Health Canada Santé Canada

Quality (chemistry and manufacturing) draft guidance: New Drug Submissions and Abbreviated New Drug Submissions

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Canada

Avant-propos

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document **may be** acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this guidance, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

Table des matières

G General

G.1 Purpose

As required by Section C.08.002 of the *Food and Drug Regulations*, a New Drug Submission (NDS) or an Abbreviated New Drug Submission (ANDS) must contain sufficient information and material to allow an assessment of the safety and effectiveness of the new drug. This document is intended to provide guidance with regard to the Quality [that is (i.e.), Chemistry and Manufacturing] portion of NDSs and ANDSs for drug substances of synthetic or semi-synthetic origin and their corresponding drug products that are filed with Health Canada pursuant to Division C.08 of the *Food and Drug Regulations*. The purpose of the guidance document is to outline the Quality technical requirements and to assist submission sponsors in preparing the NDS or ANDS to ensure an effective and efficient assessment process. It can also be used as guidance on the requirements for related drug submissions [for example (e.g.), Supplemental New Drug Submissions (SNDSs), Supplemental Abbreviated New Drug Submissions (SANDSs), Post-Notice of Compliance (NOC) Changes].

G.2 Scope

This guidance document applies to NDSs and ANDSs for drug substances of synthetic or semi-synthetic origin and their corresponding drug products for human drug use, excluding Biotechnological/Biological (Schedule D) and Radiopharmaceutical (Schedule C) drugs, that are filed with Health Canada pursuant to Division C.08 of the *Food and Drug Regulations*. It can also be used as guidance on the requirements for related drug submissions (e.g. S(A)NDSs[1], Post-NOC Changes).

Alternate approaches to the principles and practices described in this document can be acceptable provided they are supported by adequate scientific justification. Sponsors are advised to discuss, in advance, alternate approaches in their drug submission to avoid rejection or withdrawal of the drug submission.

This guidance document applies to new active pharmaceutical ingredients (APIs), existing APIs and their corresponding drug products. An existing drug substance or product is one that is not or does not contain a new medicinal ingredient, but requires the filing of a New Drug Submission (NDS), an Abbreviated New Drug Submission (ANDS) (e.g. an application for a generic product) or a Supplement. This would include, for example, submissions for new dosage forms, new strengths, and other changes to authorized products which require the filing of an S(A)NDS. When an S(A)NDS is submitted for a post-NOC change, data should be provided in accordance with the sections of the guidance which apply to the proposed change.

The Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) should be consulted to determine the extent of data generation which is necessary to support NDSs, ANDSs or S(A)NDSs. The Post-Notice of Compliance (NOC) Changes: Quality Document should be consulted for drug products that have received an NOC and have considerable commercial scale manufacturing experience for the drug substance or drug product (e.g. validation of scale-up is completed). If significant knowledge of the drug substance or drug product is not available at the time that a S(A)NDS for a post-NOC change is submitted, the application should reflect the requirements listed in this Quality (C&M) Guidance: NDSs and ANDSs guidance document.

The scientific and risk-assessment principles outlined in this document are also applicable to other types of applications (e.g. for Applications for Drug Identification Number Submissions (DINAs)).

G.3 Preamble

Background

The Common Technical Document - Quality (CTD-Q) (Module 3) outlines the format of the Quality portion of applications within the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Common Technical Document (CTD). Also, as part of the CTD guideline, the ICH process has produced recommendations for a Quality Overall Summary (QOS) (Module 2) which is a summary that follows the scope and the outline of the Quality Module (Module 3).

This Health Canada guidance document follows the format recommended in ICH's CTD-Q guideline. The text following each section title is taken directly from the ICH CTD-Q guideline.

This guidance provides information on data which should be provided in Module 3 of the CTD-Q. Where relevant, guidance has been provided on how to summarize the information in the QOS.

Terminology used in this guidance document is defined in one or more of the references listed, unless the term is specifically defined in the text of this document or in the companion Glossary of Quality Terms that accompanies this guidance document.

This guidance document supersedes Health Canada's guideline entitled Chemistry and Manufacturing: New Drugs (1990) and the draft Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) (2001 and 2013).

International Council for Harmonisations (ICH's) Quality Overall Summary (QOS) and Health Canada's Quality Overall Summary - Chemical Entities (QOS-CE) Template

Subsection C.08.005.1 (1) (c) of the *Food and Drug Regulations* stipulates that new drug submissions (NDSs), abbreviated new drug submissions (ANDSs), supplemental new drug submissions (SNDSs), and supplemental abbreviated new drug submissions (SANDSs) should include a comprehensive summary of each human, animal and in vitro study referred to or included in the submission or supplement. The intent of this requirement is to facilitate the assessment of the extensive experimental data and hence contribute toward a more effective and timely processing of drug submissions.

As previously mentioned, ICH has integrated a Quality Overall Summary (QOS) within its CTD guideline. The QOS is considered a comprehensive summary that follows the scope and the outline of the Body of Data in Module 3. The QOS should not include information, data, or justification that was not already included in Module 3 or in other parts of the drug submission.

A template entitled Quality Overall Summary - Chemical Entities (New Drug Submissions/Abbreviated New Drug Submissions) (QOS-CE (NDS/ANDS) is available on the Health Canada website to facilitate preparation of a summary of the Quality data submitted to Health Canada. The QOS-CE (NDS/ANDS) template is consistent with the directives in ICH guidelines, principles of applying sound science and risk management to the systematic development of drugs, and current Quality standards and terminologies.

ICH's QOS and Health Canada's QOS-CE (NDS/ANDS) are collectively referred to as the Quality Overall Summary or QOS throughout the remainder of this document. The guidance refers to what should be submitted, regardless of the template used.

Use of Health Canada's QOS-CE (NDS/ANDS) template is optional, although its use may facilitate the preparation of the Quality Overall Summary and may contribute to review efficiencies. It is recommended

that the QOS be limited to the minimum number of pages required to summarize key information (e.g. 40-100 pages).

Health Canada considers that the QOS is a summary created specifically for each regulatory submission and the QOS does not need to be managed over the life cycle of a product.

ICH's QOS and Health Canada's QOS-CE (NDS/ANDS) are collectively referred to as the Quality Overall Summary or QOS throughout the remainder of this document.

Module 2.3: Quality Overall Summary (Qos)

Notes on the Preparation of the Quality Overall Summary and the Quality Module

Sponsors are encouraged to devote sufficient time to prepare an accurate, consistent, and concise QOS based on the detailed information included in the Quality Module. The filing of an inaccurate or incomplete QOS will result in greater expenditure of an assessor's time in retrieving, assessing and summarizing data.

Essential elements of the minimal approach and the enhanced, Quality by Design (QbD) approach (as described in ICH's Q8 guideline) and QbD terminologies should be used to facilitate an efficient assessment process.

It is recognized that the tables included in the QOS-CE (NDS/ANDS) template may need to be modified (e.g. with data cells being split or joined, as necessary). In order to best summarize the data tabular structure should be used whenever possible. All headings listed in the default sections of the CTD should nonetheless be retained or addressed, regardless of their perceived relevance, unless the subject matter of the entire section or table is irrelevant to the drug substance or drug product in question.

If portions of the QOS (e.g. sections, tables) are clearly not relevant for the drug submission due to the nature of the drug substance or drug product, this should be indicated by the designation "Not Applicable" (e.g. under the heading of Module 2.3.P.4.5, if no excipient of human or animal origin is used in the manufacture of the drug product). Portions that are "Not Applicable" should be accompanied by an explanatory note or justification describing their inapplicability.

To facilitate the assessment, when the information in a section has been included in a prior drug submission in its entirety (e.g. in a Supplement for a new dosage form filed after the NDS/ANDS is authorised or while the NDS/ANDS assessment is in progress) and the information has not changed subsequent to that filing, the relevant section should be cross referenced, and so noted in section 1.0.7, General Note to the reviewer, the Introduction to the QOS and Quality Module (e.g. under section (b) Other Introductory Information). The Introduction should include the names of the cross-referenced drug product and sponsor, date of the Notice of Compliance (if applicable), and dossier identification and control numbers. If there are changes to any sections that have been cross-referenced, these should be summarized appropriately. Submission of information which is cross-referenced should be in accordance with the Management of Drug Submissions Guidance Document (e.g. Section 5.2, 5.5 and 5.7).

Following is additional guidance to assist sponsors in preparing the QOS and the Quality Module:

a. Examples of applicable guidance documents are identified under the various sections. Those developed by ICH are identified by their code names only (e.g. Q1A, Q2). When a guidance document or pharmacopeia is referred to, the most recent (current) version should be consulted.
b. Abbreviations should not be used in the QOS and Quality Module unless initially defined and consistently used (e.g. N/A = Not applicable), or unless they represent well-established scientific abbreviations (e.g. HPLC, UV).
c. Copies of original documents (e.g. certificates of analysis) are preferred as transcription of documents leads to frequent errors and their availability allows for verification of analytical data.
d. For new drug submissions (e.g. NDSs, ANDSs, Supplements) regarding drug substances that are no longer considered new drugs according to Part C, Division 8 of the *Food and Drug Regulations*, consult Health Canada's Quality Guidance: Applications for Drug Identification Number Submissions (DINAs) for Pharmaceuticals for the information that should be provided on the **drug substance**. If the drug substance is not covered by a compendial monograph (e.g. USP or Ph.Eur.) then additional information on the route of synthesis and impurities (e.g. mutagenic impurities) may be necessary to justify the specifications. The information that should be provided on the drug product should be as described in this document Quality Guidance: NDSs and ANDSs.
e. When filing a response to a request for additional information from Health Canada (e.g. Request for Clarification (Clarifax), Notice of Non-compliance (NON), Notice of Deficiency (NOD)), sponsors should summarize new or updated data (e.g. specifications, analytical procedures, stability results) in the response in a question and answer format, with additional documentation being provided in Module 3 of the CTD. Generally, an updated QOS should not be submitted as Health Canada uses the first QOS submitted as the basis of preparing the original Quality Assessment Report (QAR). However, in the case of an NOD or an extensive NON where the magnitude of deficiency comments warrants the filing of extensive changes to the information contained in the original drug submission, a refiled/updated QOS can be necessary. If updated documents are submitted, annotated and non-annotated versions should be submitted to expedite assessment (e.g. the Certified Product Information Document (CPID)).

References:

ICH M4 (Common Technical Document)
ICH M4Q (Common Technical Document - Quality)
Preparation of Drug Regulatory Activities in the CTD Format
Management of Drug Submissions

Health Canada's Certified Product Information Document - Chemical Entities (CPID-CE)

The CPID-CE constitutes part of the Notice of Compliance (NOC) package and provides a condensed summary of the key Quality information for NDSs and ANDSs. The CPID-CE provides an accurate record of information on the Quality of the drug substance and drug product at the time the NOC is issued. The CPID-CE is a condensed version of the QOS and represents the final, agreed upon key data from the drug submission (e.g. list of manufacturer(s), manufacturing procedure and control strategy, specifications, container closure system including delivery devices, storage conditions, retest period or shelf life, and commitments). Most importantly, it serves as a valuable knowledge management tool and a reference document to track the changes in the Quality information for the drug substance and drug product during its lifecycle. It is a useful document for both the sponsor and the regulator as an official reference document during the course of post-authorization activities. The CPID-CE template is structured to permit the rapid assembly of the CPID-CE

by copying requisite information from the corresponding portions of the QOS filed with the original drug submission.

For NDSs and ANDSs, the proposed CPID-CE should be submitted with the original drug submission, as it helps the Review Division in the planning and allocating of the required resources and for an efficient assessment process. For applications for post-NOC changes (e.g. Supplements), the appropriate annotated and non-annotated CPID-CE should be completed in its entirety and be provided at the time of filing. Only the CPID-CE for the dosage form(s) affected is required. It is acknowledged that when filing a submission for an application for post-NOC change, the updated CPID-CE may include changes that did not need prior approval by Health Canada (e.g. Level III - Annual Notifications or Level IV - Record of Changes). An annotated version highlighting changes should be submitted which distinguishes changes proposed in the S(A)NDS versus those made and submitted as Annual Notifications or Record of Changes. Health Canada's position is that data supporting these changes have been generated and assessed for their acceptability by the company prior to their implementation and that the data are available for Health Canada's assessment on request as outlined in the Post-Notice of Compliance (NOC) Changes - Quality Guidance.

Reference:
Certified Product Information Document - Chemical Entities (CPID-CE)

Introduction

The introduction should include proprietary name, non-proprietary name or common name of the drug substance, company name, dosage form(s), strength(s), route of administration, and proposed indication(s).

Sponsors should provide other introductory information in the QOS Introduction, such as a contact person's name, phone number, fax number, and e-mail address for ease of communication. The introductory information in the QOS can also include other salient points of the drug submission that may be useful to the assessor (e.g. filing and marketing status and brand name in other jurisdictions, availability of a current Certificate of Suitability to the Monographs of the European Pharmacopoeia (CEP), cross-referenced drug substance or drug product, placement of the Control Strategy Summary and, if applicable, date(s) of the Notice of Compliance (NOC), Notice of Non-Compliance (NON)/NON-Withdrawal (NON-W) or Notice of Deficiency (NOD)/NOD-Withdrawal (NOD-W), dossier identification and control numbers).

When relevant to the product under consideration, requirements from the USP and European Pharmacopoeia general chapters should be adopted.

Module 3: Information To Be Provided In Module 3 And Summarized In The Quality Overall Summary (QOS)

Unless otherwise stated in the text, the following information should be provided in detail in Module 3 and briefly summarized or cross-referenced in the QOS as appropriate. The guidance is provided to aid applicants in appropriately providing information and justifying the quality of the product using the totality of the information provided. The CTD section where the guidance has been presented does not necessarily refer to where the information should be placed in the submission, but has been discussed in a way to ensure interconnected information is provided appropriately. ICH M4(Q) should be consulted to determine the best placement for detailed information in Module 3 and appropriate cross-references made to the position of the information in alternate sections to ensure appropriate discussion and justification is present to allow for efficient assessment of the totality of the information.

S Drug Substance

In this guidance, the term "active pharmaceutical ingredient" (API) (as defined in C.01A.001(1) of the Regulations) and "drug substance" are considered interchangeable and refers to the API used as the raw (input) material in the manufacture of a drug product. In some cases, this API may undergo in-situ conversion during the drug product manufacturing process leading to a different chemical form of the same active moiety (e.g. free acid/base form to salt form). Refer to Health Canada's Notice: Interim Policy on Health Canada's Interpretation of Medicinal Ingredient (June 16, 2015) for further information.

Master Files (MFs)

Some information outlined in the various sections including the "S Drug Substance" section of the drug submission may be considered proprietary and may not be available to the sponsor of the NDS or ANDS. If this is the case, the supplier of the material (e.g. drug substance, excipient, container closure system component) can file a confidential Master File (MF) directly with Health Canada. The supplier would then be considered the MF Holder. This MF will be held in strict confidence and will be used in support of the drug submission only upon receipt of a written letter of authorization from the MF Holder or Canadian Agent (i.e. via a letter of access). Copies of letters of access should be provided in Module 1.

The sponsor should submit a copy of the non-proprietary information provided by the MF Holder (i.e. the "Applicant's Part" of MF), and other information obtained in the public domain (e.g. scientific literature, peer reviewed journals), and/or developed by the sponsor. For recommendations on the content of MFs, Health Canada's guidance document entitled Master Files (MFs) – Procedures and Administrative Requirements should be consulted. Regardless of whether the sponsor includes data obtained from the MF Holder, from published scientific literature or generates the data in-house, the source of the information should be clearly identified. The information from the Applicant's Part of the MF should be provided in various CTD sections of the drug submission and summarized in the QOS.

