GUIDANCE FOR QUALITY ASSESSORS – DRUG PRODUCT

IPRP Quality Working Group (QWG)

Version	Description of Change	Author	Effective Date
v 1.0	Original publication	Quality WG	28 May 2020

Foreword

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

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

The implementation of these documents by a given QWG member or observer, either as a whole or in part, is not mandatory. Each QWG 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 QWG member or observer may for practical reasons choose to revise the format or written language of a model document.

Disclaimer

This document reflects the views of subject matter experts participating in the IPRP Quality Working Group and should not be construed to represent the official views of any given regulatory authority participating in the IPRP.

Contents

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 Drug Product Quality Module (Module 3.2.P) 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 IPRP (which includes the four regulatory authorities of the ACSS Consortium).

G.2 Scope

This guidance document reflects information on the assessment of data contained in marketing authorization applications for chemical entities; it does not include guidance for the assessment of biologicals / biotechnological products.

G.3 Background Information

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 Drug Product Quality Module (Module 3.2.P) of the application. 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 (peer) assessment.
- The QAR should include summaries of the critical assessments by the assessor of the data provided in the 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 application that need to be addressed by the 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.
- A QAR template for the assessment of the full dossier, including the Drug Product Quality Module

(Module 3.2.P) of the application has been developed by the IPRP QWG.

- Information generated by the applicant (e.g., copied from the dossier or Quality Overall Summary) 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) or dossier as provided by the 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 application (e.g., diagrams, flowcharts) may be inserted into the QAR provided that the image is clearly legible, however, scanned information should be kept to a minimum to maintain the searchability of the QAR.
- Prompts within the QAR template may be removed when deemed appropriate by the assessor (e.g., not applicable for the application under review).
- When available, ICH terminology and the terminology in the International Pharmaceutical Regulators Programme (IPRP) Lexicon of Quality Terms[1] should be used.
- Acronyms should be spelled out the first time they are used in the QAR (and in the deficiency comments to the applicant), unless they are well-established industrial terms (e.g., HPLC, IR). The acronym may then be subsequently used in the QAR.
- The deficiencies identified during the assessment of the 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 applicant (as applicable);
    - Clear, concise and in sufficient detail describing the noted deficiency;
    - Wherever possible, the expectations for what should be included in the response to resolve the deficiency should be stated;
    - Risk-based, science-based questions and supported by existing guidelines and regulatory requirements.

[1] http://www.iprp.global/page/lexicon-quality-terms

ADMINISTRATIVE INFORMATION AND QUALITY ASSESSOR'S INTRODUCTION

A summary of the Administrative Information and a brief introduction into the general and region-specific aspects of the application relevant to the evaluation should be presented. This should include:

- The type of application being submitted (e.g. generic, worksharing).
- A brief description of the application including brand (trade) name of drug product, non-proprietary name of the drug product, non-proprietary name of drug substance, name of applicant, therapeutic classification (ATC Code), dosage form(s), strength(s), route(s) of administration, maximum daily dose (MDD) for the drug product, and the applicant's contact information.
- The dosage form and route of administration should indicate the mechanism of release (e.g. immediate, extended, delayed).
- Information on the reference product should be provided and include the brand name, dosage form and strength(s), Marketing Authorisation Holder's (MAH) name and country source of the lot of the reference product used in the bioequivalence study (e.g., domestic or specify foreign country of origin). Information on other relevant authorised products can also be included.
- Any available pharmacopoeial standards and relevant literature references applicable for the proposed product.
- If known, the marketing status in other jurisdictions (e.g. approvals, rejections, withdrawals).

S DRUG SUBSTANCE

Information to be stated in the QAR:

- The approach used by the applicant for providing information on the drug substance, i.e.,
  - Reference to an ASMF/DMF or
  - Reference to a Certificate of Suitability to the Monograph of the European Pharmacopoeia (CEP) issued by EDQM.
- Depending on the approach used, additional details should be provided as appropriate (e.g., information on the ASMF/DMF, CEP).

Points to be considered during assessment:

- Note: A separate QAR template is available and should be used if full details on the drug substance are provided by the applicant.
- For a reference to an ASMF/DMF, a brief summary should be provided of the status of the assessment of the ASMF/DMF.
- For a reference to a CEP, a brief summary should be provided of the status of the CEP and, if applicable, confirmation that all relevant attestations have been provided and are complete.

Aspects of the Drug Substance Relevant to the Drug Product

Information to be stated in the QAR:

- A discussion of the critical quality attributes of the API relevant to the drug product should be provided, i.e.,
  - Solubility
  - Particle Size Distribution
  - Crystallinity/Polymorphism
  - Sterility

CONTROL OF THE DRUG SUBSTANCE BY DRUG PRODUCT MANUFACTURER

S.4 Control of the Drug Substance

Information to be stated in the QAR:

- Summary of the proposed specification of the drug substance (including test parameters, analytical procedures and acceptance criteria) by the drug product manufacturer
- State the standard claimed by the applicant (e.g., Ph. Eur./BP/USP/Ph.Int./In-house).
- Include a discussion on the acceptability of the proposed specification and claimed standard.
- The QAR should also note those tests, acceptance criteria, or analytical procedures that are different from the drug substance manufacturer and include an assessment of analytical validation reports where relevant.
- Assessment of representative batch data of drug substance analysed by both the drug substance and drug product manufacturer.

Points to be considered during assessment:

- Of the batches included, analytical results should be provided in Module 3 for batches manufactured to a minimum of pilot scale (e.g., 1/10th commercial scale) by the same synthetic route as, and using

a method of manufacture and procedure that simulates the final commercial process to be used for the drug substance.

- Analytical data for batches used in pivotal studies (e.g. bioequivalence studies) should be supplied with the dossier and include results for critical quality attributes of the API. The results should be discussed (e.g. in P.2 Pharmaceutical Development) and used to support the justification of the drug substance specification.
- For a reference to a CEP, and as applicable, a discussion should be included for additional tests, analytical procedures and acceptance criteria that are not included in the Ph.Eur monograph (e.g., polymorphic form, particle size distribution, or other tests that may be relevant to the dosage form). Acceptance criteria for such tests should be assessed in reference to results reported for the API lots used in the manufacture of the clinical and stability batches.
- Analytical results from a GMP compliant laboratory should be provided for at least two batches from each proposed manufacturing site of the drug substance.

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.7 Stability

Information to be stated in the QAR:

- The proposed re-test period and storage conditions.
- Include a discussion on the acceptability of the proposed re-test period and storage conditions. If applicable, the re-test period of the ASMF/DMF Holder or the re-test period specified on the EDQM CEP should be included in the discussion.

Points to be considered during assessment:

- If the proposed re-test period by the drug product manufacturer/applicant is longer than that considered acceptable in the ASMF/DMF or for the CEP (as applicable), or if a re-test period is not specified in the CEP, a summary of the long-term, intermediate (if applicable), and accelerated studies conducted should be provided.
- If applicable, a summary should be provided of other relevant stability information or studies (e.g., on micronized or compacted drug substance, confirmation that the desired polymorphic form is maintained over the re-test period).

