LIST OF ABBREVIATIONS

API	Active Pharmaceutical Ingredient
ASMF	Active Substance Master File
BCS	Biopharmaceutics Classification System
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the Monographs of the European Pharmacopoeia
CCS	Container Closure System
CFU	Colony Forming Unit
CTD-Q	Common Technical Document-Quality (also referred to as M4Q)
d10, d50, d90	Representation of the midpoint and the range for particle size distribution
DMF	Drug Master File
EMA	European Medicines Agency
ICH	International Council on Harmonisation
IGDRP	International Generic Drug Regulators Programme
LOD	Limit of Detection
LOQ	Limit of Quantification
MA	Market Authorisation
MAA	Marketing Authorisation Application
NCE	New Chemical Entity
NLT	Not Less Than
NMT	Not More Than
PAR	Proven Acceptable Range
Ph. Eur.	European Pharmacopoeia
PSD	Particle Size Distribution
QAR	Quality Assessment Report
Q&A	Questions & Answers document
QbD	Quality by Design
SSTs	System Suitability Tests
USP	United States Pharmacopeia