The drug submission sponsor should ensure that the information included in the MF is up to date and that the MF has been received by Health Canada by submitting a letter of confirmation from the MF Holder. Consult HC guidance on MFs for further information.

Regardless of the information provided by the supplier of the drug substance, the manufacturer of the dosage form is responsible for ensuring that appropriate specifications and properly validated analytical procedures for the drug substance are developed and for providing the results of batch analyses. These specifications and methods should be provided from the release testing site (i.e. the site where testing is done for the purpose of releasing the drug substance) of the drug substance to be used in the manufacture of the drug product. Determination of the acceptability of the release testing site is determined by the Good Manufacturing Practices (GMP) regulations and is the responsibility of the Regulatory Operations and Regions Branch (RORB) of Health Canada.

Reference to a Master File is only necessary if the information requested by this guidance is third-party confidential information and the third-party has not provided the information to the sponsor for inclusion in the submission.

References:

Master Files (MFs) - Procedures and Administrative Requirements

Good Manufacturing Practices (GMP) Guidelines (GUI-0001)

Certificates of Suitability to the Monographs of the European Pharmacopoeia (CEPs)

Health Canada encourages the filing of CEPs when they are available. CEPs should be filed by the drug substance supplier in an Active Substance Master File (ASMF) or with full information on the drug substance in the drug submission along with the appropriate attestations. An appropriately referenced CEP will expedite the assessment of information related to the detailed method of synthesis and control of impurities and in some cases storage conditions and retest period. For current information on how CEPs should be filed in a submission and what information should be included when a CEP is referenced, refer to "Health Canada's exploration of the use of European Directorate for the Quality of Medicines (EDQM) Certificates of Suitability (CEP)" notice available on Health Canada's Website.

S.1 General Information

S.1.1 Nomenclature

Information on the nomenclature of the drug substance should be provided. For example:

a. Recommended International Non-proprietary Name (INN);
b. Compendial name, if relevant;
c. Chemical name(s);
d. Company or laboratory code;
e. Other non-proprietary name(s) (e.g. national name, United States Adopted Name (USAN), Japanese Accepted Name (JAN); British Approved Name (BAN)); and
f. Chemical Abstracts Service (CAS) registry number.

The listed chemical names should be consistent with the official name or those appearing in scientific literature (e.g. pharmacopoeia, USAN) and those appearing on the product labelling (e.g. Product Monograph, container label). Where several names exist, the preferred name should be indicated.

When an in-situ conversion of the drug substance occurs or is likely to occur based on chemical principles during the manufacture of the drug product (e.g. formation of a salt or complex), the compound in the final dosage form should also be described. In cases where this is not possible, justification and detailed information should be provided (e.g. in Section P.2 Pharmaceutical Development).

S.1.2 Structure

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.

This information should be consistent with that provided in section S 1.1 and in the Product Monograph. For drug substances existing as salts and/or hydrates/solvates, the molecular formula and molecular mass of the free base or free acid or unsolvated moiety should also be provided.

S.1.3 General Properties

A list should be provided of physicochemical and other relevant properties of the drug substance.

This information can be used in developing the specifications, in formulating dosage forms, and in the testing for release and stability purposes. Provide information on the relevant physical and chemical properties of the drug substance. Examples of information could include the physical description, solubilities in common solvents (e.g. including those used in the drug substance or drug product manufacturing process, analytical

methods or for cleaning), polymorphism, pH and pKa values, UV absorption maxima and molar absorptivity, melting point/Differential Scanning Calorimetry (DSC)/Thermogravimetric Analysis (TGA), refractive index (for a liquid), hygroscopicity, partition coefficient. This list is by no means exhaustive, but provides an indication as to the type of information that could be included. Phrases such as "sparingly soluble" or "freely soluble" should conform to USP or Ph.Eur. definitions.

Data on general properties that are not generated in-house should be noted as such and the source of the data should be clearly referenced.

Some of the more important properties to be considered for all drug substances are discussed below in greater detail.

Physical description (e.g. polymorphic form, solvate, hydrate):

The description should include appearance, colour, and physical state. Solid forms should be identified as being crystalline or amorphous. If the drug substance can exist in more than one physical form, the information included in S.1.3 should be for the form (or forms) of the drug substance that will be used in the manufacture of the drug product or formed through in situ conversion. Detailed information on the characterization of these and other physical forms should be provided in S.3.1.

References:
ICH Q6A

S.2 Manufacture

S.2.1 Manufacturer(s)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

This includes the facilities involved in the manufacture (fabrication), packaging, physical manipulation (e.g. milling), sterilization, sterilization of equipment or primary component of a container closure system (e.g. gamma irradiation) and testing of the drug substance or intermediates. If certain companies are responsible only for specific steps (e.g. milling of the drug substance) this should be indicated. The list of manufacturers should specify the actual addresses for the location where the relevant manufacturing or testing operation will be performed, rather than the administrative offices. Manufacturing sites for sterile drug substances and sites which are responsible for generating test results for release purposes for all drug substances are required to have a Drug Establishment licence or be listed on a Drug Establishment Licence in accordance with guidance from the Regulatory Operations and Regions Branch. GMP requirements for sites involved in Drug Substance manufacturing may have been published in amendments to the *Food and Drug Regulations*. Current submission requirements are on the notice Submission Filing Requirements - Good Manufacturing Practices (GMP)/Establishment Licences (EL). Where applicable (e.g. the manufacture of sterile drug substances, testing facilities), the manufacturing, packaging, labelling and testing facilities for sterile drug substances and release testing sites should have been confirmed by the Regulatory Operations and Regions Branch to be GMP compliant prior to submitting an application.

If a MF is filed with Health Canada and is cross-referenced for certain proprietary information (e.g. sections Modules S.2.2, S.2.3, S.2.4, S 2.5 and S.2.6), the MF number assigned by Health Canada should be provided in the QOS, CPID and Module 1. Reference to a CEP should also be included, if applicable.

References:

ICH Q7

Good Manufacturing Practices (GMP) for Active Pharmaceutical Ingredients (API) guidelines (GUI-0104)

Good Manufacturing Practices (GMP) Guides

Master Files (MFs) - Procedures and Administrative Requirements

S.2.2 Description of Manufacturing Process and Process Controls

The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance. Information should be provided to adequately describe the manufacturing process and process controls. For example:

A flow diagram of the synthetic process(es) should be provided that includes chemical structures (reflecting stereochemistry where applicable) of API starting materials, intermediates, and drug substance and identifies reagents and solvents. It can be supplemented by text if necessary.

A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of yield, critical steps and critical process controls (i.e. process parameters (e.g. temperature, pressure, pH, time) and in-process tests). The level of detail required in the manufacturing description depends on the significance of the process parameters in determining product quality, and information on reaction conditions and controls will generally increase for late stage synthetic and purification steps.

Alternate processes, which are validated, should be explained and described with the same level of detail as the primary process. Any data to support this justification should be either referenced or filed in S.2.6 of Module 3.

Reworking procedures are considered to be unexpected occurrences and are not pre-authorised as part of the marketing authorization. As a result, reworking procedures should not be included in regulatory submissions. Any reworking of batches is authorized on a case-by-case basis in accordance with principles defined by good manufacturing practices.

Reprocessing activities are considered to be foreseen as occasionally necessary and could be proposed and described in a submission provided that it includes the same level of detail as the primary process. However, if such proposed reprocessing is used or intended to be used for a majority of batches, such reprocessing should be included as part of the standard manufacturing process.

Any reprocessing and reworking activities are expected to be conducted as per Canadian Food and Drug Regulation C.02.014, the Health Canada GMP for API Guide (GUI-0104) - Interpretation under C.02.014, and ICH Q7.

The information on the manufacturing process should start from well-characterized API starting materials. The manufacturing process for the batch(es) used in the clinical and/or comparative bioavailability and primary stability studies should be representative of the process to be used for commercial purposes (i.e. laboratory scale batches are not considered acceptable).

If the manufacturing process includes one or more design spaces, this/these should be clearly identified in S.2.2, with supporting data in S.2.6. If Proven Acceptable Ranges (PARs) have been developed for some process parameters, the target/normal operating ranges (NORs) for all process parameters and PARs for which supporting data have been provided in S.2.6 should be included in the process description in S.2.2. However, a combination of PARs does not constitute a design space and it is expected that the manufacturing process will be conducted within the NORs for all process parameters, with excursions into the PAR for only a single parameter at a time.

API Starting Materials:

An API starting material is proposed by the applicant and assessed by Health Canada to determine whether the controls on the drug substance (e.g. impurities) and drug substance manufacturing process (e.g. control strategy, critical process controls, intermediate testing) can provide appropriate control of quality. The selection of a particular compound as the API starting material and its specifications should be justified. ICH Q7 defines the point from which GMP requirements apply to the synthetic process.

ICH's Q11 guideline describes the general principles that should be collectively considered when selecting and justifying API starting materials. In most cases, information on the preparation of the API starting material (e.g. flow chart, reagents, potential impurities) should be provided (e.g. in sections S.2.3 and S.2.6, as appropriate) in order to fully characterize the impurity profile and to justify the specifications for the API starting material and the drug substance. The information provided should permit the complete assessment of the safety and quality of the drug substance. In some cases, this information may precede the API starting material by several steps in the synthetic process. The level of detail required in the manufacturing description depends on a number of factors, including the criticality of the process parameters in determining product quality.

The information on the preparation and relevant data for the API starting materials should be provided in sufficient detail to support the justification for the selection of the API starting material and that the API starting material and drug substance specifications are appropriate (e.g. for the control of the impurity profile).

Acids, bases, salts, esters and similar derivatives of the drug substance and the racemate of a single enantiomer drug substance are considered final intermediates and should not be declared as API starting materials.

Each branch of a convergent drug substance synthesis should contain one or more API starting materials unless the point of convergence is upstream (i.e. earlier in the synthesis) of the proposed API starting material.

Information on the Drug Substance Manufacturing Process

Information on the preparation and purification of the drug substance and the API starting material should be provided (e.g. in sections S.2.2, S.2.3 and S.2.6, as appropriate) in a manner that allows the assessment of the fate and purging of all potential impurities, including theoretical, specified unidentified and identified impurities (regioisomeric and stereoisomeric impurities, toxic (including mutagenic) impurities, residual solvents and elemental impurities (e.g. residues of catalysts)) in the API starting material, intermediates and the drug substance.

This information should include:

- A flow chart and brief narrative description of the synthesis with all the reagents, solvents, and intermediates specified should be provided in the QOS.
- From the API starting material(s) onwards, complete details of the process are necessary, and these should include quantities of raw materials, description of equipment (for equipment which is critical to the product quality), reaction conditions, in-process controls, percent yields, etc.

Sterile Drug Substances

If the drug substance is prepared as sterile, a complete description should be provided for the method used in the sterilization. The controls used to maintain the sterility of the drug substance during storage and transportation should be provided. Results of process validation studies of the sterilization process should also be included in S.2.5.

Drug Substances Manufactured using a Fermentation Process

In addition to the above information, the data provided for a drug substance produced by fermentation should include:

a. source and type of micro-organism used;
b. procedures and controls for preparation of master and working cell banks
c. composition of media;
d. control of microbial bioburden in the fermentation process;
e. precursors or metabolic substrates if applicable;
f. additional details on how the reaction conditions are controlled (e.g. times, temperatures, rates of aeration); and
g. name and composition of preservatives;
h. potential for the presence of adventitious agents based on the type of micro-organism used (e.g. mycotoxins, enzymes).

Drug Substances of Plant (botanical) Origin

For drug substances of plant origin where the entire API structure is isolated intact from a plant source, include a description of the botanical species and the part of plant used, the geographical origin and, where relevant, the time of year harvested. The nature of chemical fertilizers, pesticides, fungicides, etc. should be recorded, if these have been employed during cultivation. Potential sources of contamination due to the origin should be documented (e.g. soil composition). The information to be submitted will depend on the controls and characterization of the botanical material, however it may be necessary to document all processing steps after harvesting (e.g. drying equipment and time, treatment of plant material (e.g. solvent extraction, pesticides)) to justify controls. Appropriate limits for residues resulting from such treatment should be included in the drug substance specification or as in-process controls. Discussion, including supporting data, should be provided to demonstrate absence of toxic metals and radioactivity.

Micronized/milled or Compacted Drug Substances

Micronization or milling is a critical step for certain drug substances, e.g. for a low solubility drug substance used in a tablet or powder inhalers or to ensure process capability. In such instances, the type of equipment (e.g. make and milling sieve) and critical process parameters or the procedure used to establish the parameters for a batch (equipment setting, and operating conditions) necessary to produce lots with consistent particle size distribution should be described. The same information should be provided for compacted materials.

Design Space

The design space can be described in this section (and if appropriate in S.2.4). The manufacturing process development section (S.2.6) is the appropriate place to summarize and describe studies which provide the basis of the design space.

Non-isolated Intermediates

If an intermediate is not isolated, an in-process control to test for completeness of reaction should be included before advancing to the next step, unless otherwise justified (e.g. in a case when a reaction resulting in a non-isolated intermediate is consistent and well controlled). Tests for completeness of reaction are deemed to be critical and should be included in S.2.4 unless data is provided to support that the completion of the reaction is non-critical.

References:
ICH Q7, Q8, Q11, M7

S.2.3 Control of Materials

Materials used in the manufacture of the drug substance (e.g. raw materials, API starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process.

Information on the quality and control of these materials should be provided. Information demonstrating that materials meet standards appropriate for their intended use should be provided, as appropriate.

The names and addresses of each manufacturing site of an API starting material should be provided along with the route of manufacture at each site. The data provided should justify the proposed API starting material specifications and the purging of potential impurities (including known and potentially mutagenic impurities) should be discussed. This information may be cross-referenced to a MF, however in that case the MF Holder should provide an attestation to inform the drug product manufacturer if there is any change in the supplier of the API starting material or in the route of synthesis for the API starting material.

The specification of a starting material should include tests for identity and purity (e.g. controls on impurities) and, where applicable, could include acceptance criteria for assay, specified, unspecified and total impurities, residual solvents, reagents, elemental impurities and mutagenic impurities. The applicant should provide justification of the tests included on the specifications (e.g. purging studies). Special consideration should be given to potential isomeric impurities and mutagenic impurities, particularly those that could be carried through the synthesis to the drug substance.

For drug substances, or drug substances manufactured with reagents obtained from sources that have potential of transmitting Transmissible Spongiform Encephalopathy (TSE) agents (e.g. ruminant origin), a letter of attestation (with supporting documentation) should be provided confirming that the material is not from a TSE affected country/area, and/or data should be provided demonstrating that the material is not at risk of transmitting TSE (e.g. an EDQM Certificate of Suitability). Attestation and/or evidence that Specified Risk Materials are excluded and appropriate production methods are used to ensure TSE inactivation should be provided.

References:

ICH Q6A, Q11, M7
Stereochemical Issues in Chiral Drug Development
Master Files (MFs) - Procedures and Administrative Requirements
EDQM guidance documents related to TSE risk reduction
Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3) (2011/C 73/01)

S.2.4 Controls of Critical Steps and Intermediates

Critical Steps: Tests and acceptance criteria (with justification including process development data in S.2.6) performed at critical steps identified in S.2.2 of the manufacturing process to ensure that the process is controlled should be provided.

Process parameters considered critical (e.g. temperature, equipment controls during micronization) should be listed and scientifically justified (e.g. in S.2.6).