P DRUG PRODUCT

P.1 Description and Composition of the Drug Product

Information to be stated in the QAR:

- A description of the dosage form and its composition.
- The description of the dosage form should include a physical description, the proposed strengths and release mechanism (e.g. immediate release, modified release, dispersible tablets).
    - e.g. *ABC 100 mg tablets are available as yellow, round, scored tablets, debossed with '100' on one side and plain on the other side*.
    - e.g. *XYZ is a clear, colourless, aqueous solution in a clear glass vial or ampoule available in a single 200 µg/2 mL strength.*
- The composition of the dosage form, in tabular form, should include:
    - a list of all components, including proprietary mixes (e.g. flavours, printing inks)
    - reference to quality standards (e.g. compendial monographs or manufacturer's specifications) and, if applicable, specific grades
    - the function of each component
    - their amounts on both a per-unit and % w/w basis
- For dosage forms supplied with reconstitution diluents that are not commercially available or have not been authorised in connection with another application, information on the diluents should be discussed in P.2.6 and a separate Drug Product ("P") portion with all relevant subsections filled, as appropriate.
- The type of container and closure used for the dosage form and, if applicable, administration equipment (e.g. oral syringes, oral measuring cups) and other co-packed medical devices should be sufficiently described.
    - e.g. *The product will be packaged in blisters, which are constructed from PVC/PVDC-laminate foil with a pre-printed Aluminum foil.*

Points to be considered during assessment:

- Drug substances and excipients should be listed using their INNs.
- The description of the dosage form should include all components including those used in the manufacturing process. This may include components that may not be added to every batch (e.g. acid and alkali), removed during manufacture (e.g. solvents) and others (e.g. nitrogen gas blanket).
- The amounts should be included on both a per-unit basis and % w/w basis although other units might be more relevant such as per container and per actuation for inhaled products, or % w/v basis for liquids. Based on the % of API in the product, it could be emphasised in the QAR if the product is a low content product (e.g. active substance <2%).
- In general, the strength of the drug product should be expressed in terms of the active moiety.
- The table summarising the formulation should clearly indicate if there are any differences in the form of the substance for the active pharmaceutical ingredient (the input material), the active substance in the finished drug product and the form of the active moiety.
- If the strength is based on a form of the drug substance that is different from the form used as the API (the input material) in the formulation (e.g. if the drug product is formulated using a salt or solvate and the strength is declared in terms of the active moiety in the form of a base), then the conversion to the active ingredient should also be clearly indicated (e.g. "1.075 mg of active ingredient hydrochloride = 1 mg of active ingredient base").
- Where relevant, the table should have a footnote with a formula for calculating potency adjustment including the assay and moisture content of individual API batches, and compensation with the diluent to result in the combined (API + diluent) theoretical weight.
- All overages should be noted and justified in 3.2.P.2.2 (e.g. "contains 2% overage of the drug substance to compensate for manufacturing losses"). The use of an overage of a drug substance to

compensate for degradation during manufacture or a product's shelf life, or to extend the shelf life, is generally not acceptable and discouraged.

- The function of each component (e.g. diluent/filler, binder, disintegrant, lubricant, glidant, granulating solvent, coating agent, antimicrobial preservative) should be identified.
- Flavours are often made up of a complex mixture of ingredients. Therefore, the general qualitative composition should be listed and contain the main constituents, including those that have a recognised action or effect, with an appropriate process of identification to ensure the consistency of the composition.
- Colourants in the product, coatings, components in capsule shells, and any printing inks, including all proprietary mixes, should be appropriately stated (qualitatively and quantitatively).
- If the product is to be injected, it should be stated if it is isotonic. If it is not isotonic, this should be referred to the clinical assessor for comment.
- It is recommended that different strengths of the product are readily distinguishable (e.g. by differences in size, colour, shape, markings). This distinction is more important for products supplied in bottles, compared to those supplied in blisters where identification per unit is less prone to error.
- Where a waiver to perform in-vivo bioequivalence studies is provided for certain strengths, indicate if the different strengths (or what parts of the strengths) are (or are not) quantitatively proportional.
- Containers for both the dosage form and, if applicable, accompanying reconstitution diluent should be described.

References:

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

P 2 Pharmaceutical Development

P 2.1 Components of the Drug Product

P.2.1.1 Drug Substance

Information to be stated in the QAR:

- The chemical form of the drug substance/active pharmaceutical ingredient (e.g. salt, acid, free base, ester), the form of the active substance in the finished dosage form for the generic drug product, and the form for the active moiety (e.g., in the case of a possible in-situ conversion during the manufacturing process for the dosage form). Where appropriate, relevant justification should be provided. Discussion should be provided regarding the form of the active substance in the reference product.
- Physicochemical characteristics of the drug substance (e.g., water content, solubility over the physiological pH range, particle size distribution, polymorphic form, Biopharmaceutics Classification System (BCS) classification) that can influence the performance of the drug product.
- The compatibility of the drug substance with excipients listed in 3.2.P.1.

Points to be considered during assessment:

- The physical, chemical, biological and, if applicable, mechanical properties of the drug substance that may impact both the manufacture and the performance of the drug product.
- Discuss the drug substance attributes that may impact the drug product critical quality attributes (CQAs) and the risk assessment provided by the applicant in this regard.

- State whether the excipients listed in 3.2.P.1 are compatible with the drug substance, and the reason for this assessment (e.g. evidence from compatibility studies and/or qualitative same composition as the reference product, and/or from lack of trends from stability studies).
- Briefly discuss drug substance–excipient compatibility experiments, however, this may not be required when there is evidence (e.g. in the SmPC/PI/Product Monograph) that the excipients are consistent with those present in the reference product.
- For fixed-dose combination products, the compatibility of the drug substances with each other should be confirmed. References to reference products/related products or the formulation of the test product (e.g. if APIs are in separate granules/layers) may suffice.
- An API may be converted to a different chemical or physical form (e.g. in situ conversion of a free base to a salt or from polymorphic form I to polymorphic form II) during the drug product manufacturing process. Such a conversion which could be intended or inadvertent (e.g. processing condition in commercial lot) may adversely affect the performance, safety and efficacy of the drug product and should be carefully assessed and discussed.
- Instances where there is a potential for in-situ conversion based on the physicochemical properties of the API or due to the formulation and/or method of manufacture of the drug product, justification and supporting data should be provided to establish whether a conversion occurs, leading to a different physical or chemical form of the drug substance form contained in the final dosage form. Where investigation of the drug product reveals that the physical (e.g. polymorphic, pseudopolymorphic or particle size distribution) or chemical (e.g. free acid/base to salt) form of the API is altered during the manufacturing process or during storage of the drug product, relevant information (e.g. solubility, crystalline structure) should be provided for the API and information regarding the form contained in the finished drug product. In order to make a risk-based decision on the acceptability of the in-situ transformation, information on the in-situ form should include information on the form (e.g., salt form) if it were present as an isolated compound (e.g. solubility). Where complete characterisation of the original or in-situ form is not possible, this should be discussed and justified.
- If the form of the active substance in the generic drug product is different from that in the Reference Product, consultation with the clinical/non-clinical assessor should be initiated early in the assessment process and additional information may be necessary in order to support the safety and efficacy of the form of the active substance in the final dosage form for the proposed generic product.

References:

- ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
- EMA 3CC29a Investigation of Chiral Active Substances
- Guidance on compatibility studies is provided in Appendix 3 of the WHO Guidelines for registration of fixed-dose combination medicinal products (WHO Technical Report Series, No. 929, 2005, Annex 5)

P.2.1.2 Excipients

Information to be stated in the QAR:

- The choice of excipients should be justified.
- Comment on the choice of excipients.
    - Indicate if they are conventional for the proposed dosage form and comment on any unusual excipients and the reasons for their inclusion in the formulation (in particular, if not included in the Reference Product).
    - Discuss any excipient characteristics that may influence drug product performance.

Points to be considered during assessment:

- All of the excipients (including colorants, preservatives, flavourings and sweeteners) should be appropriate and acceptable for use in human medicines.
- The ability of excipients (e.g. antioxidants, preservatives, release controlling agents) to perform their intended function throughout the proposed drug product shelf life should be demonstrated.
- The use of preservatives in single use injections or solid orals should be justified.
- Absorption modifiers (e.g. enhancers, inhibitors) and aids, such as surfactants, could significantly influence bioavailability.
- For surfactants, if used as an excipient, the lowest concentration should be used.
- Excipients used outside of established quantitative ranges generally require justification. If possible, compare excipient quantities in the proposed product with other products using the same route of administration (e.g. sub-cutaneous injection) to ensure that exposure levels are acceptable.
- If an excipient is used for a new route of administration this is to be justified and assessed by non-clinical assessors.