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Generally, these specifications would include tests and acceptance criteria for appearance, identity, purity, and assay. Well-defined controls of potential impurities should be included. Special consideration should be given to potential isomeric impurities and mutagenic impurities, particularly those that could be carried through the synthesis to the drug substance.

Non-isolated intermediates

Where the test for completeness of reaction is critical it should be listed in this section.

References:
ICH Q6A, Q11
Stereochemical Issues in Chiral Drug Development

S.2.5 Process Validation and/or Evaluation

Process validation and/or evaluation studies for aseptic processing and sterilisation should be included in the submission (e.g. a validation report for the sterilization steps).

It is expected that the manufacturing processes for all drug substance are properly controlled and validated before the commercial distribution of the resulting drug product. For **non-sterile** drug substances, process validation and/or evaluation studies need not be provided in a regulatory submission.

References:
Good Manufacturing Practices (GMP) Guidelines
Validation Guidelines for Pharmaceutical Dosage Forms
ICH Q7, Q11

S.2.6 Manufacturing Process Development

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

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

This section is the appropriate place to summarize and describe process development studies that provided the basis for the design space(s) or which are used to justify specifications, manufacturing parameters, etc.

Where a QbD approach has been used for development of the drug substance synthesis, care should be taken to:

a. use terminology in a manner that is consistent with ICH definitions (e.g. Proven Acceptable Ranges (PARs) vs. design space).
b. be clear about claims and proposed flexibility supported by enhanced development (e.g. design space(s), PARs, Real Time Release (RTR) Testing, omission of API specification test for impurity(ies)).
c. discuss the role of QbD in the overall control strategy (e.g. describe purging studies to demonstrate removal of impurities from synthetic process).

Where PARs or a design space have been claimed in S.2.2, studies which support the proposed ranges should be described in S.2.6. Studies conducted to assess criticality of process parameters or material attributes identified in S.2.3 and/or S.2.4 should also be described in S.2.6.

Any differences in stereochemistry, polymorphic form or particle size distribution of the drug substance used during development compared to the drug substance used in the commercial product should be discussed in terms of the potential impact on the drug product performance, safety and efficacy. References to specific sections in the drug product pharmaceutical development (P.2) should be made as necessary.

References:
ICH Q3A, Q7, Q8, Q11

S.3 Characterisation

S.3.1 Elucidation of Structure and other Characteristics

Confirmation of the molecular structure of the drug substance, based on spectroscopic and other relevant techniques, should be provided. Data should be provided that addresses potential isomerism, including absolute and relative stereochemistry, where applicable. When elucidating the internal structure of the drug substance (such as amorphous or alternative crystalline forms), characterization should use appropriate techniques (such as single crystal and powder x-ray diffraction). Samples that are representative of the proposed manufacturing process should be used.

Module 3 should include copies of the spectra, peak assignments, and a detailed interpretation of the data.

For drug substances with a compendial reference standard, it is generally sufficient to provide copies of the Infrared (IR) and Ultraviolet (UV) spectra of the drug substance for each source. The sample should be run concomitantly with a suitable primary reference standard. A suitable primary reference standard could be obtained from the Schedule B compendia (e.g. USP, Ph.Eur, BP) or a batch of the drug substance that has been fully characterized (e.g. IR, UV, Nuclear Magnetic Resonance (NMR), Mass Spectra (MS)). See section S.5 for further details on References Standards or Materials.

If comparative studies with the Canadian Reference Product are necessary to establish equivalence (e.g. for polymeric APIs in an ANDS), Module 3 should include data from the comparative physicochemical studies performed.

The studies carried out to elucidate and/or confirm the chemical structure of new chemical entities normally include IR, UV, NMR, and MS studies. Other tests could include elemental analysis, X-ray diffraction (XRD), solid state studies or Molecular weight distribution where relevant.

It is recognized that some drug substances (e.g. certain antibiotics, enzymes, and peptides) present challenges with respect to structural investigation. In such cases, more emphasis should be placed on the purification and the specification for the drug substance to ensure a reproducible drug substance.

If a drug substance consists of more than one active component (e.g. conjugated estrogens), where possible, the physicochemical characterization of the components and their ratio should be submitted. A justification should be provided for why the information is not available and that the lack of information is not relevant or critical.

Summarization of Data in the QOS:

The QOS should include a list of the studies performed, a brief summary of results, and a conclusion from the studies (e.g. if the results support the proposed structure). In addition, to establish pharmaceutical equivalence, a summary of any comparative studies should be included.

Potential for Isomerism and Identification of Stereochemistry:

When a drug substance contains one or more asymmetric centres, structural elucidation should confirm whether the drug substance is a specific stereoisomer or a mixture of stereoisomers or a meso isomer.

If, based on the structure of the drug substance, there is no potential for isomerism, it is sufficient to include a statement to this effect.

Polymorphs:

The potential of polymorphism should be investigated and discussed in terms of potential impact to the drug product performance, safety and efficacy. References to specific sections in the Drug Product Pharmaceutical Development section (P.2) should be made as necessary. Results from an investigation of several batches of

the drug substance, recrystallized from several solvents, should be provided to determine if the drug substance exists in more than one crystalline form. The study should include the characterization of the batch(es) used in the clinical and/or comparative bioavailability studies, using a suitable method (e.g. X-ray Diffraction (XRD), Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR)). The absence of the potential for polymorphism can further be confirmed by providing the results of a literature search.

Polymorphism can also include solvation or hydration products (also known as pseudopolymorphs) which should be appropriately characterized using solid state studies.

Particle Size Distribution:

The particle size distribution of the drug substance can have an effect on the in vitro and/or in vivo behaviour (e.g. absorption of the drug from the gastrointestinal tract) of the drug product, in particular for low solubility drug substances. Particle size can also be important in dosage form performance (e.g. optimum delivery of inhalation products to the lungs), achieving uniformity of content in low-dose tablets (e.g. 5 mg or less), achieving a smooth suspension to prevent irritation in ophthalmic preparations, and stability and redispersibility of suspensions.

If particle size distribution is important (e.g. as in the above cases, nanosized particles), results from an investigation of at least three, pilot or commercial scale, batches of the drug substance should be provided, including characterization of the pivotal batch(es) (e.g. batches used in the pivotal clinical and/or comparative bioavailability studies). Justification of specifications should be presented in S.4.5 in accordance with ICH recommendations. If applicable, the acceptance criteria should include controls on the particle size distribution to ensure consistency with drug substance in the batch(es) used in pivotal studies (e.g. limits for d_{10}, d_{50}, and d_{90}). The following is provided for illustrative purposes as possible acceptance criteria for particle size limits:

D(v,0.9) NMT XXX micrometer (µm)
D(v,0.5) XX-XX µm
D(v,0.1) NLT XX µm (if control of fines is necessary)

The choice of particle size acceptance criteria (single point, multiple point controls) should be discussed based on the desired goal for particle size control and the particle size distribution observed (e.g. bimodal, polydisperse, monodisperse). Histograms should be provided to show the distribution observed.

If the drug substance is dissolved during the drug product manufacturing process then control of particle size distribution may not be necessary.

Biopharmaceutics Classification System (BCS) information:

If known, the relevant information should be provided as per the Biopharmaceutics Classification System Based Biowaiver Guidance Document.

The information on drug substance particle size, BCS information and in-situ conversion may be discussed in other sections of the CTD such as S.2.6, S.4.5, P.2).

References:

ICH Q6A
Stereochemical Issues in Chiral Drug Development

S.3.2 Impurities

Information on impurities should be provided.

Identification of Potential and Actual Impurities:

The study of impurities can be considered one of the most important aspects of the Quality portion of the drug submission. The sponsor should provide a discussion of the potential and actual impurities arising from the synthesis, manufacture, and/or degradation. The tables in Health Canada's QOS-CE (NDS/ANDS) template can be used to summarize the information on impurities (e.g. names, structures, origin, results). The origin refers to how the impurity was introduced (e.g. "Synthetic intermediate from Step 4 of the synthesis", "Potential by-product due to rearrangement from Step 6 of the synthesis"). It should also be indicated if the impurity is a metabolite or degradation product of the drug substance. The discussion on the fate of these impurities should lead to a clear conclusion regarding the need or absence thereof to control them in the drug substance specification. Spiking studies may be necessary to demonstrate purging.

A discussion should be included of the possible isomers that can result from the manufacturing process, the steps where they were introduced, and a summary of the results of the studies carried out to investigate the physical, chemical, and biological properties of these isomers. If there is a preferred isomer or isomeric mixture, the drug substance specification should include a test to ensure isomeric identity and purity.

The list of impurities should include both drug-related impurities (e.g. API starting materials, by-products, intermediates, chiral impurities, degradation products) and process-related impurities (e.g. residual solvents, reagents, catalysts). For process-related impurities, the step where the compound is used or formed in a synthesis should be identified.

Purging of impurities originating from the API starting material and intermediates should be discussed in detail. For non-mutagenic related impurities that are present in intermediates at levels above the ICH identification threshold that are not specified in the final drug substance specifications, they should either be shown to be purged to below this threshold in downstream steps or it should be shown that the analytical method(s) used to test the API for related substances can detect these impurities and hence they are controlled as unspecified impurities. A similar concept may apply to reagents and catalysts which are not detected by the related substance method.

The potential for the presence of adventitious agents, including viral and bacterial agents, residual proteins and TSE agents and the probability of removal by manufacturing processes should be discussed.

Potential impurities should be examined for structural alert(s). Assessment and control of any potentially mutagenic impurities, including the potential formation or introduction of high- potency mutagenic carcinogens identified in the ICH M7 guideline as the cohort of concern (comprising aflatoxin-like, N-nitroso and alkyl-azoxy compounds) should be performed as per ICH M7 when appropriate.

The ability of the related substances analytical method(s) used to detect and control potential impurities (e.g. intermediates) should be discussed (e.g. including potential impurities that would be controlled as unspecified impurities in the final drug substance specifications).

Justification of Proposed Acceptance Criteria:

This justification should be discussed in section S.4.5. The various ICH and Health Canada guidance documents outline a number of options for justifying and qualifying acceptance criteria for impurities. It is recognized by the compendia that drug substances can be obtained from multiple sources, and thus can contain impurities not considered during the preparation of the monograph. Furthermore, a change in the production or source may give rise to impurities that are not adequately controlled by the published compendial analytical procedure. As a result, each drug submission is assessed independently to consider the

potential impurities that may arise from the proposed route(s) of synthesis. Regardless of whether there is a higher general limit for unspecified impurities in a compendial monograph, impurities in synthetic drug substances should be identified and qualified in accordance with the ICH Thresholds. This is in accordance with the expectations as expressed in the General Chapters in the USP (General Notice 5.60.10) and Ph.Eur. (General Text 2034). Health Canada would generally accept the recommendations in Ph. Eur. Table 2034.-2 regarding reporting, identification and qualification of organic impurities in peptides obtained by chemical synthesis (i.e. reporting threshold of 0.1%, ID threshold of 0.5%, qualification threshold of 1.0%), although different thresholds (either higher or lower) should be considered in some cases, depending on the particular indication, dose and duration of treatment.

If there are identified impurities in a compendial monograph (e.g. as in a Ph.Eur. Transparency section) that are not monitored by the proposed routine analytical method, a justification should be provided for their exclusion from the specifications (e.g. the impurities are not formed by the synthetic route). Alternatively, if acceptable justification cannot be provided and a house method is used, it should be demonstrated that the house method is capable of controlling the impurities identified in the compendial monograph at an acceptable level as unspecified impurities (i.e. with a limit corresponding to the Identification Threshold). Method validation data would be provided in S.4.3.

Depending on the nature of the drug substance, and the extent of the chemical modification steps, the general principles on the control of impurities (e.g. identification and qualification) can also be extended to drug substances of semi-synthetic origin. As an illustrative example, a drug substance whose precursor molecule was derived from a fermentation process, or a natural product of plant or animal origin, and has subsequently undergone several chemical modification reactions generally would fall within this scope, whereas a drug whose sole chemical step was the formation of a salt from a fermentation product generally would not fall within this scope. It is understood that there can be some latitude for these types of drug substances provided an acceptable justification supported by a scientific rationale and data is provided (e.g. a limit of NMT 0.20% for unspecified impurities, rather than a limit corresponding to the ICH Identification Threshold).

For a subsequent entry (generic) drug product, actual test results of impurities/degradation products using an acceptable method determined in at least one recent batch of an appropriately stored sample of the Canadian Reference Product should be provided if impurity levels are above ICH Qualification Thresholds. A limit equivalent to the level found in the Canadian Reference Product or a Health Canada authorised marketed generic product would be considered supportive.

The basis for setting the acceptance criteria for the impurities should be provided and discussion in S.4.5. This is established by considering the identification and qualification thresholds for drug-related impurities (e.g. related substances), the threshold of toxicological concern (e.g. for mutagenic impurities) and the concentration limits for process-related impurities (e.g. residual solvents) as per the applicable ICH guideline (e.g. Q3A, Q3C, M7). For drug related impurities, these thresholds are determined on the basis of potential exposure to the impurity, i.e. by the maximum daily dose (MDD) of the drug substance and the duration of treatment (e.g. acute vs chronic) considering all doses and routes of administration. This is normally achieved by using the highest potential MDD, rather than the maintenance dose. For injectable products, the maximum hourly dose of the drug substance should also be considered to justify that acute toxicity is not an issue.

The acceptance criteria for total impurities should be set taking into consideration the actual levels of impurities found in several batches of the drug substance from each source, including the levels found in the batches used for the nonclinical, clinical, comparative and stability studies. For quantitative tests, it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or

"conforms". In the cases where a large number of batches have been tested, it is acceptable to summarize the total number of batches tested with a range of analytical results.

Whenever a proposed acceptance limit for an impurity or degradation product exceeds the applicable ICH Q3A/B(R2) qualification thresholds, the sponsor should ensure that **all** the required toxicological studies or other scientifically acceptable justification such as metabolite studies and data (as per ICH) supporting the proposed limit is included in the submission (Module 4). It is essential to establish the link between the proposed qualified limit for a specified impurity and the study(ies) in which it was qualified (i.e. the toxicity study). A clear reference as to where the qualification studies can be found in Module 4 should also be included in both the QOS and Module 3. The use of a tabulated summary in the QOS which includes batch numbers, levels of impurities and study reference numbers for qualifying studies is strongly encouraged.

Elemental impurities should be addressed in way that compliance of the drug product with ICH Q3D can be affirmed.

Safety information should be provided in Module 4 to qualify the limits for Residual solvent(s) not listed in ICH Q3C guidance (e.g. by calculating the Permitted Daily Exposure (PDE) limit using NOAEL/NOEL obtained from scientific literature).

Mutagenic impurities:

Actual impurities and potential impurities likely to be present in the drug substance should be evaluated for mutagenic potential as described in ICH M7. This assessment and the control strategies proposed by the applicant for identified mutagenic or potentially mutagenic impurities should be described in the dossier. The assessment may be described in S.3.2 or a reference included to discussion elsewhere in the submission.

Summarization of Data in the QOS:

The QOS should include summaries of the data on potential and actual impurities arising from the synthesis, manufacture and/or degradation, and should summarize the basis for setting the acceptance criteria for individual and total impurities. It should also summarize the impurity levels in batches of the drug substance used in the non-clinical studies, in the clinical trials, and in typical batches manufactured by the proposed commercial process. Summaries should be precise and include ranges of impurities rather than actual data unless the actual impurity level is critical for justifying the sponsor's position (e.g. in qualification studies).

The QOS should include information on how the proposed impurity limits are qualified. For any predicted or confirmed mutagenic impurity, a detailed description of the control strategy (supported by data) to ensure levels below the Threshold of Toxicological Concern (TTC of 1.5 µg/day, or higher as applicable in accordance with ICH M7) in both the drug substance and drug product should be included in the submission. The sponsor should ensure that any toxicological studies and data ruling out mutagenicity of any impurity (e.g. AMES test) are included in the submission (Module 4). A clear reference as to where the qualification studies can be found in Module 4 should also be included in both the QOS and Module 3. If a complete description of impurities is not included in this section, then the QOS should include references to the appropriate sections for relevant information on impurities (e.g. S.4.4 Batch Analyses, S.2.4 Controls, Module 4 for toxicity information). Where data could appear in multiple sections, cross-referencing should be used to direct the assessor to the relevant sections.

References:

ICH Q3A, Q3C, Q3D, Q6A, M7
Stereochemical Issues in Chiral Drug Development
Nitrosamine impurities in medications: Guidance

S.4 Control of the Drug Substance

S.4.1 Specification

The specification for the drug substance should be provided.

As defined in ICH's Q6A guidance document, a specification is a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug substance, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and authorised by regulatory authorities as conditions of authorisation.

The assay should include the chemical formula so that it is clear as to how the dose is declared (i.e. free acid/base vs. salt).

Chemical names or unambiguous designations of impurities (e.g. USP or Ph.Eur. naming conventions or unambiguous company codes) that align with the description of the impurity structures in S.3.2 of Module 3 or in the analytical procedure should be used in the drug substance specification and the summary of the specification in 2.3.S.4.1 and in the CPID.

Specifications

A copy of the drug substance specification from the company responsible as per C.02.009 (5)(c) of the *Food and Drug Regulations* for release of the drug substance for drug product manufacture should be provided. The specifications should include tests, acceptance criteria, and reference to analytical methods, in a manner that clearly identifies the methods used. The specification reference number, version, and date should be provided for version control purposes. For drug substances where a compendial monograph exists, the specification can include reference to the compendial analytical procedures in the current version of the monograph with details of any non-compendial analytical procedures to be used.

Specifications must be acceptable to the Minister. If a Prescribed Standard (e.g. a Canadian Standard Drugs is listed in Part C, Division 6 of the *Food and Drug Regulations*) then the specifications must meet this standard. If a Compendial Standard as per Schedule B of the *Food and Drugs Act* (e.g. USP, Ph.Eur., BP) is declared, then the specifications must meet all compendial requirements (including general chapters) as per the applicable pharmacopoeia.

If a Schedule B compendial monograph is applicable to the drug substance, a sponsor can choose to declare a Manufacturer's Standard on the labelling (which indicates that the material may differ in some respect from the compendial standard).

ICH's Q6A guidance document outlines recommendations for a number of universal and specific tests and criteria for drug substances. If the results of studies conducted on the physical and chemical properties of the various crystalline forms indicate that there is a preferred polymorph, a control strategy that may include a test in the drug substance specification should be described in the dossier. This control strategy should ensure polymorphic equivalence of the commercial material to the batch(es) used in the clinical and/or comparative bioavailability studies. If the polymorphic form is unstable the test criteria should be capable of monitoring for conversion of polymorphic form.

Generally, controls on polymorphism are less likely to be necessary for drug substances that are highly soluble (as determined by the dose/solubility volume), although potential impact of polymorphism on manufacturability and stability should be considered. Justification of proposed controls or exclusion of

controls for polymorphism should be provided and supported by data, in particular for low solubility drug substances. Where the drug substance is a solvate or a hydrate, specifications for the solvated drug substance should include a range for the percent content by weight of the solvent supported by data.

A test for bacterial endotoxins with an appropriate limit should be included in the specifications for drug substances used in injectable products.

The drug substance specification should include routine testing for nitrosamine impurities when the risk for presence is high or the concentration of any nitrosamine is at significant levels (for example, greater than 30% of the acceptable intake limit).

Periodic test schedules 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. The data required to support testing which is not performed on a batch-by-batch basis varies. In general, to reduce or skip testing after a certain point, supporting data from commercial scale batches using the current manufacturing method should be provided. The number of batches necessary to support reduced testing will be based on the risk of failure of a batch (e.g. less testing will be necessary to support that a theoretical impurity is not formed than to show that a particular parameter routinely complies with a specification). Any proposal for periodic test schedules or alternate testing frequencies should be clearly highlighted in the discussion of the specifications and should be fully justified and based on sufficient supporting data, scientific rationale and a suitable risk assessment (e.g. data from a minimum 3 commercial batches). Reduced testing schedules are always assessed on a case-by-case basis and will only be considered in cases where the supportive data are obtained from commercial scale batches.

Summary of specifications in the QOS:

The specification can be summarized according to the table recommended in Health Canada's QOS-CE (NDS/ANDS) template including the Tests, Method Types, Sources, and Code Number/Version/Date. The acceptance criteria should also be provided in the summary of the specification. The Method Type should indicate the kind of analytical procedure used (e.g. visual, FT-IR, UV, HPLC, Ultra Performance Liquid Chromatography (UPLC), laser diffraction); the Source refers to the origin of the analytical procedure (e.g. USP, Ph.Eur., BP, House); and the Code Number/Version/Date should be provided for version control purposes.

References:

ICH Q3A, Q3C, Q3D, Q6A, M7
Stereochemical Issues in Chiral Drug Development
Nitrosamine impurities in medications: Guidance

S.4.2 Analytical Procedures

The analytical procedures used for testing the drug substance should be provided.

In-house analytical procedures used for routine testing should be provided in Module 3. Method development history and summaries of changes between current and Historical analytical procedures that have been used during drug development, but are not intended for routine testing purposes, can be provided in this section, however information regarding method development history should be clearly explained in S.4.4 (for batch analyses) or S.7.3 (for stability testing), if it is applicable. Unless modified, it is not necessary to provide copies of Schedule B compendial analytical procedures. For modified Schedule B compendial analytical procedures, complete details of the revisions/modifications should be described. There are restrictions in the compendia as to allowable modifications to methods. If compendial procedures are modified to a greater extent than that allowed by the compendia the method should be claimed as a house method and full details provided in the submission.

Although HPLC/UPLC is normally considered the method of choice for determining drug-related impurities, other chromatographic methods such as GC and TLC can also be used if appropriate and justified. Generally, for impurity methods, reference standards should be prepared for each of the identified impurities, particularly those suspected or known to be toxic, and the concentration of the impurities quantitated against their own reference standards. It is considered acceptable to use the drug substance as an external standard to estimate the levels of impurities if justified (e.g. the response factors (RF) are greater than 80% when compared to the RF for the drug substance). In cases where the response factor is not close to that of the drug substance, it is acceptable to use the drug substance as an external standard, provided a correction factor is applied or the impurities are, in fact, being overestimated. Unspecified impurities should be quantitated using a solution of the drug substance as the reference standard at a concentration corresponding to the limit established for unspecified impurities (i.e.. the ICH Identification Threshold).

System suitability tests (SSTs) are an integral part of chromatographic analytical procedures. At a minimum, HPLC, UPLC and GC methods should include SSTs for repeatability for assay methods and repeatability and resolution for impurities. Determination of repeatability for control of drug-related impurities is typically done using a solution of the drug substance with a concentration corresponding to about the limit for unspecified impurities. The SSTs serve to demonstrate that the chromatographic system is capable of producing accurate and reproducible results at the concentrations under test. In accordance with the USP General Chapter on Chromatography, the repeatability test should include an acceptable number of replicate injections (i.e. five or six). Resolution of the two closest eluting peaks is generally recommended. However, choice of alternate peaks can be used if justified (e.g. choice of a toxic impurity). Number of theoretical plates and tailing factor can be used as additional SSTs for column performance or if there are no suitable impurities for the determination of resolution. For TLC methods, the SSTs should verify the sensitivity and ability of the system to separate impurities (e.g. by applying a spot corresponding to the drug substance spiked at a concentration corresponding to the limit of unspecified impurities).

The summary of the analytical procedures in the QOS should provide a sufficient level of detail to be accurate and concise. This would include details on the various parameters of the method (e.g. as in the case of an HPLC/UPLC impurity method, a summary of the column, mobile phase, detector, sample/reference solution preparation, SSTs). A brief tabulation of the data is recommended (where the level of detail of the summary of the analytical procedures will interrupt the flow of the QOS, the tables can be appended to the QOS). Care should be taken to clarify the data describing solution concentration particularly when it is listed in terms of percentage units (e.g. a foot-note can be added to clarify whether percentages are against the label claim of the drug substance or as % w/w or % w/v).

References:

ICH Q2
General Chapters of the USP and Ph.Eur.

S.4.3 Validation of Analytical Procedures

Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance, should be provided.

Validation reports for the analytical procedures employed for routine testing should be provided in S.4.3 of Module 3. Validation of current methods to show equivalency with historical methods should be provided if historical methods were used during pivotal clinical trials or during pivotal stability studies. This should be provided in Sections S.4.4 (for batch analyses) or S.7.3 (for stability testing), whichever is applicable.

Different sources of the same drug substance may exhibit different impurity profiles which may not have been considered during the development of the monograph and the extent of studies which should be provided is determined by the novelty of the impurities. If compendial methods are modified to include a

limit for unspecified impurities at the ICH identification threshold, the method should be validated to ensure that it is sufficiently sensitive and precise at that lower limit. If a Schedule B compendial method is used to control specified impurities that are not listed in the monograph, full validation is expected for those specified impurities.

If a Schedule B compendial standard is claimed and a House method is used in lieu of the compendial method (e.g. for assay or for specified impurities), equivalence of the House and compendial methods should be demonstrated. This could be accomplished by performing analyses of a batch containing significant levels of impurities by both methods and providing comparative results from the study. Alternate approaches to demonstrating equivalency of analytical procedures should be scientifically justified.

With respect to the control of residual solvents, it is acknowledged that GC methods for determining residual solvents are generally sensitive, linear, and reproducible. In past experience, it has been found that a sponsor will use essentially the same GC method to determine residual solvents in a number of drug substances. Therefore, although it is expected that a company will initially perform full validation of the methods used to determine residual solvents, it is acceptable that only limited validation data be submitted (e.g. recovery, repeatability, limit of detection/limit of quantitation, and selectivity of the method). Recovery and repeatability should be determined using a sample of the drug substance spiked with the residual solvents at their acceptance criteria.

It should be ensured that the summary of the validation reports for the analytical procedures included in the QOS provides a sufficient level of detail and is accurate and concise. This would include details on the various validation parameters (e.g. as in the case of the validation an HPLC/UPLC impurity method, a summary of the results for specificity, linearity, range, accuracy, precision (repeatability, intermediate precision), LOD, LOQ, robustness, stability of solutions). A tabulation of the data is recommended (where the level of detail of the summary of the analytical procedures will interrupt the flow of the QOS, the tables can be appended to the QOS). It is recommended that the tables are used for summarizing analytical validation data in the QOS. Care should be taken to clarify the data describing solution concentration particularly when it is listed in terms of percentage units (e.g. a foot note can be added to clarify whether percentages are against the label claim of the drug substance or as % (w/w) or (w/v)). Representative chromatograms should be provided with the validation report.

If validation of analytical methods has not been performed in a GMP compliant facility, the method transfer protocol should be provided. This protocol should include impurity studies where the impurities are present at close to the specified limits or are spiked at the limits.

References:

ICH Q2

S.4.4 Batch Analyses

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

It is expected that drug substance lots used to manufacture drug product lots used in pivotal clinical studies and those submitted in the regulatory application (e.g. to establish specifications for assay, purity and retest period) are manufactured and tested according to the principles of GMP in order to ensure the reliability of the analytical test results. Deviations and Out of Specification (OOS) test results should be investigated in a timely manner and the results of the investigation summarized in the submission. Justifications with supporting data where necessary should be provided to support the use of the identified lots for setting regulatory specifications for release and stability.

A tabulated summary in the QOS of batch number, batch size, date and site of production, and specific use including clinical/pre-clinical study information, the testing site, etc. should be provided for the batches used

to support the drug submission. The test site for pivotal batches should be clarified if multiple testing sites are possible. Of the batches included, analytical results should be provided in Module 3 for those batches used in nonclinical, clinical, comparative bioavailability, comparative in vitro, and stability studies, including 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 process to be used for, production batches.. If the scale of the batch is less than 1/10th commercial scale, a justification of why the smaller scale is representative should be provided. The number of batches should be sufficient to support the specification(s) and assess consistency in manufacturing. Analytical results from a GMP compliant laboratory should be provided for at least two batches from each proposed manufacturing site of the drug substance.

Certificates of analysis should be provided for the pivotal batches but may be provided in the regional information. In Module 3 a tabulated summary of batch analysis results should be provided and be sufficiently detailed including range, mean and relative standard deviation, where applicable, of individual results, results of all tests conducted, quantitative results for all tests ('complies' is not sufficient), RRT (or other specific designation of impurities) and quantity of all unspecified impurities greater than the ICH reporting limit or the Limit of Quantitation (LOQ), as long as the LOQ is less than or equal to ICH reporting limits, and limits of detection where applicable (e.g. when impurities are not detected). Results of additional tests may be provided here or in S.4.5 to justify omission of certain tests from the specification.

The discussion of 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. For quantitative tests (e.g. individual and total impurity tests, assay, residual solvents), it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms". When results are reported as 'none detected', 'less than LOD' or 'less than LOQ', a footnote should be included that specifies the LOD and LOQ value for each analytical method or impurity as applicable. A discussion and justification should be provided for any incomplete analyses (e.g. batches not tested according to the proposed specification).

If the batch analyses have been discussed elsewhere in the drug submission (e.g. S.3.2 Impurities) these data should be cross-referenced rather than repeating the information.

References:

ICH Q3A, Q3C, Q6A
Stereochemical Issues in Chiral Drug Development

S.4.5 Justification of Specification

Justification for the drug substance specification should be provided.

This should include a discussion on the inclusion or exclusion of certain tests, choice of analytical procedures, acceptance criteria, and take into account any applicable compendial standard, etc. If the Schedule B compendial methods have been modified or replaced, a discussion should be included. Limits for specified, identified impurities in a compendial monograph are considered qualified. However, general limits in a compendial monograph for unspecified impurities that exceed the applicable ICH Identification Threshold are not considered acceptable (e.g. a general compendial limit of NMT 0.2% for unspecified impurities would not be considered acceptable when the applicable ICH Identification Threshold is NMT 0.10%). Furthermore, a general limit for unspecified impurities would not be considered acceptable as qualification for a new identified impurity if it exceeds the applicable ICH Qualification Threshold.

If this information is discussed in P.2 or S.2.6, then a cross-reference to the appropriate CTD section where the information is included is sufficient.

This section should be used to include elements of the overall drug substance control strategy. Ideally this should be provided in tabular form as per the examples ICH Q11. Alternatively, a cross reference should be provided to the position of the summary of the control strategy elsewhere in Module 3 (e.g. S.2.6)

The justification for certain tests, analytical procedures, and acceptance criteria may have been discussed in other sections of the drug submission (e.g. impurities, particle size) and does not need to be repeated here, although a cross-reference to the location of the discussion should be provided.

References:
ICH Q3A, Q3C, Q3D, Q6A, Q11, M7
Stereochemical Issues in Chiral Drug Development

S.5 Reference Standards or Materials

Information on the reference standards or reference materials used for testing of the drug substance should be provided.

The source(s) of the reference standards or materials used in the testing of the drug substance should be provided (e.g. for the identification, purity, assay tests).

Primary reference standards can be obtained from official sources such as those recognized in the Schedule B compendia. Primary reference standards from official sources do not need further structural elucidation.