References:

- EMA: Guideline on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product, EMEA/CHMP/QWP/396951/2006
- EMA: Note for Guidance on Quality of Water for Pharmaceutical Use, CPMP/QWP/158/01
- US FDA Inactive Ingredient database
- US FDA Generally Recognized as Safe (GRAS) list
- Rowe RC, Sheskey PJ, Quinn ME (eds), *Handbook of pharmaceutical excipients*, London/ Washington, DC, Pharmaceutical Press/American Pharmacists Association.

P 2.2 Drug Product

P 2.2.1 Formulation Development

Information to be stated in the QAR:

- A brief summary describing the development rationale and the studies used to support the proposed commercial formulation.
- A summary of drug product critical quality attributes - aspects of the formulation that have been identified as potentially high risk to drug product performance.
- Significant differences between the proposed formulation and the reference drug formulation that may have an influence on drug product performance.
- Differences between clinical formulations (e.g. batches used in the bioequivalence studies) and the formulation described in 3.2.P.1.*Components of the Drug Product.*
- Information from comparative *in vitro* studies (e.g., dissolution) or comparative *in vivo* studies (e.g., bioequivalence) that supports the proposed commercial formulation should be summarized. A cross reference to the studies (with study numbers) should be provided.
- Any special design features of the drug product (e.g., tablet score/break line, overfill for solutions, anti-counterfeiting measure as it affects the drug product) should be identified and justified.
- The discriminative power of the dissolution method should be discussed and verified.
- If relevant (e.g., for modified-release products), results of in vitro/in vivo correlation studies (IVIVC) and cross-reference to the studies (with study numbers) should be provided along with an assessment of acceptability.

Points to be considered during assessment:

- A brief summary of the development of the drug product formulation should be provided and differences between clinical compositions and the proposed commercial formulation, if any, should be discussed and justified by the applicant.

- Which formulation variables have a high risk of impacting the drug product CQAs?
- In the case of systemically acting tablets, capsules or suspensions, appropriate dissolution and/or bioavailability data should be provided to confirm that the product has the required release characteristics and the product can be concluded to have the same safety and efficacy as the comparator product, unless otherwise justified.
- Dissolution methods should be product specific and appropriate for the products release mechanism and the choice of method (e.g. apparatus, rotation speed, and medium) should be justified.
    - The discriminatory ability of the dissolution method should be demonstrated (e.g. moderated formulation changes in critical excipients and/or challenging process parameters that may affect performance) including when the applicant proposes a publicly available method.
    - The use and the concentration of a surfactant should be justified. The concentration should be at the lowest possible level. A surfactant is generally not accepted if there is at least one pH across the physiological pH range at which the drug substance is soluble.
- A previously accepted IVIVC can assist in the selection of appropriate dissolution acceptance criteria for modified release products, and can potentially reduce the need for further in vivo studies following changes to the product or its manufacturing process.
- If tablets are scored to allow fractional dosing, evidence that the tablets split evenly and the fragments comply with the Ph Eur/USP requirements should be provided.
- If the product is sterilised by heat or radiation, comment on the adequacy of any data provided to confirm that no physical or chemical damage to the product and no formation of harmful degradation products results.

References:

- ICH Q8 (R2) Pharmaceutical Development
- EMA: Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action EMA/CHMP/CVMP/QWP/336031/2017

P 2.2.2 Overages

Information to be stated in the QAR:

- The amount of any overages (not including non-functional film coatings) used in the manufacture of the drug product.
- The company's justification for the overage (e.g., to compensate for expected and documented manufacturing losses).

Points to be considered during assessment:

- Any overages used in the manufacture of the drug product (manufacturing overages), whether they appear in the final formulated product or not, should be justified. The target release assay of a product formulated with a manufacturing overage should be ~100% of the label claim.
- The inclusion of an overage to extend the shelf-life of the drug product (stability overages where release assay is >100.0%) is generally not acceptable and discouraged.
- The overage should be included in the amount of drug substance listed in the batch formula (3.2.P.3.2 *Batch Formula*).

References:

- ICH Q8 (R2) Pharmaceutical Development

P 2.2.3 Physicochemical and Biological Properties

Information to be stated in the QAR:

- Physicochemical and biological properties relevant to the safety, performance or manufacturability of the drug product should be discussed as applicable.

Points to be considered during assessment:

- Parameters relevant to the performance of the drug product, such as pH, ionic strength, viscosity, dissolution, redispersion and fineness of dispersion, reconstitution, particle size distribution of the drug substance in the product, aggregation, polymorphism, osmolality, rheological properties, biological activity or potency, and/or immunological activity, should be addressed.

References:

- ICH Q6A Specifications: Test Procedures And Acceptance Criteria For New Drug Substances And New Drug Products: Chemical Substances; Decision Tree #4 (Part 3) and Decision Tree #7 (Part 1)

P 2.3 Manufacturing Process Development

Information to be stated in the QAR:

- The method of manufacture of the finished product should be briefly described.
- Comment on any significant differences between the manufacture of batches used in pivotal clinical studies (safety, efficacy, bioavailability, bioequivalence) or primary stability studies and the manufacturing process intended for commercial production of the product.
- The suitability of the manufacturing equipment for the proposed products should be discussed.
- The method of sterilisation and its validity.
- Discussion of manufacturing process development to support a design space and/or real time release (if proposed).

Points to be considered during assessment:

- Is this a non-standard (critical) dosage form and manufacturing process?
- The selection and optimisation of the manufacturing process described in P.3.3, particularly its critical process parameters, should be discussed and justified.
- The choice of manufacturing and packaging processes that may influence drug product quality and performance should be discussed (e.g. granulation type, requirements to protect form light/moisture).
- It is important to consider the critical formulation attributes alongside the manufacturing process options in order to assess the selection of the manufacturing process and the appropriateness of the components.
- The manufacturing process development should identify any critical process parameters to be monitored or controlled (e.g., rate of addition of granulating fluid, massing time, and granulation end-point) to ensure that the product is of the desired quality - these studies can be used to justify the drug product specification (3.2.P.5.6). The report should confirm that the outcomes of the studies are reflected in the proposed commercial production process.
- Where there is no intended scale-up from primary batches (including the clinical batches), the commercial production should closely follow the manufacture of the clinical batches. Differences should be minimized when there is scale-up, i.e. should be limited to the necessities of scaling up to larger equipment.
- An assessment of the robustness of the process (e.g., the performance of the process under different operating conditions, at different scales, or with different equipment) may be provided.
- Where a Quality by Design (QbD) approach has been used for development of the drug product 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 product specification test for impurity(ies)).
- Discuss the role of QbD in the overall control strategy.

References:

- ICH Q8 (R2) Pharmaceutical Development
- ICH Q9 Quality Risk Management
- ICH Q10 Pharmaceutical Quality System
- EMA: Note for Guidance on Development Pharmaceutics, CPMP/QWP/155/96
- EMA: Decision Trees for the Selection of Sterilisation Methods, CPMP/QWP/054/98 Corr (Annex to CPMP/QWP/155/96)
- EMA: Guideline on process validation for finished products - information and data to be provided in regulatory submissions (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1) Annex II

P 2.4 Container Closure System

Information to be stated in the QAR:

- The container closure system (CCS) should be briefly described (reference to 3.2.P.7 *Container Closure System*).
- The suitability of the CCS for the storage, transportation and use of the drug product should be discussed.
- Discussion on any extractables or leachables studies performed as applicable (e.g. for CCSs used to package liquid or semi-liquid dosage forms).
- If applicable, performance studies for dosing devices (e.g. dropper pipette, pen injection device, dry powder inhaler) appropriate for their intended purpose (e.g. accuracy and precision under normal conditions of use for the lowest intended dose).
- Uniformity of dose data for any associated integrated devices (e.g., pMDIs, multiuse and pre-filled syringes, etc).
- The influence of the drug product manufacturing process on the container closure system where applicable (e.g. sterilisation conditions). Compliance with appropriate guidelines should be stated.