A primary reference standard other than a compendial standard should be highly purified and fully characterized (e.g. FT-IR, UV, NMR, MS). All data supporting structure elucidation, strength and purity should be submitted. Data regarding assay should also be submitted with the assay assigned based on mass balance or a determination of absolute purity.

A secondary reference standard (e.g. working standards) should be standardized against the compendial reference standard or other primary reference standard. The secondary reference standard should be fully characterized to confirm identity (IR and UV spectra should be submitted for both the primary and secondary reference standards run concomitantly) and purity, and data (e.g. chromatograms) or copies of certificates of analyses should be provided.

In all cases, alternate manufacturing processes or additional purification steps used to increase the purity of an API for the purpose of generating a reference standard should be described.

References:
Q6A

S.6 Container Closure System

A description of the container closure system(s) (CCS) should be provided, including the size and identity of materials of construction of each primary packaging component (i.e. in direct contact with the API), and their specifications. The specifications should include description and identification (e.g. IR). Non-compendial methods (with validation) should be included, where appropriate.

For functional secondary packaging components, information relevant to the function should be provided (e.g. capacity to protect against light). For non-functional secondary packaging components (e.g. those that do not provide additional protection), only a brief description should be provided.

The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including sorption

to container and leaching of container components, and/or safety of materials of construction. Examples of this would include confirmation of conformance with USP, Ph.Eur. standards or applicable US Code of Federal Regulations (CFR) or European Commission (EC) Regulations for food safe materials. Certificates of compliance from vendors can be provided to confirm suitability of use of the CCS for the proposed drug substance.

Include whether the product is packaged under an inert atmosphere or if desiccants are added, if applicable.

S.7 Stability

As outlined in ICH's Q1A guidance document, the purpose of stability testing is to provide evidence on how the quality of a drug substance varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a retest period for the drug substance and recommended storage conditions.

Although the ICH stability guidances were developed by ICH to provide guidance on the information that should be provided in new drug applications to ensure the stability of new drug substances and drug products, the recommendations also should be applied to applications for existing drug substances (e.g. generics).

References:
ICH Q1A, Q1B, Q1C, Q1E

S.7.1 Stability Summary and Conclusions

The types of studies conducted, protocols used, and the results of the studies should be summarised. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate. The data summarized in the QOS should be tabulated in a manner that clearly supports the proposed shelf-life and should be condensed to include an overall summary of relevant data rather than data from individual batches (e.g. ranges, highlighting any trends and/or batch to batch variability, if applicable).

Data on unidentified impurities which is reported in accordance with ICH guidelines should be recorded with the relative retention time (or other specific designation) of the peaks to allow for appropriate batch-to-batch and timepoint-to-timepoint comparisons.

Retest period:

The retest period should begin at the date of manufacture of the drug substance. Additionally a retest period for blended batches should be based on the manufacturing date of the oldest tailings or batch in the blend. The use of seed crystals is not considered as blending of batches with regard to the start of the retest period.

Stress testing:

As outlined ICH's Q1A guidance document, stress testing of the drug substance can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. Stress studies should also consider potential changes to physical properties such as polymorphism and particle size distribution. The nature of the stress testing will depend on the individual drug substance and the type of drug product involved. Stress testing (e.g. heat, humidity, oxidation, photolysis, acidic/basic solutions) is normally carried out under more severe conditions than those used for accelerated testing.

The objective of the stress testing study is not to completely degrade the drug substance, but to generate sufficient degradation to achieve its intended purpose. This is typically 10-20% loss of active by assay when

compared with the non-degraded compound. This target is chosen such that some degradation occurs, but it is not so severe that secondary degradation products (i.e. degradation products of degradation products) are generated. Effort should be made to obtain this target level of degradation. Degradation outside of this range should be scientifically justified. Mass balance can be used to demonstrate that methods are stability indicating and all degradation products are detected by the methodology. Mass balance should be demonstrated by comparing the assay and impurities content on the same sample which have been subjected to identical stress conditions.

Tables can be used to summarize the results from the stress testing in the QOS. This summary should include the treatment conditions (e.g. concentrations of solutions prepared, storage temperatures and durations) and the observations for the various test parameters (e.g. assay, degradation products) as well as a discussion of the results (e.g. mass balance, potential impact on drug product manufacture, likelihood of formation of impurities under long term conditions).

Representative chromatograms of stress studies (e.g. showing around 10-20% of degradation of the API) should be submitted.

Accelerated and long term testing:

Recommendations for the stability testing of new drug substances are outlined in various ICH Stability guidelines.

Data on at least three pilot scale batches (at least 10% of commercial scale and representative of the commercial process) or two pilot scale batches and one small scale batch (if justified as representative of the commercial process) should be submitted for existing drug substances (e.g. generics).

Table 1: General case for stability studies of the drug substance

Study	Storage Condition	Minimum Time Period Covered by Data at Submission
Long term	25°C ± 2°C / 60% RH ± 5% RH	12 months (6 months for existing drug substances)
Intermediate	30°C ± 2°C / 65% RH ± 5% RH	6 months (if applicable as per ICH)
Accelerated	40°C ± 2°C / 75% RH ± 5% RH	6 months

Other storage conditions can be proposed based on the proposed labelled storage conditions. It is recommended that alternate storage conditions are based on evaluation of mean kinetic temperature over the labelled storage range.

To support alternate drug substance manufacturing sites that maintain the same route of manufacture and process conditions, a stability commitment should be included to place the first commercial batch of drug product manufactured with drug substance from the alternate site into the long term stability program. When API is micronized or compacted, the stability studies should be carried out using micronized/compacted API unless otherwise justified (e.g. when micronization/compaction is done immediately prior to use by the drug product manufacturer). If the route of synthesis is changed, then results for at least 2 pilot scale batches with a minimum of 3 months of long term and accelerated (or intermediate, as appropriate) testing should be provided at the time of filing. In these cases, it is expected that the original stability data is also available to Health Canada either in the same submission or-cross-referenced to a previously authorised one.

In exceptional cases, information available in the public domain may be sufficient to establish an appropriate retest period, e.g. when a substantial body of evidence exists that establishes that the drug substance is inherently stable. In all instances, sponsors are encouraged to provide all relevant information available on the stability of the drug substance and to fully justify how this information supports the proposed re-test period.

The information on the stability studies should include batch number, batch size, manufacturing site, container closure system, storage conditions and completed/proposed test intervals. The discussion of results 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 potency), it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms". Where trends in the data are noted, these should be highlighted and discussed. Statistical analysis of the data should be used as necessary to justify conclusions.

Proposed storage conditions and retest period:

The proposed storage conditions should normally include a temperature range (e.g. upper and lower temperature limits) representative of temperature conditions for which supporting data were provided. The proposed retest period for the drug substance should be provided.

When the drug substance has been shown to be stable (e.g. under the ICH conditions with long term studies at 25°C ± 2°C/60% RH ± 5% RH and accelerated studies at 40°C ± 2°C/75% RH ± 5% RH) without any adverse trends, the following storage recommendation would generally be considered acceptable:

"Store at room temperature (15°C to 30°C)"

Based on the assessment of the stability data, other storage precautions should be assessed and precautionary statements added to the labelling if warranted (e.g. "Protect from light", "Protect from moisture", "Store in the overwrap provided"). Precautionary statements should not be a substitute for selecting the appropriate container closure system.

After the end of the established retest period, a batch of drug substance destined for use in the manufacture of a drug product should be retested for compliance with the specification and then used immediately, i.e. within 30 days of conducting the test. For drug substances known to be labile (e.g. certain antibiotics), it is more appropriate to establish a shelf life than a retest period.

Monitoring of transportation

For a drug substance posing a higher risk (e.g. sterile drug substance), a transportation study is recommended to support the proposed strategy for shipping and handling until the drug substance is ready to be used for the manufacture of the drug product. The transportation study should be adequate to support conclusions regarding selection of appropriate packaging materials, mode(s) of transportation, necessary controls on shipping conditions (e.g. temperature and humidity), maintenance of sterility, and retest/expiry date. The data that should be included to support the transportation of drug substances will vary depending on the nature of the drug substance and the mode of transportation, but the same principles and recommendations as those described for drug product transportation and products in transit should be considered.

Reference:

Guidelines for Temperature control of Drug Products during Storage and Transportation

S.7.2 Post-approval Stability Protocol and Stability Commitment

The post-approval stability protocol and stability commitment should be provided.

When available long term stability data on commercial scale batches do not cover the proposed retest period or shelf life (as appropriate) granted at the time of approval, a commitment should be made to continue the stability studies post-approval in order to firmly establish the retest or expiry period. The long term stability studies for the Commitment Batches should be conducted through the proposed shelf life/retest period (and the accelerated studies for six months, if relevant) on at least three production batches (see section S.7.1).

At least one batch per year of API 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 Commitment and Continuing batches should include, but are not limited to:

a. Number of batches and batch sizes;
b. Tests and acceptance criteria;
c. Container closure system(s);
d. Testing frequency; and
e. 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.

S.7.3 Stability Data

Results of the stability studies (e.g. forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Tabular formats are preferred for presenting raw data from the stability studies used to support the proposed retest period or shelf life.

P Drug Product

P.1 Description and Composition of the Drug Product

A description of the drug product and its composition should be provided. The information provided should include, for example:

- Description of the dosage form;

The description of the dosage form should include the physical description, available strengths, release mechanism, as well as any other distinguishable characteristics (e.g. "The proposed drug product is available as a blue, oval, immediate-release, film-coated tablet in three strengths (5 milligrams [mg], 10 mg, and 20 mg) each debossed with the markings "XXX". The two higher strengths include a score line to facilitate the breaking of the tablets.").

- Composition, i.e. list of all components of the dosage form, and their amount on a per unit basis (including overages, if any), the function of the components, and a reference to their quality standards (e.g. compendial monographs or manufacturer's specifications);

The composition should express the quantity of each component on a per unit basis (e.g. mg per tablet, mg per millilitre (mL), mg per vial) and percentage basis (e.g. calculated based on the tablet core (if a non-functional coating is applied) or capsule fill weight), including the total weight or measure of the dosage unit.

This should include all components used in the manufacturing process and incorporated in the final drug product (e.g. pH adjusters).

The basis for the declaration of the strength should be clearly evident in the summary of the composition of the drug product.

If the strength is based on a form of the drug substance that is different from the form used 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), then the conversion to the active ingredient should be clearly indicated (e.g. "1.075 mg active ingredient hydrochloride = 1 mg of active ingredient base").

All overages should be clearly indicated (e.g. "Formulated with 2% overage of the drug substance to compensate for validated 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 not acceptable.

The components should be identified by their proper or common names, quality standards (e.g. USP, Ph.Eur., House) and, if an excipient is available in more than one grade, their grades (e.g. "Microcrystalline Cellulose NF (PH 102)").

Intra and extra-granular excipients should be listed separately in tabular form. The qualitative and quantitative composition should be provided for all components or blends (e.g. capsule shells, colouring blends, imprinting inks). Reference to a Master File can be provided for the proprietary quantitative composition; however, the qualitative composition should be included in the submission.

The function of each component (e.g. diluent/filler, binder, disintegrant, lubricant, glidant, granulating solvent, coating agent, antimicrobial preservative) should be identified. Where an excipient could have multiple functions, the most critical function (as per the policy Bioequivalence of Proportional Formulations) should be identified. If the most critical function is not declared, scientific data should be provided to show how the excipient functions in the formulation and evidence that the excipient is not functioning in a more critical fashion. For example, Microcrystalline Cellulose should be assessed as a binder not a filler unless data

is provided to support that its primary function is not as a binder (e.g. other binders are present). If a multifunctional excipient is used and the variation between strengths is greater than what is allowed by the policy Bioequivalence of Proportional Formulations, then justification should be provided in P.2.2 for the proposed variation (e.g. granule size distribution, tablet hardness, dissolution).

Adjustment of a filler at the API dispensing stage to account for as-is-assay of the active pharmaceutical ingredient is acceptable and should be clearly documented (e.g. as a footnote to a composition table).

- Description of accompanying reconstitution diluent(s); and

For drug products supplied with reconstitution diluents that are not commercially available in Canada or have not been assessed and authorized in connection with another drug submission with Health Canada, information on the diluents should be provided in a separate Drug Product ("P") portion, as a subsection under the relevant drug product section, as appropriate.

- Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.

The description for the container closure system used for the dosage form (and accompanying reconstitution diluent, if applicable) should be brief with further details provided under P.7 Container Closure System (e.g. "The product is available in HDPE bottles with polypropylene caps and in PVC/Aluminum foil unit dose blisters.").

P.2 Pharmaceutical Development

The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the application. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and drug product quality. Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical Development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the application.

The pharmaceutical development section should include elements defining the quality target product profile (QTPP) of the drug product as it relates to quality, safety and efficacy. Critical quality attributes (CQAs) of the drug product should be identified.

Typical quality attributes and process parameters vary for different dosage forms. Some attributes could be critical and should be established by the company on a case-by-case basis depending on the complexity of the dosage form and manufacturing process presented by the product.

Dosage and Administration - Directions for Use

The usage instructions found in the Dosage and Administration section of the Product Monograph need to be supported by acceptable data (e.g. in-use periods, compatibility with listed administration media (e.g. juices, apple sauce)/diluents, uniformity of split scored tablets, studies to support sprinkling of the content of capsules on food, dispersion in liquid, use of a feeding tube, storage of admixtures).

The testing to support the in-use period should be performed at the end of the in-use period on a batch near the end of the proposed shelf-life for the drug product and provided in P.8. If data is not available at the time of filing, data based on an in-use study performed at an earlier date and projected stability at the shelf-life should be provided. A commitment should be provided to reconfirm the studies at the end of the shelf-life unless stability data clearly supports that no significant degradation is expected. The testing should be

performed in such a way that the use of the drug product mimics consumer use (e.g. the final remaining amount of the product is tested after opening and closing the bottle and removing product) as listed in the Product Monograph.

If a range of dilution concentrations is listed in the Product Monograph, the results from the studies performed should bracket the listed concentrations.

For existing drug products, (e.g. generics), the Dosage and Administration section and directions for use should be the same as that listed in the Product Monograph of the Canadian Reference Product (e.g. identical diluents/reconstitution solutions, in-use storage conditions and durations, types of containers [if specified]).

A summary and discussion should be provided of the following:

- the measures taken during development to mitigate the presence of high- potency mutagenic carcinogens identified in the ICH M7 guideline as the cohort of concern (comprising aflatoxin-like, N-nitroso and alkyl-azoxy compounds) in the drug product and its components
- a risk assessment for the potential presence of nitrosamine impurities in the drug product
    - provided in sections 2.3 and 3.2.P.2 of the drug application

Relevant analytical data, procedures and proposed controls should be provided in relevant sections of the drug application (e.g. 3.2.S.2, 3.2.S.4, 3.2.S.7, 3.2.P.3, 3.2.P.4, 3.2.P.5, 3.2.P.7, 3.2.P.8)

References:

ICH Q6A, Q8, M7
Validation Guidelines for Pharmaceutical Dosage Forms (including product specific validation guidelines)
Nitrosamine impurities in medications: Guidance

P.2.1 Components of the Drug Product

P.2.1.1 Drug Substance

The compatibility of the drug substance with excipients listed in P1 should be discussed. Additionally key physicochemical characteristics (e.g. water content, solubility, particle size distribution, polymorphic or solid state form) of the drug substance that can influence the performance of the drug product should be discussed. For drug products that are a combination of multiple APIs, the compatibility of drug substances with each other should be discussed.

Specific attributes (CQAs) of the drug substance that can impact manufacturability should be identified (e.g. particle size distribution). Additionally, specific attributes (CQAs) of the drug substance that can be affected by manufacturing conditions and consequently have an impact on the drug product CQAs should be identified (e.g. assay and impurities CQAs due to sensitivity of the drug substance to light, heat, moisture or environment).

Solubility/quantitative aqueous pH solubility profile:

Information on the solubility of the drug substance in e.g. the solvents used for drug product manufacturing and equipment cleaning should be provided. Information on the solubility over the physiological range (e.g. pH 1.2-6.8), should also be provided to determine the Dose/Solubility volume ratio where applicable (e.g. for solid orals). If this information is not readily available (e.g. literature references, MF), it should be generated in-house.

The dose/solubility volume is calculated as the highest therapeutic dose (milligrams) divided by the solubility of the substance (milligrams/millilitres [mg/mL]) at a given pH and temperature. The dose/solubility volume should be determined in the physiological pH range (pH 1.2-6.8) and temperature (37 ± 0.5°C). High solubility

drugs are those with a dose/solubility volume of less than or equal to 250 mL throughout the physiological pH range.

For example, at 37 ± 0.5°C, compound A has a solubility of 1.0 mg/mL at pH 6.8 which is its lowest solubility in the pH range1.2 - 6.8. It is available in 100 mg, 200 mg, and 400 mg strengths and the highest therapeutic dose is 800 mg (2 x 400mg). This drug would be considered a low solubility drug as its dose/solubility volume is 800 mL (800 mg/1.0 mg/mL), which is greater than 250 mL.

In-Situ Conversion:

An API may be converted to a different chemical or physical form (e.g. in situ conversion of free base to salt, change of stereoisomer or polymorphic form) during the drug product manufacturing process. Such a conversion could be intended or inadvertent (e.g. processing condition in commercial lot). Nevertheless, such a conversion may adversely affect the performance, safety and efficacy of the drug product and may impact on the assessment of pharmaceutical equivalence for a subsequent-entry drug product. 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, section S.3.1 should include relevant information (e.g. solubility, crystalline structure) for the API and as much information as possible regarding the in-situ chemical 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 salt form if it were present as an isolated compound (e.g. solubility). Where complete characterization of the original or in-situ form is not possible, this should be discussed.

Published literature could also be presented as supporting information/data to justify the presence or absence of in-situ conversion.

For a subsequent entry product, if an in-situ conversion occurs to a form of the drug substance which is different from that in the Canadian Reference Product, additional information should be submitted to support the safety and efficacy of the form of the drug substance in the final dosage form for the subsequent entry product.

Known or potential incompatibilities (e.g. lactose with drug substance containing primary amine) should be discussed and the controls to minimize the effect of these potential incompatibilities should be identified (e.g. control of impurities, physical separation via manufacturing techniques).

References:

Interpretation of "Identical Medicinal Ingredients" policy
Notice regarding Interpretation of "Identical Medicinal Ingredient" policy

P.2.1.2 Excipients

The choice of excipients listed in P1, their concentration, their characteristics that can influence the drug product performance should be discussed relative to their respective functions.

Detailed information should be provided to identify the excipients (e.g. grades, potato vs corn starch, excipients with multiple origins such as magnesium stearate). The potential CQAs of the excipients including the selection of their type/grade and amount, and their effect on the delivery of the drug product of the desired quality should be discussed. When compendial monographs allow for different acceptance criteria for tests for different grades of excipients, the selection of the appropriate grade should be discussed. It may be

necessary to control an excipient using tighter limits if the monograph is not suitable to control the critical properties for the excipients (e.g. viscosity of a rate controlling excipient).

As absorption modifiers (e.g. enhancers, inhibitors) and aids such as surfactants could significantly influence bioavailability their use should be justified.

Use of novel excipients or excipients at levels higher than routinely used should be supported by documented evidence of their safety for use in patients (e.g. a reference to the appropriate section in Module 4 should be included, when applicable).

None of the excipients which are in the drug product should be on the list of prohibited colouring agents listed in the Canadian *Food and Drugs Act* and Regulations.

P.2.2 Drug Product

P.2.2.1 Formulation Development

A **brief** summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The formulation development should use a systematic, science and risk-based approach, as described in ICH Q8. The rationale for choosing the particular type of drug delivery system should be provided (e.g. matrix or membrane based controlled delivery systems, transdermal patches, liposomal, microemulsion, depot injection). The choice of higher risk manufacturing process (e.g. aseptic processing instead of terminal sterilization, direct compression instead of granulation) should also be justified. The rationale should be linked to the QTPP. All CQAs and the critical process parameters (CPPs) should be identified, and a Control Strategy should be proposed to ensure the batches meet the predetermined specification.

The master formula and manufacturing process used in the executed and commercial batches should be same as those used in the pivotal clinical lots or the lot used in the bioavailability study. Any differences in the formulations for the batches used in the clinical and/or comparative bioavailability and the formulation (i.e. composition) described in P.1 should be discussed. Results from comparative in vitro studies (e.g. dissolution, physicochemical properties) or comparative in vivo studies (e.g. bioequivalence) should be discussed, when appropriate.

When assessing the data elements needed for multiple strengths or variations in composition between the batches used in the clinical and/or comparative bioavailability and the commercial formulation, Health Canada's policy Bioequivalence of Proportional Formulations: Solid Oral Dosage Forms should be consulted. If a request for waiver of bioequivalence studies is proposed, the allowed variations in formulation should comply with this policy. In general, a more stringent approach in the assessment of excipient roles would be taken during assessment as some of the functions of excipients cannot be ignored based on concentration alone. For example, microcrystalline cellulose would be assessed as a binder rather than a filler unless data to justify its role as a filler is provided.

For drug products where a biowaiver is supported by an in vitro - in vivo correlation (IVIVC), the correlation study reports should be provided in Module 5 (Section 5.3.1.3). Requests for waivers and justification statements should be in provided in Module 1.6.1 Comparative Bioavailability Information.

For drug products requesting a waiver of the requirements to demonstrate in vivo comparative studies for an aqueous solution, a comparison of the relevant pharmaceutical characteristics of the test product and the Canadian Reference Product should be provided. Depending on the particular dosage form, a comparison of the relevant pharmaceutical characteristics would include comparison of the: (i) formulation, (ii) physicochemical properties, and (iii) device attributes. Health Canada's guidance document Pharmaceutical Quality of Aqueous Solutions should be consulted.

Where antioxidants are included in the formulation, the effectiveness of the proposed concentration of the antioxidant should be justified and verified by appropriate studies.

Reference:
ICH Q8A
Bioequivalence of Proportional Formulations: Solid Oral Dosage Forms

P.2.2.2 Overages

Any overages in the formulation(s) described in P1 should be justified.

Overage for the sole purpose of extending the shelf life of the drug product is not acceptable. However, if the overage is required to make up for a validated loss during the manufacturing process (e.g. loss during vacuum transfer) or to fill void space (e.g. excess coating solution to fill the tubing) it should be presented along with justification and supporting data for the necessity and quantity of the overage.

P.2.2.3 Physicochemical and Biological Properties

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

Scored tablets:

If the proposed dosage form is a scored tablet, additional information should be provided with respect to its design such as geometry of the tablet and break-line, choice of manufacturing process (e.g. hardness that would be conducive to splitting the tablet). The design of tablet score should be confirmed by tests and the results of a study should be provided testing the uniformity of dosage units of the tablet. The tablet should be split as described in the patient instructions (e.g. manually-split or split with a device that would be readily available to a patient). The data provided in the drug submission should include a description of the test method, individual values, mean, and relative standard deviation (RSD). Uniformity testing (i.e. content uniformity or weight variation, depending on the dose present in the split tablet) should be performed on each split portion from a minimum of 15 randomly selected whole tablets. As an illustrative example, the number of units (i.e. the splits) would be 30 halves for bisected tablets or 30 quarters (taken randomly from 10 tablets) for quadrisected tablets (statistical tests equivalent to the USP <905> or Ph.Eur. 2.9.40 requirements which are suitable for larger sample sizes may be used if more than 30 sections are sampled). Loss of mass from the tablets during splitting should be documented and should not be more than 3.0%. At least one batch of each strength should be tested. The study should cover a range of the hardness values. If this study is not performed during development, then the acceptability of the hardness range should be confirmed during process validation by including a tablet splitting study on high and low hardness tablets in the process validation protocol. The splitting of the tablets should be performed in a manner that would be representative of that used by the consumer (e.g. manually split by hand or using a tablet splitter). The uniformity test on split portions can be demonstrated on a one-time basis and does not need to be added to the drug product specification(s). The acceptance criteria (range and variation) should be as described in the general chapters of the pharmacopoeia (e.g. USP General Chapter <905>, Ph.Eur. 2.9.40).

In order to allow a score line on a modified release tablet the formulation design has to be suitable (e.g. tablet should not disintegrate) and splitting the tablet should not compromise drug release from the split halves (e.g. meets predetermined release profile). For modified release products with a score line, in addition to content uniformity, equivalent rates of release should be demonstrated for the split tablets vs. whole tablets.

If immediate or modified release products cannot be split or the splitting of the tablets is not listed in the directions of the Product Monograph, a score line should not be present. A scoring configuration which differs from the Canadian Reference Product should be justified.

If present, the tablet description on the drug product specifications, and under the Availability section of the Product Monograph, should reflect the presence of a score.

Reference:

Bioequivalence of Proportional Formulations: Solid Oral Dosage Forms
Biopharmaceutics Classification System Based Biowaiver Guidance Document
Pharmaceutical Quality of Aqueous Solutions Guidance Document

P.2.3 Manufacturing Process Development

The selection and optimisation of the manufacturing process described in P.3.3, in particular its critical process parameters, should be identified and explained. Where relevant, the method of sterilization (e.g. aseptic vs. terminal) should be explained and justified. Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in P.3.3 that can influence the performance of the drug product should be discussed.

In accordance with C.08.002(2)(m) and C.08.002.1(2)(d) of the *Food and Drug Regulations*, the information provided in the pre-market submission should provide evidence that all test batches of the new drug used in any studies conducted in connection with the submission were manufactured and controlled in a manner that is representative of market production.

The QOS should briefly document any changes to the manufacturing process throughout the life-cycle of the drug product covered by the submission. A side-by-side table comparing the manufacturing process of the product used for pivotal studies to the product currently proposed (e.g. the proposed commercial process or the revised process proposed in a Supplemental New Drug Submission or Abbreviated New Drug Submission) is recommended. A discussion of the significance of the differences should be included as well as any data (e.g. in-vitro testing or biostudies) supporting the proposed changes.

The scientific rationale using the principles of risk management for the choice of the manufacturing, filling, packaging processes, and storage conditions that can influence drug product quality and performance should be explained and linked to the QTPP. It is the sponsor's responsibility to establish which of the quality attributes and process parameters are critical and how to control them in a consistent manner. Developmental work conducted to establish appropriate controls to avoid deterioration of the API during the manufacturing process and storage should be discussed (e.g. protection from heat, light (UV or visible), oxygen or moisture).

For drug products developed using an enhanced approach, QbD, details of risk assessment and results from the design of experiments should be summarized in this section. Care should be taken to:

a. use terminology in a manner that is consistent with ICH definitions (e.g. PARs vs. design space).
b. be clear about claims and proposed flexibility supported by enhanced development (e.g. design space(s), PARs, Real Time Release (RTR)testing, omission of certain drug product specification tests).
c. discuss the role of QbD in the overall control strategy (e.g. to support RTR testing or elimination of certain tests from finished product specifications).

Where PARs or a design space have been claimed in P.3.3, studies which support the proposed ranges (space) should be described in P.2.3. Studies conducted to assess criticality of process parameters or material attributes identified in P.3.4 should also be described in P.2.3.

If environmental controls over and above routine controls are necessary to ensure the stability of the drug product during the manufacturing process, the additional controls such as reduced lighting or a different lighting source, temperature and humidity control or use of an inert atmosphere should be discussed and rationalized in the submission.

Recommendations for the number of batches to be manufactured and be included in a drug submission are outlined in sections P.5.4 (Batch Analyses) and R.1.1 (Executed Production Document) of this guidance document.

Drug product intermediate

A drug product intermediate is a material that is the result of a drug substance having undergone at least one processing step in the presence of any other substance (used in the manufacture of the drug product whether it appears in the finished dosage form or not) which must undergo further processing step(s) to become the finished dosage form.

That first processing step of the drug substance in the presence of any other substance would be considered a drug product manufacturing activity, subject to Part C, Division 2 of the *Food and Drug Regulations*, and would define the date from which the expiry date for the drug product would be established.

Mixtures of two APIs are considered a drug product intermediate and the date of manufacture would be considered the date that the two APIs are first mixed. If the drug product intermediate is not used immediately and an expiry date or retest date is set for the drug product intermediate, then the stability data to support the expiry date of the finished dosage form should be based on data from batches of drug product which have been manufactured using the drug product intermediate just before its proposed expiry date.

Sponsors having situations that might be an alternative to the above interpretation (e.g. inability to isolate the drug substance in a pure and stable form or mixing with excipients for safety or stability purposes, e.g. nitroglycerin, cholecalciferol) should discuss their case and scientific justification in advance with the pre-market approval bureau/office.

Scale-up during manufacturing process development:

The scientific rationale for the selection, optimization, and scale-up of the manufacturing process described in P.3.3 should be explained, in particular the CPP that are linked to CQAs of the drug product (e.g. the rate of addition of granulating fluid, massing time, granulation end point, drying end point, and in process control range for the LOD which determine the quality of the granules). The equipment which is critical for ensuring product quality should be identified (e.g. model and item number) by operating principles and working capacity.

During scale-up development, if there is a proposed change of equipment used for critical steps within the same Scale-up and Post-Approval Changes (SUPAC) class but different SUPAC subclass (as described in the United States Food and Drug Administration's guideline), at least one batch of the product should be made using the proposed equipment. Additional batches may be required depending on the complexity of the process and product.

The rationale for selection of manufacturing processes should be fully outlined and the suitability of the selected manufacturing process and control strategy should be demonstrated on at least one commercial size lot of each strength. This lot would serve as a proof of concept, to demonstrate scalability and commercialization. Although production of a commercial scale batch is recommended for all products, it is expected for high risk products as outlined below:

1. When the drug substance is a Critical Dose Drug and the drug product is not a solution.
2. Strength (low dose): When the drug product strength is 5 mg or lower and/or the drug substance forms 2% w/w or less of the total mass of the drug product content.
3. When the chosen manufacturing process is:
    - prone to variability (e.g. direct compression process for manufacturing a low dose product).
    - complex (e.g. use of coating technology to add the drug substance and/or a rate controlling function to granules, processes which include lyophilisation or microencapsulation).

A Critical Dose Drug is defined in the guidance document - Comparative Bioavailability Standards: Formulations Used for Systemic Effects.

For complex dosage forms, such as modified release products, if the proposed commercial product differs significantly from the pivotal clinical product or the product used in the bioequivalence study, a bridging study would be required. Examples of significant differences include changes in manufacturing site, manufacturing principle and equipment class or operating principle. Sponsors who wish to propose a biowaiver rather than a bridging study (e.g. if proposing to submit scientific justification which is accompanied by supporting data (e.g. comparative dissolution data, BCS class 1 products or when an IVIVC has been established) should consult with the review bureau prior to submission.

Sterile drug products

For sterile drug products, terminal sterilization is considered to be the method of choice to ensure sterility of the final drug product. Hence, sterile drugs should be manufactured using aseptic processing only when terminal sterilization is not feasible. Manufacturers who choose to manufacture a sterile product without terminal sterilization (e.g. aseptic processing) should provide adequate scientific justification and supporting data for the proposed sterilization technique.