Points to be considered during assessment:

- The immediate and any outer packaging materials, closures, induction or tamper-proof seals, pack sizes, any dosing device, and any desiccant or cotton wool contained in the package should be appropriate for the product.
- The information provided by the sponsor should cover:
  - the choice of materials
  - the ability of the CCS to provide protection from moisture and light
  - the compatibility of CCS with the dosage form
  - safety of material of construction
  - performance (e.g. reproducibility of dose delivery from dosing device)
- Consider if the product needs to be packaged in a container equipped with a child-resistant closure and if so, comment on the acceptability of the closure.
- Compatibility of the product with processing tubes should be addressed.

References:

- Glass containers:
  - Ph.Eur. 3.2.1: Glass Containers for Pharmaceutical Use
  - USP <660> Containers - Glass
- Plastic containers:
  - Ph.Eur. 3.2.2: Plastic Containers And Closures For Pharmaceutical Use
  - Ph. Eur. 3.2.2.1: Plastic Containers For Aqueous Solutions For Parenteral Infusion
  - USP <661> Containers - Plastics
- Rubber/elastomeric closures:
  - Ph.Eur. 3.2.9: Rubber Closures For Containers For Aqueous Parenteral Preparations, For Powders and for Freeze-Dried Powders
  - USP <381> Elastomeric Closures for Injections
- USP <671> Containers - Performance Testing
- USP <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems
- USP <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems
- European 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: Guideline on Plastic Immediate Packaging Materials, CPMP/QWP/4359/03
- EMA: Note for Guidance on Dry Powder inhalers, CPMP/QWP/158/96
- EMA: Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products, EMEA/CHMP/QWP/49313/2005 Corr
- FDA: Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics, 1999
- FDA: Guidance for Industry Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products, 2008

P 2.5 Microbiological Attributes

Information to be stated in the QAR:

- If applicable, a brief summary of the microbiological control strategy.
- Justification of the microbial testing regimen.
- Compliance with pharmacopeial monographs should be referenced

Points to be considered during assessment:

- The selection and effectiveness of preservative systems in products containing antimicrobial preservative.
- The lowest specified concentration of any antimicrobial preservative should be justified in terms of efficacy and safety.
- The presence of an appropriate assay for a preservative in the drug product specifications.
- For sterile products, the integrity of the container closure system with regards to microbial contamination should be discussed.

References:

- ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances - Decision Tree #8
- EMA: Note for guidance on Maximum Shelf-life for Sterile Products for Human Use After First Opening or Following Reconstitution, CPMP/QWP/159/96 Corr
- Ph. Eur. 2.6.1: Sterility
- USP <71> Sterility tests
- Ph. Eur. 2.6.12: Microbiological examination of non-sterile products: microbial enumeration tests

- Ph. Eur. 2.6.13: Microbiological examination of non-sterile products: test for specified micro-organisms
- Ph. Eur. 2.6.14: Bacterial endotoxins
- USP <85> Bacterial endotoxins test
- Ph.Eur. 5.1.3, Efficacy of antimicrobial preservation
- Ph. Eur. 5.1.4, Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use
- USP <1111> Microbiological examination of non-sterile products: acceptance criteria for pharmaceutical preparations and substances for pharmaceutical use

P 2.6 Compatibility

Information to be stated in the QAR:

- If relevant, summarise and assess the information on in-use stability testing relating to the compatibility of the product with reconstitution/dilution fluids for the labelled storage directions and durations and/or delivery devices.
- Comment on the acceptability of the compatibility studies conducted with all diluents over the range of dilution proposed in the labelling.

Points to be considered during assessment:

- Where relevant, compatibility of the drug product with reconstitution diluents (e.g. Lactated Ringers, 5% Glucose in Water, 0.9% Sodium Chloride in Water, 20% Mannitol in Water) or dosage devices (e.g., no precipitation of drug substance in solution, no sorption on injection vessels, satisfactory stability of the resulting solution) should have been adequately established.
- Data should support labelling information.
- Studies should support the duration of storage reported in the labelling (e.g. 24 hours under controlled room temperature and 72 hours under refrigeration). Studies for sterile products should also include testing for microbiological and sterility attributes.
- Compatibility studies should preferably be conducted on two batches, one should be near the end of the proposed shelf-life, at the recommended storage temperature and at the likely extremes of concentration.
- Unless qualified, verify that no leachables (e.g. from infusion tubes or dosage devices) are above the Threshold of Toxicity Concern (TTC) based on the maximum daily dose.

References:

- EMA: Note for Guidance on In-Use Stability Testing of Human Medicinal Products, CPMP/QWP/2934/99
- ICH M7(R1) Assessment And Control Of DNA Reactive (Mutagenic) Impurities In Pharmaceuticals To Limit Potential Carcinogenic Risk

P 3 Manufacture

P 3.1 Manufacturer(s)

Information to be stated in the QAR:

- List the name, address and responsibility for each manufacturing, sterilisation (if applicable), packaging, labelling, and testing site.

Points to be considered during assessment:

- The name, address, and responsibility of each manufacturer and site involved in manufacturing and testing of the drug product should be provided.

- Manufacturers performing the following steps should be included: any part of the manufacture of the drug product (including intermediates), testing including contract testing of any parameter(s) in the specifications, primary packaging, secondary packaging, labelling and batch release.
- Sites involved in sterilisation of primary container closure systems (e.g. gamma radiation) not subsequently exposed to terminal sterilisation should be listed.
- The list of manufacturers should specify the actual production or manufacturing site(s) involved, rather than the administrative offices.
- The information provided should be complete, clear and unambiguous, and in line with the information provided in Module 1 and the Application Form..

P 3.2 Batch Formula

Information to be stated in the QAR:

- State the proposed size(s) of commercial batch(es) in line with the data presented in section 3.2.P.5.4.
- The manufacturing batch formula, including all components used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards and, if applicable, their grades.
- The summary should include all components used in the manufacturing process, regardless if they appear in the final drug product (e.g. solvents, headspace nitrogen if it is applied during the processing).
- If the amount of drug substance is adjusted (e.g. based on the potency of the active moiety), then the table should have a footnote with a formula for calculating potency adjustment including the assay and moisture content of individual API batches, and compensation with the diluent to result in the combined (API + diluent) theoretical weight.
- If the strength is not based on the API, the equivalency formula should be indicated as a footnote (e.g. 100 mg of the base is equivalent to 125 mg of the salt).
- Indicate if there are any overages for any of the ingredients, and/or any overfills of containers, and the manufacturer's reasons for these, and comment on their acceptability (may be previously justified in P.2.2).

Points to be considered during assessment:

- Check and indicate if the batch formulae are correct and correspond to the unit formula.
- Any ranges of quantities for excipients, or overfill of the container(s) should be appropriate and justified. Ranges for excipients are generally not accepted. Similarly, batch sizes should generally be discrete sizes which are individually validated, and not ranges of sizes.
- Overfills (not to be confused with overages) are excess volumes intended to ensure the minimum required extractable volumes to allow for correct dosage delivery.
- Overages (e.g., to compensate for loss of potency during stability) are typically not permitted. However, in certain situations, an overage may be scientifically justified (e.g., a validated loss during manufacturing).

P 3.3 Description of Manufacturing Process and Process Controls

Information to be stated in the QAR:

- A flow diagram and narrative description of the manufacturing process should be provided.
- The description should include all steps of the manufacturing process, including packaging and pre-sterilisation of the packaging materials (if relevant).