Evidence should be provided to confirm that the sterilization process will produce a sterile product with a high degree of reliability and that the physical and chemical properties as well as the safety of the drug product will not be affected. Details such as F0 range, temperature range and peak dwell time for a drug product and the container closure system should be provided. Justification should be provided for reduced temperature cycles or elevated temperature cycles with shortened exposure times, although standard autoclaving cycles of 121°C, 15 minutes or more, would not need a detailed rationale.

If ethylene oxide is used, acceptance criteria should be included in specifications to control the levels of residual ethylene oxide and related compounds.

The suitability of filters selected for sterilization should be established by studies evaluating bacterial retention and viability, compatibility with the product during the maximum contact time, extractables and leachables, and adsorption of the drug substance or any of the formulation components. If applicable, the description and the data for a validated flush program should be submitted to demonstrate that the filter is suitable for the filtration process.

The suitability and compatibility of the manufacturing equipment (e.g. extractables and leachables) should be demonstrated for non-solid dosage forms.

Minimum product rinse volumes should be established.

References:

ICH Q8, Q9, Q10

P 2.4 Container Closure System

The suitability of the container closure system (described in P7) used for the storage, transportation (shipping) and use of the drug product should be discussed. This discussion should consider, e.g. choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the drug product).

The information that should be included for the qualification of the container closure system includes packaging materials that:

a. come in direct contact with the dosage form (container, closure, liner, desiccant);
b. are used as a protective barrier to help ensure stability or sterility;
c. are used for drug delivery;
d. are necessary to ensure drug product quality during transportation.

The following table outlines parameters which should be used to establish the suitability of the container closure system.

Table 2: Parameters to establish the suitability of the container closure system

Parameter	Oral and Topical Products	Inhalation Products	Sterile Products (including Ophthalmics)
Name, physical description, dimensions (e.g. thickness, volume, diameter)	✓	✓	✓
Specific identification tests (e.g. IR) for components that come in direct contact with the dosage form	✓	✓	✓
Tests for reproducibility of dose delivery (or packaging materials responsible for delivery of a dose)	✓ (if applicable)	✓	✓ (if applicable)
Composition and drawings for all novel or product specific components (including cap liners, coatings for metal tubes, elastomers, adhesives, silicone, etc.)	✓	✓	✓
Description of any additional treatments[1]	✓	✓	✓ (sterilization and depyrogenation of the components)
USP <661> Plastic Packaging Systems and their materials of construction (Includes 661.1 and 661.2)	✓	✓	✓ (includes USP <87> / <88> /<1031> tests)
USP <671> Containers – Performance Testing	✓	✓	✓
USP <381> Elastomeric Closures for Injections	--	--	✓ (includes USP <87> / <88> tests)
Additional tests	[2]	[2]	[2]

Parameter	Oral and Topical Products	Inhalation Products	Sterile Products (including Ophthalmics)
Compatibility with drug product (e.g. adsorption to the container and related substances)	✓ (Liquid oral products and liquid or semi-solid topical products)	✓	✓
Extractable and Leachable studies	✓ (Liquid oral products)[3]	✓ 3	✓ 3

✓ Information should be submitted
- - Information does not need to be submitted
1. e.g. coating of tubes, siliconization of rubber stoppers, sulphur treatment of ampoules/vials, blanketing with inert gas
2. Refer for the guidance document "Pharmaceutical Quality of Aqueous Solutions" for details of additional tests required (e.g. Extractables and Leachables, performance tests for metered dose drug delivery)
3. Refer to the USP <1663> and <1664> / <1664.1> for guidance on extractables and leachables testing. This information can be provided in a master file, if relevant.

The information on the composition of packaging used for parenteral and liquid/semi-solid products should be available to Health Canada either in the drug submission or in a Master File. Refer to Health Canada's guidance document Master Files (MFs) - Procedures and Administrative Requirements for filing requirements for Type II MF's (Container Closure Systems).

References:

Pharmaceutical Quality of Aqueous Solutions
Master Files (MFs) - Procedures and Administrative Requirements
USP <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems
USP <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery systems
USP <1664.1> Orally Inhaled and Nasal Drug Products

P.2.5 Microbiological Attributes

Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products (ref. ICH Q6A) and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives, or the anti-microbial effectiveness of products that are inherently antimicrobial. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

Where an antimicrobial preservative is included in the formulation, the effectiveness of the agent should be demonstrated using a batch of the drug product with the preservative a concentration at the lower limit of the proposed acceptance criteria for the assay of the preservative. Schedule B compendial tests for antimicrobial effectiveness testing are considered acceptable. The use of anti-microbial preservatives in single-dose preparations is not recommended.

As outlined in ICH's Q1A guidance document, a single primary stability batch of the drug product should be tested for antimicrobial preservative effectiveness (in addition to preservative content) at the proposed shelf

life for verification purposes, regardless of whether there is a difference between the release and shelf life acceptance criteria for preservative content. If this information is not available at the time of submission, a commitment should be provided that a single primary stability batch will be tested for antimicrobial effectiveness at the end of proposed shelf life.

P.2.6 Compatibility

The compatibility of the drug product with reconstitution diluent(s) or dosage devices (e.g. precipitation of drug substance in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labeling.

Where sterile, reconstituted products are to be further diluted, compatibility should be demonstrated with all diluents over the range of dilution proposed in the labelling. These studies should be conducted on aged samples. Where the labelling does not specify the type of containers, compatibility (with respect to parameters such as appearance, pH, assay, levels of individual and total degradation products, sub-visible particulate matter and extractables from the packaging components) should be demonstrated in the specified container(s) (e.g. glass, PVC, and polyolefin containers). However, if one or more containers are identified in the labelling, compatibility of admixtures needs to be demonstrated only in the specified containers.

Studies should cover the duration of storage reported in the labelling (e.g. 24 hours under controlled room temperature and 72 hours under refrigeration).

When sponsors are qualifying limits for degradation product, they should consider the maximum level observed for impurities in the reconstituted product at the end of the in-use period. For existing drugs (e.g. generics), if levels of impurities or other parameters warrant, reconstitution studies should be carried out in parallel with the Canadian Reference Product to adequately qualify the impurity and other limits proposed in the drug product specification(s).

For sterile drug products, results of studies should be provided demonstrating compatibility (e.g. hold time studies, extractables and leachables data, ICH Q3D compliance) with manufacturing equipment (e.g. coated vessels, sterilization filters, transfer tubing).

P.3 Manufacture

If a Master File (MF) is filed with Health Canada and cross-referenced for certain proprietary information, provide the MF number assigned by Health Canada.

P.3.1 Manufacturer(s)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing, packaging and testing should be provided.

This includes the facilities involved in the manufacture (fabrication), packaging and release and stability testing of the drug product. If certain companies are performing only specific steps in the process (e.g. manufacturing of an intermediate), this should be indicated. 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 manufacturing, packaging, labelling and testing facilities should have been confirmed by the Regulatory Operations and Regions Branch to be GMP compliant prior to submitting an application.

P.3.2 Batch Formula

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages. A reference to the quality standard used should be noted in the QOS (e.g. USP, Ph.Eur., House, etc.).

The batch formula should express the quantity of each component on a per batch basis for each proposed commercial batch size of each strength, including the total weight or measure of the batch.

The table should include all components used in the manufacturing process, regardless if they appear in the final drug product (e.g. solvents, headspace nitrogen, silicone for stoppers if it is applied during the processing). If the amount of active pharmaceutical ingredient is adjusted (e.g. based on the assay of the active moiety), then the correction should be clearly indicated at a footnote (e.g. x mg of hydrochloride added = target amount as base * (MW HCl / MW base) / Assay)). If there is a granulation step using intra and extra-granular excipients these should be listed separately.

The batch formula should be written to provide 100% of the label claim unless overages have been adequately justified. All overages should be clearly indicated (e.g. "Contains 5 kg overage of the drug substance to compensate for manufacturing losses."). An overage of film-coating suspension can be justified in a footnote to the batch formula table.

The components should be declared by their proper or common names, quality standards (e.g. USP, Ph.Eur., House) and, if applicable, their grades (e.g. "Microcrystalline Cellulose NF (PH 102)").

P.3.3 Description of Manufacturing Process and Process Controls

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

A narrative description of the manufacturing process, including packaging, which represents the sequence of steps undertaken and the scale of equipment, where relevant, should also be provided. The narrative description should be based on the details listed in the master production documents for the proposed commercial batch size. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g. tumble blender, in-line homogeniser) and working capacity, where relevant.

Steps in the process should have the appropriate process parameters identified, such as time, temperature, or pH. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in Section P.3.4. In certain cases, environmental conditions (e.g. low humidity for an effervescent product) should be stated.

Specific process parameters (e.g. mixing speed, granulation end point) should be included and should correspond with the target and normal operating ranges (NORs) included in the master production documents for commercial scale batches. 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. A tabular summary of process parameters and design space is often the clearest and most succinct way of presenting the information. Where PARs for discrete process parameters have been supported by data in P.2.3, the manufacturing process should be described in terms of targets and NORs identified in the master batch records and those PARs for which supporting data were provided. However, a combination of PARs does not constitute a design space and it is expected that the manufacturing process will be conducted within the NORs for all process parameters, with excursion into the PAR for only a single parameter at a time.

Validated maximum manufacturing process times (including hold times should be specified in the Master Production Documents (MPDs). Unless clearly stated and authorized, the start of manufacturing (for purposes of establishing the drug product shelf life) is defined as the date of the first processing step of the drug substance in the presence of any other substance used in the manufacture of the drug product.

Unless data are available to support longer manufacturing process times, the time from start of manufacture to the end of manufacture should not be more than 30 days and to the end of packaging in the final container closure system should not be more than 60 days for solid drug products.

Unless data are available to support longer manufacturing process times the time from the start of manufacturing to the end packaging in the final container closure system (i.e. end of sealing including the sterilisation procedures or start of the lyophilization process, if applicable) should not be more than 24 hours for liquid drug products.

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.

Proposals for the reprocessing of materials should be justified and the data to support this justification should be either referenced or filed in this section (P.3.3). Reprocessing of materials is not expected in a validated process and will only be considered in exceptional circumstances. Therefore, if reprocessing of materials is expected (e.g. recirculation of fines) and intended to be done in a routine basis, then this should be submitted as part of the manufacturing process with relevant supporting data. The acceptability of such reprocessing of materials is determined on a case-by-case basis based on the data showing control of the drug product.

For sterile drug products, details of validated sterilization parameters (e.g. load size, autoclave program, gamma radiation dose, processing aids) and equipment (e.g. compounding vessels, sterilizing filters, filling syringes) should be listed for the drug product and all relevant stages of the manufacturing process (e.g. for the washing, sterilization and depyrogenation of packaging components). The sterilization cycle should be described where contract manufacturers are used for sterilization of packaging components, or alternatively this information could be provided in a Master File (MF).

As outlined in the general chapters of the pharmacopoeia, each container of an injectable drug product should be filled with a volume that slightly exceeds the content indicated in the product labeling. These excess volumes (i.e. also known as overfills, which are not to be confused with overages) are intended to ensure the minimum required extractable volumes to allow for correct dosage delivery. As such, the master manufacturing documents should include target fills and tolerance limits to ensure that at least 100% of the label claim of the drug substance will be available. Overfills that exceed the recommended excess volume in USP <1151> should be justified and supported by data.

P.3.4 Controls of Critical Steps and Intermediates

Critical Steps: Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified in P3.3 of the manufacturing process, to ensure that the process is controlled.

Drug Product Intermediates: 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).

In-process tests are performed during manufacturing for the purpose of adjusting process parameters within an operating range to ensure the entire batch meets the expected quality attributes. Hence, in-process test limits may be used as action limits. For tablet compression the quality attributes tested in-process could

include, for example, weight, hardness, disintegration time and friability and need not be included in the batch release specification depending on the relevance to product performance (Reference ICH Q6 A). All routine in-process controls should be listed in this section, whether critical or not. If an in-process control is not critical, it is acceptable to state that it is just monitored. All process parameters (critical and non-critical) are managed under the product quality change management system. The applicant manages critical parameter ranges as regulatory commitments and any changes in the critical ranges would be provided for regulatory assessment in compliance with the current Post-NOC Changes guidance document. The applicant also manages non critical process parameters internally in the Pharmaceutical Quality System and changes in non-critical process parameters are not reported to the regulatory agencies. In the rare case where a non-critical parameter range is changed and the resulting change is determined to impact a drug product critical quality attributes, the non-critical parameter would be re-designated as a critical parameter and the regulatory authorities would be notified following current regulatory guidelines. In-process controls monitored during process validation only should be described under P.3.5. Sampling frequency and acceptance criteria should also be listed. A tabular format is recommended.

Examples of potential in-process controls include: (i) granulations: moisture, blend uniformity, bulk and tapped densities, granule particle size distribution, granulation end point, (ii) solid oral products: average weight, weight variation, hardness, thickness, friability, disintegration, weight gain during coating; (iii) semi-solids: viscosity, homogeneity, pH, evaluation of phase separation; (iv) transdermal patches: assay of drug-adhesive mixture, weight per area of coated patch without backing, adhesion strength cut patch dimensions and tolerances; (v) metered dose inhalers: fill weight/volume, leak testing, valve delivery; (vi) dry powder inhalers: assay of drug-excipient blend, moisture, weight variation of individually contained doses such as capsules or blisters; (vii) liquids: pH, specific gravity, clarity of solutions, bioburden; (viii) parenterals: bioburden prior to sterilization, 100% visual inspection (appearance, clarity), pH, fill volume/weight, filter integrity tests (determined pre and post filtration using appropriate methods (e.g. bubble point or forward flow)), particulate matter, container closure integrity test.

Weight variation in-process controls:

The generally accepted standard for in-process limits for weight variation for the core tablets and hard capsule fill weight, which is achievable for a product with a robust process using a modern tablet press and encapsulation equipment is considered to be:

- Average tablet weight: target weight ± 3 – 5 %
- Individual tablet weight: target weight ± 5%

These limits would be necessary to achieve an assay of 95% at the time of batch release. A need for a less stringent limit would indicate issues with granule flow and inadequacy of the manufacturing process to produce good quality tablets. The in-process control strategy is separate from the end product content uniformity test, which is based on very limited sampling.

A less stringent limit is considered acceptable in exceptional cases where it is difficult to achieve a tighter control and justification with data is required if wider limits are proposed, e.g. a dosage form that presents challenges in manufacturing, very small tablets, bilayer tablets. The dose of API from a tablet or capsule is affected by the weight of the tablet or capsule; therefore, acceptability of weight variation limits beyond individual limits of +/-5% and average limits of 3-5% are determined on a case-by-case basis; based on the data showing control of the drug product. Justification for less stringent limits can be provided based on the criteria outlined below.

Categorization of drug products based on risk on not meeting label claim:

A. The following situations are considered high risk:
   a. Critical Dose Drug where dose accuracy is considered clinically necessary or other clinical risk considerations.
   b. Drug products that are manufactured using a potentially variable process.

B. The following situations are considered medium risk:
   a. Drug products not falling into above (A) high risk category.
   b. Demonstrated evidence of robust process in commercial size batches or internal action limits are more stringent than regulatory limits.
   c. Soft gelatin capsules

C. Others: Unique dosage forms that may present challenges in manufacturing (e.g. films) are generally not subject to typical weight variation limits applicable to IR tablets. The weight variation limits for these products are similar to Spot Checks (and not an in-process test that could be monitored periodically and controlled). The proposed controls for these dosage forms should be fully described and justified.