- Hold-times (e.g. drug product intermediate, bulk product) should be specified and their acceptability discussed.
- Any proposals for the reprocessing of materials and their acceptability.

Points to be considered during assessment:

- The processes should be adequately described.
- The flow diagram should include all process steps and show where materials enter the process.
- As appropriate manufacturing equipment should, at least, be identified by type (e.g. tumble blender, in-line homogeniser), function and working capacity.
- The data should detail the controls applied to each step including mixing times and speeds, etc. and the appropriate process parameters identified (e.g. time, temperature, pH).
- Critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified and ranges for critical steps justified in Section 3.2.P.3.4 *Controls of Critical Steps and Intermediates*.
- The in-process controls (including temperatures, mixing times and speeds, filter integrity), test methods, acceptance limits and testing frequency at each step in the manufacturing, sterilising (if any) and packaging processes should be defined, appropriate and adequate to assure batch quality and unit-to-unit consistency.
- If data to support a design space is provided in P.2.3, then the proposed design space should be clearly described in P.3.3.
- The acceptability of proposals for the reprocessing of materials is determined on a case-by-case basis and is based on the data showing acceptable control of the drug product.
- Examples of specific in-process controls include:
    - granulations: moisture (e.g. loss on drying), blend uniformity (e.g. low dose tablets), and non-routine controls such as bulk and tapped densities, particle size distribution;
    - solid oral products: average weight, weight variation, hardness, thickness, friability, fineness of dispersion (for dispersible tablets) and disintegration checked periodically throughout compression, weight gain during coating;
    - parenterals: appearance, clarity, fill volume/weight, pH, filter integrity tests, particulate matter, leak testing of ampoules, pre-filtration and/ or pre-sterilisation bioburden testing;
    - semi-solids: viscosity, pH, homogeneity, evaluation of phase separation;
    - transdermal dosage forms: assay of API - adhesive mixture, weight per area of coated patch without backing, adhesion strength cut patch dimensions and tolerances;
    - metered dose inhalers: fill weight/volume, leak testing, valve delivery;
    - dry powder inhalers: assay of API – excipient blend, moisture, weight variation of individually contained doses such as capsules or blisters;
    - liquids: pH, specific gravity, clarity of solutions.
- If alternative processes or manufacturers are intended for some steps in the manufacture, these should be justified and shown to yield drug product of equivalent quality.
- Proposals for reworking of failed batches will not be assessed during the pre-market assessment and should not be submitted. Any reworking of batches is authorized on a case-by-case basis in accordance with principles defined by good manufacturing practices.
- If relevant, any processing of the containers (e.g. neutralising, cleaning, washing, sterilising) before filling should be adequately controlled.
- Include information on micronisation of the drug substance by the drug product manufacturer, if applicable.
- If sterilisation of the product or container is by treatment with ethylene oxide, it should be established that its use is the only viable option and the residue level should be controlled in accordance with M7. The acceptable daily exposure should be based on the maximum daily dose.
- The maximum holding time for non-sterile intermediates and bulk product (product prior to final packaging, e.g. tablets in HDPE drums) should be stated. If significant the holding time should be supported by stability data as appropriate to the intermediate (e.g. WHO reference).
- Start of shelf life of the finished product should be declared.

- For an aseptically processed drug product, sterile filtration of the bulk and filling into final containers should preferably be continuous; any holding time should be justified.

References:

- ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
- ICH Q8 (R2) Pharmaceutical Development
- ICH Q9 Quality Risk Management
- ICH Q10 Pharmaceutical Quality System
- EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1 Guideline on Process Validation for Finished Products - Information and Data to be Provided in Regulatory Submission.
- EMA: Guideline on Manufacture of the Finished Dosage Form, EMA/CHMP/QWP/245074/2015
- EMA: Note for Guidance on Quality of Water for Pharmaceutical Use, CPMP/QWP/158/01
- General Guidance on Hold-time Studies (WHO Technical Report Series, No. 992, 2015, Annex 4)
- EMA: Note for guidance on start of shelf-life of the finished dosage form, CPMP/QWP/072/96

P 3.4 Controls of Critical Steps and Intermediates

Information to be stated in the QAR:

- The critical in-process controls and/or parameters used in the manufacture of the drug product and the steps at which these control tests or parameters are conducted and the frequency of testing.
- Indicate if there are any intermediate products and comment on the quality control applied to these and any representative batch data.

Points to be considered during assessment:

- Summarise and comment on the suitability of tests and acceptance criteria and the frequency of testing for critical steps in the manufacturing process.
- The tests and acceptance criteria and the frequency of testing should be provided (with justification, including experimental data) for the critical steps identified in P.3.3 of the manufacturing process, to ensure that the process is controlled. An assessment should be made in conjunction with the process validation data.
- If there is an intermediate product isolated during the production process, it should be controlled by separate specifications (as distinct from the in process controls) that control identity and physical and chemical properties, as applicable. Information on the quality and control of intermediates during the process should be provided (e.g. co-precipitates, API micronised by the drug product manufacturer, bulk tablets and solutions).
- Satisfactory representative batch analytical data should be provided.

References:

- ICH Q8 (R2) Pharmaceutical Development
- ICH Q9 Quality Risk Management
- ICH Q10 Pharmaceutical Quality System

P 3.5 Process Validation and/or Evaluation

Information to be stated in the QAR:

- The batch size and batch numbers of drug product used in process validation studies.

- A brief description of the process validation studies and discuss their ability to demonstrate that the drug product manufacture has been satisfactorily developed and is capable of manufacturing product of the required quality.
- Summarise any hold-time studies performed.
- Indicate if the validation studies carried out thus far are adequate to support the proposed commercial batch size(s) or if additional validation data are required.
- If applicable, the choice of sterilisation method should be described and comment made on its acceptability.
- Summarise any commitment given by the manufacturer.
- If appropriate, comment on any process validation protocols supplied for future validation work.

Points to be considered during assessment:

- The main objective of process validation is to demonstrate that a process, operated within defined parameters, yields a product meeting its pre-defined quality criteria.
- All critical steps in the manufacturing process should be adequately developed and validated at each manufacturing site at production scale
- As part of the process validation lifecycle, some studies may be performed on pilot scale (in the case of solid dose forms, ≥ 10% of full scale or 100,000 units, whichever is the greater - unless otherwise justified - using production scale equipment, or at full scale if the production scale is to be less than 100,000 units).
- If a process validation report has not been provided on three consecutive commercial size batches of the drug product, the following information should be provided:
    - a copy of the process validation protocol and a commitment that three consecutive commercial scale batches will be manufactured and subject to prospective validation
    - the process validation protocol should be specific to the drug product, identify the critical equipment and critical process parameters (CPP) that can affect the critical quality attributes (CQA) of the drug product, and define testing parameters, sampling plans, analytical procedures, and acceptance criteria (Control Strategy).
- In certain cases, it is necessary to provide production scale validation data with the application, for example, where a non-standard method of manufacture is proposed (specialized pharmaceutical dose forms [e.g. modified-release, suspensions/emulsions, low content drugs {≤ 2%}], conventional processes using new technologies [e.g. new drying technology], specialised processes [e.g. lyophilisation, asceptic processing, implants and depots], non-standard methods of sterilisation). The number of batches should be justified.
- A bracketing approach may be acceptable for different strengths, batch sizes and pack sizes. In the case of a common blend, at least three batches of the blend should be validated, as well as at least three batches of the additional stages (e.g. compression) for each strength.
- It should be justified that variations in batch size will not adversely alter the critical quality attributes of the drug product.
- If the product is stored (or transported) in a bulk container for a significant time period between manufacture and final packaging, it should be established that the product remains stable under the recommended storage conditions and for the likely maximum storage time involved.
- If the degradation is greater under the bulk conditions, compared to the final container, the shelf life should be adjusted accordingly.
- Steam sterilisation is considered to be the preferred method to ensure sterility of the final drug product and other methods should be scientifically justified. The sterilisation process should be described in detail and sufficient evidence should be provided to demonstrate that it will produce a sterile product with a high degree of reliability and that the physicochemical of the drug product will not be affected.
- Process validation review of sterile products should also include validation of the sterilisation and depyrogenation of container components, filters etc.
- Where applicable, reports from recent media fill runs and filter validation (including compatibility and extractables/leachable) should be reviewed.

- Continuous process verification in which process performance is continuously monitored and evaluated, may be performed as an alternative, or in addition, to traditional process validation. This may include in-line, on-line or at-line monitoring.

References:

- ICH Q8 (R2) Pharmaceutical Development
- ICH Q9 Quality Risk Management
- ICH Q10 Pharmaceutical Quality System
- EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1, Guideline on Process Validation for Finished Products - Information and Data to be Provided in Regulatory Submissions

P 4 Control of Excipients

P 4.1 Specifications

Information to be stated in the QAR:

- List the excipients, grades and standards (pharmacopoeial or "in house").
- For non-pharmacopoeial excipients, an appropriate specification should be based on: Physical, identification, purity, assay and other relevant tests.

Points to be considered during assessment:

- The identity and physical, chemical and microbiological quality of all excipients (including capsule shells and their constituents, coating materials, colorants, and any gases used in filling vials or ampoules) should be controlled by either pharmacopoeial or appropriate in-house specifications.
- The specifications should be provided for all non-pharmacopoeial excipients (e.g. in-house excipients).
- In general, for a pharmacopoeial excipient no specification is required. It is satisfactory to state that the excipient is tested according to the requirements of that standard.
- Functionality-related characteristics that are recognised as being relevant control parameters for one or more functions of the excipient should be appropriately controlled and details provided. If developmental studies show that a particular characteristic is critical for the functionality (e.g. viscosity or particle size of release controlling excipients) it should be included in the specifications.
- For some excipients (specific grade), limits in addition to those in the monographs are used. Comment on their acceptability, especially if missing (e.g. PSD for lactose in an inhalation).
- Colorants in the product or in capsule shells should comply with pharmacopoeial or WHO/FAO specifications and/or EC Directive 231/2012.

References:

- ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
- EMA: Guideline on Excipients in The Dossier for Application for Marketing Authorisation of a Medicinal Product, EMEA/CHMP/QWP/396951/2006

P 4.2 Analytical Procedures

Information to be stated in the QAR:

- Comment as appropriate on any non-pharmacopoeial procedures used for testing excipients.

Points to be considered during assessment:

- Copies of pharmacopoeial analytical procedures do not need to be submitted.

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

P 4.3 Validation of Analytical Procedure

Information to be stated in the QAR:
- Comment as appropriate on the validation data for any non-pharmacopoeial procedures used for testing excipients.

Points to be considered during assessment:
- Copies of analytical validation information are generally not submitted for the testing of pharmacopoeial excipients, with the exception of the validation of in-house methods where appropriate.

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

P 4.4 Justification of Specifications

Information to be stated in the QAR:
- Comment on the acceptability of any proposed non-pharmacopoeial specifications, and any batch data provided.

Points to be considered during assessment:
- Pharmacopoeial specifications do not normally require justification.
- Justification needs to be provided for any proposed non-pharmacopoeial specifications.
- Justification should be provided for any excipient functionality related characteristics critical to drug product performance (e.g. viscosity, dispersion).
- Satisfactory representative batch analytical data should be provided for any excipients controlled by non-pharmacopoeial specifications.

References:
- ICH Q3A(R2) Impurities In New Drug Substances

P 4.5 Excipients of Human or Animal Origin

Information to be stated in the QAR:
- For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g. sources, specifications, description of the testing performed, viral safety data).
- Comment as appropriate on any excipients of human or animal origin used in the product (e.g. gelatin, stearic acid, magnesium stearate and other stearates) and their TSE status.

Points to be considered during assessment:
- Adequate measures should be taken to ensure that any animal-derived ingredients (e.g. gelatin, magnesium or calcium stearate, stearic acid) used in the product are free from TSE contamination in accordance with CHMP and Agency requirements.

- For excipients manufactured from raw material obtained from sources that have potential of transmitting Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalopathy (TSE) agents (e.g. ruminant origin, a letter of attestation should be provided confirming that the excipients used to manufacture the drug product are without risk of transmitting agents of BSE/TSE.
- If possible, materials of animal origin should be avoided.
- When available, a CEP demonstrating TSE compliance should be provided.
- For excipients of natural origin, microbial limit testing should be included in the specifications where appropriate.

References:

- ICH Q5A(R1) Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin
- EMA Note for Guideline on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMA/410/01, rev 3, July 2011)

P 4.6 Novel Excipients

Information to be stated in the QAR:

- Identify any novel excipients.
- Assess the manufacture, characterisation, and quality control data submitted.
- The composition of complex or multi-component excipients should be qualitatively and quantitatively described.

Points to be considered during assessment:

- For excipients used for the first time in a drug product, full details of manufacture, characterisation, and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided. This includes new excipients that are part of a Proprietary Ingredient, in which case a master file may be required.
- For a novel excipient the documentation provided should include:
    - Name and address of manufacturer
    - Outline of manufacture and purification
    - Structure and physical, chemical properties, identification and purity tests.
    - Analytical validation and batch analysis results (including impurity profiles).
    - Stability data
    - Justification of specification
- The requirements for the chemistry, manufacture and quality control data are similar to those for a new chemical entity drug substance.
- Toxicology data for the novel excipient relevant to the dosage form and route of administration should be included in Module 4.

References:

- ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
- EMA: Guideline on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product, EMEA/CHMP/QWP/396951/2006

P.5 Control of Drug Product

P.5.1 Specifications

Information to be stated in the QAR:

- Release and shelf life specifications (including test parameters, acceptance criteria, test methods).
- Indicate if there is reduced testing proposed for certain parameters.
- State the standard claimed by the applicant (e.g., Ph. Eur./BP/USP/Ph.Int./In-house).

Points to be considered during assessment:

- Specifications applicable for release and shelf life should be clearly identified.
- Periodic test schedules (skip lot testing) or alternate testing frequencies proposed in accordance with ICH Q6A should be indicated on the specifications with the testing frequency clearly marked as a footnote.

References:

- ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
- ICH Q3B(R2) Impurities in New Drug Products
- ICH Q3C(R7) Impurities: Guideline for Residual Solvents
- ICH Q3D Guideline for Elemental Impurities
- Ph. Eur. General Monographs - Dosage Forms

P.5.2 Analytical Procedures

Information to be stated in the QAR:

- State if compendial or in-house analytical procedures are applied.
- Short description of all in-house analytical procedures, which may include analytical conditions, system suitability tests, relative response factors, method of quantification (external standard, normalisation).

Points to be considered during assessment:

- The test procedures used should be either referenced to a recognised pharmacopoeia or described with sufficient detail to enable them to be carried out by a regulatory laboratory.
- Where relevant, test procedures should be subject to appropriate system suitability tests. The system suitability criteria (including but not limited to Assay, Related Substances) should be in line with pharmacopeia general chapters and/or results obtained from validation data.
- Sample preparation should be clearly described.
- Formulae for calculations of quantitative results should be provided and be correct.
- Ph.Eur. 2.6.12. Microbiological examination of non-sterile products: the enumeration method should be defined (membrane filtration, plate-count or most-probable-number).
- Ph.Eur. 2.6.14. Bacterial endotoxins: the test method should be defined (gel-clot method limit test, gel-clot method quantitative test, turbidimetric kinetic method, chromogenic kinetic method, chromogenic end-point method, turbidimetric end-point method).

References:

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

P.5.3 Validation of Analytical Procedures

Information to be stated in the QAR:

- State if the validation is in accordance with ICH Q2(R1) 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 and 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 the range, 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.
- For sterile products, the test for sterility (e.g., Ph. Eur. 2.6.1) and bacterial endotoxins (e.g., Ph. Eur. 2.6.14) should be validated with the drug product.
- If an in-house method is used instead of the pharmacopoeial method and the pharmacopoeial standard is claimed: cross-validation data should be provided to demonstrate equivalency 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
- Verification of compendial purity/assay methods, generally specificity, accuracy and method precision as well as full validation for impurities not controlled by the monograph, should be established to show the method is suitable for the proposed formulation.

References:

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

P.5.4 Batch Analyses

Information to be stated in the QAR:

- Briefly describe/tabulate the batches (e.g., strength, batch number and size, use of the batch) and batch results.
- 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:

- The description of the batches provided in the dossier should include the batch number, strength, manufacturing site, batch size, date of manufacture, API batch number and use of the batch.
- Suitability of the presented batch sizes should be assesssed considering whether the process is standard or non-standard.
- Batch analysis data should be provided and demonstrate that the product meeting the required quality can be consistently manufactured at each of the proposed commercial manufacturing sites. If there are multiple sources of an API, batches will preferably include API from each supplier.
- Complete and satisfactory recent analytical reports should be provided for several batches of the final market formulation(s) for each strength of each dose form for product manufactured at a minimum of pilot scale.
- Analytical data for batches used in pivotal clinical or bioequivalence studies and batches used for qualification of impurities should be provided with the dossier (e.g. module P.2, P.5.4, P.5.6) and used to support the proposed drug product specification.
- The results of all batches should comply with the proposed specifications and demonstrate the consistent quality of the material
- A pilot scale batch of a drug product is a batch manufactured by a procedure fully representative of

and simulating that to be applied to a full production scale batch. In addition,
    - for solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is the larger;
    - for liquid dosage forms (including lyophilized powders for reconstitution into a solution), a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 20 litres, whichever is the larger. If the maximum proposed commercial batch size is less than 20 litres, the executed batches included in the drug submission should be manufactured at the maximum proposed commercial batch size.
- Numeric values for the data where possible ('complies' should be avoided).

References:
- ICH Q3B(R2) Impurities in New Drug Products

P.5.5 Characterisation of Impurities

Information to be stated in the QAR:
- State if all potential degradation products have been discussed.

Points to be considered during assessment:
- Potential degradation products may include impurities identified in 3.2.S.3.2 and degradation products resulting from interaction of the drug substance with excipients or container-closure system.
- Related substances controlled in relevant pharmacopoeial dosage form monographs should be included or their absence should be justified.
- ICH Q3D risk assessment should be provided.

References:

- ICH Q3B(R2) Impurities in New Drug Products
- ICH Q3C(R7) 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

P.5.6 Justification of Specifications

Information to be stated in the QAR:
- Summarise the justification of specifications for relevant tests and comment on the suitability, adequacy and acceptability of the tests and the proposed acceptance criteria.

Points to be considered during assessment:
- The acceptance criteria are set taking into consideration the relevant guidelines, pharmacopoeial requirements and actual levels found in batches of the drug product manufacturer, with emphasis on the levels found in the batches used for nonclinical, clinical, and bioequivalence studies.
- ICH's Q6A guideline outlines recommendations for a number of universal and specific tests and criteria for drug products.
- The Ph. Eur./Ph.Int./B.P./USP dosage form monographs provide specific tests for each dosage form.
- Maximum daily dose of the drug product (route of administration: e.g., inhalation, oral).
- 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. 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.
- Acceptance criteria for assay release should be within 95.0 to 105.0 %, unless justified in 3.2.P.2.2.
- Qualification of impurities: the qualification of an identified impurity can be based on toxicological data or actual test results of impurities/degradation products using validated methods determined in one or more batches of appropriately stored sample of the Reference Product (e.g., the innovator product), if justified by the manufacturer. The presence of a limit for a specified impurity in a pharmacopoeial monograph at or exceeding the proposed limit is also considered qualification. In the latter case the age of the sampled Reference Product batches should be considered.
- Inhalation and nasal products: expected specifications are listed in the EMA guideline on the pharmaceutical quality of inhalation and nasal products.
- If relevant, dissolution limits should be in line with the observed dissolution of the biobatch (e.g. in line with the requirements of EMA/CHMP/CVMP/QWP/336031/2017).
- Transdermal patches: expected specifications are listed in the EMA guideline on quality of transdermal patches.
- Medicinal gases: expected specifications are listed in the EMA guideline on medicinal gases.
- Justification of omitted tests.
- Justification of periodic test schedules (skip lot testing) or alternate testing frequencies in accordance with the concepts presented in ICH Q6A

References:

- ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
- ICH Q3B(R2) Impurities in New Drug Products
- ICH Q3C(R7) Impurities: Guideline for Residual Solvents
- ICH Q3D Guideline for Elemental Impurities
- Ph. Eur. General Monographs - Dosage Forms and the chapters in other pharmacopoeia
- Specifications and Control Tests on the Finished Product Directive - 75/318/EEC - 3AQ11a
- Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action - EMA/CHMP/CVMP/QWP/336031/2017
- Guideline on Quality of Oral Modified Release Products EMA/CHMP/QWP/428693/2013
- Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products EMEA/CHMP/QWP/49313/2005 Corr
- Guideline on Quality of Transdermal Patches EMA/CHMP/QWP/608924/2014
- Guideline on Medicinal Gases CPMP/QWP/1719/00 Rev1
- Guideline on Radiopharmaceuticals EMEA/CHMP/QWP/306970/2007

P.6 Reference Standards or Materials

Information to be stated in the QAR:

- Reference to Section 3.2.S.5 if the same reference standard(s) is/are used in the testing of the product. Otherwise, the following should be stated:
    - Description and source of reference standards or reference materials for analysis of the drug substance and impurity(s).
    - 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 product (e.g., for the identification, purity, potency tests). If a compendial reference standard is used for quantitative analysis, the reference standard should be tested 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, data to include IR, UV and certificate of analysis.
- Impurity standard (characterisation, purity), if applicable.

References:

- Ph. Eur. Chapter 5.12. Reference Standards
- USP General Chapter <11> Reference Standards

P.7 Container Closure System

Information to be stated in the QAR:

- State the description and specification of the container closure system used in the storage and/or transportation (shipping) of the bulk drug product, if applicable.
- State the description, including the identity of materials of construction, and specification of all the packaging components of the primary container closure system for drug product including container, closure, liner and desiccant.
- If there are any associated components (e.g. drug delivery device) to be packaged in the market package of drug product, then their description and specification should also be captured.
- Capture additional information such as specification or other relevant properties for functional secondary packaging component (e.g. protection from light, moisture, oxygen).
- State if the specifications for the container closure system are acceptable which should include but not limited to description, identification, critical dimension, physical and chemical properties etc.
- State whether declaration of compliance in accordance to appropriate guidelines or policy has been provided.

Points to be considered during assessment:

- The details of suitability study for container closure system such as protection from light/moisture, glass type, integrity, extractable/leachable could be captured in P.2.4.
- Specifications for each primary packaging component should be assessed thoroughly to ensure critical parameters are being monitored. This include but not limited to description, identification, critical dimensions (with drawing where appropriate).
- It is acceptable for the drug product manufacturer to perform reduced testing.
- Complete and satisfactory representative batch analytical data should be provided for any primary packaging materials, containers, and closures.
- For functional secondary packaging components, additional information to demonstrate its functionality should be provided. Note that a secondary packaging component, such as a carton, becomes a functional packaging component when it is necessary to protect the product, such as for

permeable blisters containing light sensitive products.

- Any delivery device(s) (e.g. inhaler, syringe, dropper) supplied with the product should be clearly defined, suitable for pharmaceutical use, and adequately controlled for identity, dimensions, physical and chemical properties, manufacturing defects, sterility and dose delivery, as applicable.
- If the material has not previously been assessed and approved for use with pharmaceuticals destined for the country market, the details of the manufacturer, formulation, identification code and evidence of material safety in accordance with the Ph Eur or USP requirements should be provided.
- Declaration of compliance with appropriate standards, e.g., food contact EC/10/2011, Ph. Eur. Chapter 3, USP, could be provided by the vendor or drug product manufacturer.
- In the case of packaging components pre-sterilised by the supplier, description and validation of the process should be provided if relevant.

References:

- ICH Q2(R1) Validation of Analytical Procedures: Text and Methodology
- 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.
- USP General Chapters (e.g. USP <381> Elastomeric Closures for Injections, <659> Packaging and Storage Requirements, <660> Containers-Glass, <661> Containers Plastics, <670> Auxiliary Packaging Components, <1663> Assessment of Extractables associated with Pharmaceutical Packaging/Delivery Systems, <1664> Assessment of Drug Product Leachables associated with Pharmaceutical Packaging/Delivery Systems)
- FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics

P.8 Stability

P.8.1 Stability Summary and Conclusion

Information to be stated in the QAR:

- Summarise the studies undertaken to support the proposed shelf-life. Information to state includes: strength, batch numbers and sizes, manufacturing site, manufacturing date, container closure system(s), orientation for liquid dosage forms (e.g. upright, inverted), storage conditions (long-term, intermediate (if applicable), accelerated) and completed (and proposed) testing intervals.
- Summarise the conditions and results of stress testing the studies of the drug product.
- State the proposed shelf-life and storage conditions (and, if applicable, in-use storage conditions) and comment whether or not they are justified.

Points to be considered during assessment:

- For conventional dosage forms (e.g. immediate release solid oral dosage forms, solutions) and when the active substance is known to be stable, stability information from accelerated and long term testing should be provided on an appropriate number of primary batches of each strength manufactured and packaged in each type of container closure system proposed for marketing.
- For critical dosage forms (e.g., modified release dosage form) and when the active substance is known to be unstable, stability testing should be provided on at least three primary batches of each strength. Two of these three batches should be at least pilot scale batches, and the third one can be smaller, if justified.

- If relevant, orientation of containers should be defined and appropriate for the product. For injection vials stability data should be provided for samples stored in both upright and inverted positions.
- Bracketing and matrixing can be applied, if scientifically justified (e.g. based on surface area to volume ratio, headspace to volume ratio, water vapour permeation rate or oxygen permeation rate per dosage unit or unit fill volume).
- Stability results should be provided at the time of filing.
- Extrapolation of the shelf-life should generally be based on ICH Q1E. However, Q1E is primarily for zone II regions, where intermediate data may be considered. For zone IVb regions, e.g. WHO, where intermediate studies are not available for Q1E considerations, extrapolation should be allowed exceptionally and generally is applied more conservatively.
- Stress testing:
    - As outlined in ICH Q1A guidance document, photostability testing should be conducted on at least one primary batch of the drug product if appropriate.
    - Results of the stress studies conducted to show degradation of the drug product should demonstrate that the analytical procedures used for the purity and potency tests are stability-indicating via peak purity and observation of the mass-balance (process of adding together the assay value and levels of degradation products to add up closely to 100%).
    - Additional stress testing of certain types of dosage forms may be appropriate (e.g. cyclic freeze-thaw studies for liquids, orientation of the container closure system (such as inverted), semi-solids and transdermal patches).
- Accelerated and long term testing:
    - Stability information from accelerated and long term testing should be provided on at least two primary batches of each strength (or, on at least three primary batches for Health Canada)) manufactured and packaged in each type of container closure system proposed for marketing. Bracketing and matrixing can be applied, if scientifically justified.
- In use testing:
    - Changes to a product after opening should be assessed for multiple-dose sterile products, for solid oral products in bulk packages (e.g. hospital
    - dispensing packs containing hygroscopic or moisture-sensitive APIs) and for products where the labelling indicates a specific in-use period (this information may also be provided in P.2.6).
    - The testing to support the in-use period should be performed at a reasonable interval and at the end of the in-use period on two batches including a batch near the end of the proposed shelf-life for the drug product. If data on a batch near the end of the proposed shelf-life is not available, data should be provided to support the in-use period and a commitment should be provided to repeat these studies on a batch near the end of the shelf-life. In-use periods should be justified with data where applicable and consistent with product labelling (e.g. for ophthalmic products containing a preservative in use periods should be justified with experimental data).
    - The in-use study should indicate handling of the container to be representative of use, for example each solid oral product container should be opened daily and a number of tablets (1-3) extracted per opening. At time points which do not require analysis, product may be immediately returned to the container for later analysis in the case of smaller bottle size. At the analysis time points (e.g. 0, 15, 30, 60 days), a sufficient number of tablets should be taken for analysis.
    - Multiple-dose ophthalmic products with no in-use period are assumed to have an in-use period of 28 days. Data should be provided to support this period or a period that would cover the use of the entire product.
- 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.

    - If a packaging component is required for protection, the labeling should reflect this, e.g. "Store tablets in original packaging."
- If the form of the drug substance (e.g. amorphous, crystalline polymorph) is susceptible to change, and this new form may alter *in vivo* performance of the drug product, the applicant should demonstrate the stability of the drug substance form and phase under the proposed storage conditions.

References:

- ICH Q1A(R2) Stability Testing of New Drug Substances and Products
- Guideline On Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products - CPMP/QWP/122/02, rev 1 corr
- Note for Guidance on In-Use Stability Testing of Human Medicinal Products - CPMP/QWP/2934/99
- Stability testing of active pharmaceutical ingredients and finished pharmaceutical products (WHO Technical Report Series, No. 1010, 2018, Annex 10)

P.8.2 Post-approval Stability Protocol and Stability Commitment

Information to be stated in the QAR:

- A summary of the post-approval stability protocol and stability commitments 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 long term stability data has not been provided for three commercial scale batches, a protocol and commitment to conduct these studies should be submitted.
- When available long term stability data on primary batches do not cover the proposed shelf life 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 (and the accelerated studies for six months, if relevant) on at least three production batches.
- Stability protocol and commitment for the continuing/annual stability monitoring programme should be provided. At least one batch per year of each strength of drug product 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.
- The stability protocols for the Commitment Batches (primary and commercial batches as necessary) and Continuing (i.e. ongoing) Batches should include, but not limited to:
    - Number of batches per strength and batch sizes;
    - Tests and acceptance criteria;
    - Container closure system(s);
    - Testing frequency; and
    - Storage conditions (and tolerances) of samples.
- Any differences in the stability protocols used for the primary batches and those proposed for the Commitment or Continuing batches should be scientifically justified.

References:

- ICH Q1A(R2) Stability Testing of New Drug Substances and Products

P.8.3 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 P.5.1.
- Method validation should be discussed if the analytical method used is different from that as described in section P.5.2.

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".
- For dissolution, the individual values (for meeting the three stage limits) and average values (for assessing trends) are required to be reported and discussed.
- 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
- Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products - CPMP/QWP/122/02, rev 1 corr
- Stability testing of active pharmaceutical ingredients and finished pharmaceutical products (WHO Technical Report Series, No. 1010, 2018, Annex 10)

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 applicant (as applicable);
- clear, concise and sufficient detail describing the noted deficiency;
- Wherever possible, the expectations for what should be included in the response to resolve the deficiency should be stated;
- risk-based, science-based questions and supported by existing guidelines and regulatory requirements.

Once they are considered acceptable, include copies of the active/drug substance and the medicinal/drug product specifications as Appendices 1 and 2 (respectively).

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
IPRP	International Pharmaceutical 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
TSE	Transmissible spongiform encephalopathies
USP	United States Pharmacopeia