Table 3: Maximum recommended limits for in-process weight variation

Risk based category	Conditions/Comments	In-process weight variation limits
Compressed Tablets (IR and MR)		
1. High risk	a. Critical Dose Drug* where dose accuracy is considered clinically necessary. b. Manufactured using a process that shows variability (e.g. direct compression with micronized API) and scale-up study not performed and experience with commercial size lots not included in pre-market submission.	• Average: target ± 3 - 4 %. • Individual: target ± 5%.
2. Medium risk	a. Do not fall into above high risk category. b. Demonstrated evidence of robust process in commercial size batches or internal action limits are stringent than regulatory limits. c. Coated granules/pellets that are already controlled for amount of API though other means (e.g. in-process assay).	• Average: target ± 5%. • Individual: target ± 7.5%.
3. Medium risk, smaller tablets	d. For tablets with an average mass of 80 mg or less	• Average: target ± 5%. • Individual: target ± 10%.
Capsules		
4. Hard Gelatin capsules	Weight of capsule content (powder/granules) demonstrated to meet more stringent limits.	• Average: target ± 5%.
5. Soft gelatin capsules	Capsule fill weight controlled and monitored by other means (e.g. accuracy of fill volume etc.).	• Average: target ± 5%.

Risk based category	Conditions/Comments	In-process weight variation limits
Unique dosage forms		
6. Example: Films, wafers, etc.	Dosage weight controlled and monitored by other means, e.g. coating uniformity etc.	• Average: target ± 5%.
* Critical Dose Drug as defined in the guidance document - Comparative Bioavailability Standards: Formulations Used for Systemic Effects.		

Use of the limits outlined in Ph.Eur. 2.9.5 are only considered acceptable as a spot check performed by QC.

Controls for packaging should be provided when critical for ensuring appropriate quality, e.g. leak testing and controls for orientation of vials or bottles for sterile products and appropriate filling of blisters (e.g. for co-packaged tablets such as contraceptives).

References:
ICH Q2, Q6A

P.3.5 Process Validation and/or Evaluation

Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process (e.g. validation of the sterilisation process or aseptic processing or filling). Viral safety evaluation should be provided in A2, if necessary.

As per Health Canada GMP it is an expectation that prospective validation would be conducted prior to the distribution of either a new product or a product made under a modified production process, where the modifications are significant and may affect the product's characteristics. This is a pre-planned scientific approach and includes the initial stages of formulation development, process development, setting of process specifications, developing in-process tests, sampling plans, designing of batch records, defining raw material specifications, completion of pilot runs, transfer of technology from scale-up batches to commercial size batches, listing major process equipment and environmental controls. Traditional process validation is generally performed prospectively, using three consecutive commercial size batches. Continuous Process Verification (CPV) is an alternative approach to traditional process validation in which manufacturing process performance is continuously monitored and evaluated and could be applied to drug products developed with QbD principles (ICH Q8).

The following information should be provided for traditional process validation:

a. A copy of the process validation protocol or validation report (for 3 consecutive commercial scale batches) specific to the drug product, which identifies the critical equipment and critical process parameters (CPP) that can affect the critical quality attributes (CQA) of the drug product and defines testing parameters, sampling plans, analytical procedures, and acceptance criteria (Control Strategy).
b. Confirmation that three consecutive, production-scale batches of the drug product have been or will be subjected to prospective validation in accordance with Health Canada's Validation Guidelines for Pharmaceutical Dosage Forms and Cleaning Validation Guidelines. Alternative approaches to prospective validation should be accompanied by a detailed justification.

For sterile products validation of the sterilization process(es) should be completed prior to submission and a summary of these process validation studies should also be provided. The following data should be included in validation reports:

a. Process parameters of the sterilization cycle.
b. Washing, treatment, sterilizing, and depyrogenation of containers, closures, and equipment.
c. Filtration of solutions.
d. The lyophilization cycle.
e. The integrity test of filled and sealed container closures.
f. Final inspection of the product.

For sterile products which undergo aseptic processing, the aseptic manufacturing process should also be validated. The results of a media fill study (or aseptic process simulation study) which is sufficiently representative of the proposed commercial manufacturing process (e.g. with respect to the process type, batch size, container/closure configuration, container size, volume to be filled per unit, filling speed, process duration, number of units filled, etc.) should be provided. Scientific justification should be provided for any differences between the media fill process parameters and those proposed for the commercial process.

References:

Good Manufacturing Practices:
Validation Guidelines for Pharmaceutical Dosage Forms and Cleaning Validation Guidelines
Validation Documentation Requirements and Responsibilities for Drug Fabricators, Packagers/Labellers, Distributors and Importers

Sterilization Guidances:
Process Validation: Terminal Sterilization
Aseptic Processes for Pharmaceuticals, Form-Fill-Seal for Pharmaceuticals, Gaseous Sterilization for Pharmaceuticals, Irradiation Sterilization for Pharmaceuticals, Moist Heat Sterilization for Pharmaceuticals

P.4 Control of Excipients

P.4.1 Specifications

The specifications for excipients should be provided.

This would include the specifications for all excipients, including processing aids that do not appear in the final drug product (e.g. solvents, nitrogen, silicone for stoppers).

If the standard claimed for an excipient is a Schedule B compendial monograph, it is sufficient to state that the excipient is tested according to the requirements of that standard, rather than reproducing the specifications found in the Schedule B compendial monograph. If the standard claimed for an excipient is a non-Schedule B compendial monograph (e.g. House standard) or includes tests that are supplementary to those appearing in the Schedule B compendial monograph, a copy of the specification and non-compendial test methods for the excipient should be provided.

If a Manufacturer's standard is claimed, testing should be at least as stringent as specified in the Schedule B compendia monograph, should one or more exist. If a Compendial standard is claimed, the standard only has to meet the requirements of the appropriate monograph. Excipients derived from natural sources should have appropriate microbial tests and limits.

For excipients which are mixtures that are provided by 3rd party manufacturers such as flavours, colourants, capsules and non-functional coatings, a qualitative list of the ingredients should be provided along with the specifications. Additional proprietary information on capsules and functional coatings should be provided in a MF (e.g. quantitative composition, grades of materials used during manufacturing).

Refer to section S.4.1 for further information on specifications.

Functionality-related characteristics

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 novel excipients, information should be provided in P.4.6 or cross-referenced to the Master File number which includes complete information.

References:
ICH Q6A

P.4.2 Analytical Procedures

The analytical procedures used for testing the excipients should be provided, where appropriate.

Copies of analytical procedures from Schedule B compendial monographs do not need to be submitted.

References:
ICH Q2

P.4.3 Validation of Analytical Procedures

Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate.

Analytical validation information should be submitted for novel test methods (i.e. test methods not included in a Schedule B compendium or methods which do not use a common method such as those described in the compendia, (e.g. UV, HPLC, laser diffraction). Validation reports for commonly used test methods (e.g. compendial methods, particle size testing by laser diffraction) for excipients are normally not submitted, however the reports should be on file in-house and provided to Health Canada on request.

If a validation report is submitted, it is recommended that tables are used for summarizing analytical validation data in the QOS. Refer to S.4.3 for more information on presenting validation information.

Reference Guidances:
ICH Q2

P.4.4 Justification of Specifications

Justification for the proposed excipient specifications should be provided, where appropriate.

This would include the tests that are supplementary to those appearing in the Schedule B compendial monograph.

References:
ICH Q3C

P.4.5 Excipients of Human or Animal Origin

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). (Details in 3.2.A.2)

This information should include biological source, country of origin, manufacturer, production methods which are used to ensure TSE inactivation and a brief description of the suitability of use based on the proposed controls.

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 (with supporting documentation) should be provided attesting that the excipient is not at risk of transmitting BSE/TSE. A current certificate of suitability provided by EDQM may be used as an attestation.

Alternatively, the relevant information supporting the safety of the source from the proposed supplier should be provided (e.g. in a Master File, which is registered with Health Canada).

Health Canada does not allow does not allow use of Specified Risk Materials as defined by Health of Animals Regulations to be used in the manufacture of pharmaceuticals.

References:
ICH Q5A, Q5D, Q6B
EDQM guidance documents related to TSE risk reduction
Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3) (2011/C 73/01)

P.4.6 Novel Excipients

For excipient(s) used for the first time in a drug product, at a greater daily exposure than normally administered or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the drug substance and/or drug product format. (Details in 3.2.A.3)

A decision as to whether an excipient is novel is based on prior usage of that excipient in products marketed in Canada.

For novel excipients where a large amount of information is submitted, a high level summary of that information should be provided in this section and 3.2.A.3 should be referenced for additional information.

Supporting information for excipients used in paediatric products at levels not previously used, should be provided in this section.

A summary of toxicological information submitted in Module 4 to support a novel excipient or daily exposure of excipient should be listed here.

P.5 Control of Drug Product

P.5.1 Specification(s)

The specification(s) for the drug product should be provided.

The concept of "release and shelf life specifications" versus "regulatory acceptance criteria" is described in ICH Q6A. Health Canada would consider either approach acceptable. More stringent release acceptance criteria for assay should be proposed in order to ensure that shelf life acceptance criteria are met throughout the labelled shelf life of the drug product. For example, release assay limits of 93.0-108.0% label claim would generally be acceptable when the shelf-life assay limits are 90.0-110.0% and degradation product levels increase less than 2.0% over the shelf-life period.

If a Schedule B compendial monograph is applicable to the drug product, a sponsor can choose to declare a Manufacturer's Standard on the labelling which indicates that the material may differ in some respect from the compendial standard. However, the specifications must be acceptable to the Minister.

A copy of the drug product specifications in accordance with C.02.018 and C.02.019 of the *Food and Drug Regulations* should be provided from the site responsible for release (e.g. drug product manufacturer, importer or distributor).

The assay should include the chemical formula so that it is clear as to how the dose is declared (i.e. free acid/base vs. salt.)

Dissolution method parameters (e.g. dissolution apparatus, rotation speed, dissolution medium and volume) should be listed as a footnote to the table or directly in the description of the test.

Chemical names or unambiguous designations of impurities (e.g. USP or Ph.Eur. naming conventions or unambiguous company codes) that align with the description of the impurity structures in S.3.2 or P.5.5 of Module 3 or in the analytical procedure should be used in the drug product specification and the summary of the specification in 2.3.P.5.1 and in the CPID.

If specifications are different for sterile powders and their reconstituted solutions, this information should be clearly identified.

Periodic test schedules (skip lot testing) or alternate testing frequencies (sunset testing) proposed in accordance with ICH Q6A should be indicated on the specifications with the testing frequency clearly marked as a footnote. The data required to support testing which is not performed on a batch-by-batch basis varies. In general to reduce or skip testing after a certain point, supporting data from commercial scale batches using the current manufacturing method should be provided. The number of batches necessary to support reduced testing will be based on the risk of failure of a batch (e.g. reduced microbial testing for a solid oral product will require less justification than reduced residual solvent testing for products granulated with a solvent). Any proposal for periodic test schedules or alternate testing frequencies should be clearly highlighted in the discussion of the specifications and should be fully justified and based on supporting data, scientific rationale and a suitable risk assessment. Reduced testing schedules are always assessed on a case-by-case basis and will only be considered in cases where the supportive data are obtained from commercial scale batches.

ICH's Q6A Guideline outlines recommendations for a number of universal and specific tests and criteria for drug products. The following table provides suggestions on specific tests and criteria that are not addressed by ICH's Q6A guideline.

Table 4: Recommended tests to be included in Specifications

Dosage Form	Specific Tests Recommended*
Modified-release products	A drug-release method which is shown to be discriminatory with respect to formulation and/or manufacturing variables.
Inhalation and Nasal Products	Consistency of delivered dose* (throughout the use of the product), particle or droplet size distribution profiles* (comparable to the product used in in vivo studies, where applicable), and if applicable for the dosage form, moisture content, leak rate, microbial limits, preservative assay, sterility, and weight loss.
Suppositories	Uniformity of dosage units, melting point.

Dosage Form	Specific Tests Recommended*
Transdermals	Peel or shear force, mean weight per unit area, in vitro drug release, monitoring for crystal growth.
Aqueous Solutions	pH, uniformity of dosage units (if packaged in a single-unit container), antimicrobial preservative content (if present), antioxidant preservative content (if present), osmolality/osmolarity (if relevant), particulate matter (for sterile products) For sterile solutions - sterility, bacterial endotoxins
* Where tests are more appropriate as developmental tests these would be provided in P.2 and justification for not including them as routine tests would be provided in P.5.6.	

If impurity specifications proposed for the reconstituted products are different from the shelf-life specifications for the unreconstituted product, this should be clearly identified.

Routine testing for nitrosamine impurities should be included in the drug product specification when:

- the potential for nitrosamine introduction during drug product manufacturing, packaging and storage is identified or
- a nitrosamine impurity is detected in the drug product during confirmatory testing and the root cause of presence is unknown

Where such a risk is identified, a test and acceptance criteria for both release and shelf life specifications should be included in the drug application.

Finished products are also expected to meet residual solvents requirements as per USP <467>.

Although microbial control may be explicitly mentioned in the specification of certain dosage forms (e.g. liquid oral dosage forms), all products are expected to meet the minimum requirements for microbial control in accordance with USP <1111>. For low risk products, justification can be provided to omit testing from the specifications for routine product release.

References:

ICH Q3B, Q3C, Q6A
Pharmaceutical Quality of Aqueous Solutions
Nitrosamine impurities in medications: Guidance

P.5.2 Analytical Procedures

The detailed summaries of analytical procedures used for testing the drug product should be provided.

Compendial methods:

The compendia give guidance as to how much variation is acceptable in a chromatographic method. All methods meeting these requirements do not need to be submitted.

House methods:

The house analytical procedures proposed for routine testing should be provided in Module 3. Summaries of methods used for drug development or differences between these methods and routine quality control

methods (e.g. those used to support testing results in the drug submission) should be provided in P.5.4 or P.8 of Module 3 as appropriate.

The system suitability tests (SSTs) are an integral part of chromatographic analytical procedures. At a minimum, HPLC/UPLC and GC assay methods should include a SST for repeatability. For HPLC/UPLC methods to control degradation products, a SST for resolution or other appropriate indicators of column performance should also be included. Repeatability is typically demonstrated using a solution of the drug substance with a concentration corresponding to the limit for unspecified degradation products. Resolution of the two closest eluting peaks is generally recommended as a SST. However, choice of alternate peaks (e.g. choice of a toxic impurity) or another appropriate test to determine column performance could be used with justification. In accordance with the USP General Chapter on Chromatography, the repeatability test should include an acceptable number of replicate injections (i.e. five or six).

References:
ICH Q2

P.5.3 Validation of Analytical Procedures

Analytical validation information, including experimental data, for the analytical procedures used for testing the drug product, should be provided.

For compendial methods confirmation should be provided stating that the method validation/verification has been completed successfully as per the requirements in the relevant compendium.

If a Schedule B compendial standard is claimed and a House method is used in lieu of the compendial method (e.g. for potency or for specified degradation products), equivalency of the House and compendial methods should be demonstrated. This could be accomplished by performing analyses of a batch containing significant levels of impurities by both methods and providing the results from the study.

Partial revalidation may be necessary for methods that appear in a Schedule B compendial monograph (e.g. if excipients could interfere with assay). The compendial methods, as published, are typically validated using a drug substance or a drug product originating from a specific manufacturer. Different sources of the same drug substance or drug product can contain impurities and degradation products that were not considered during the development of the monograph.

Refer to S.4.3 for more information on presenting validation information.

References:
ICH Q2

P.5.4 Batch Analyses

A description of batches and results of batch analyses should be provided.

It is expected that drug product lots used in pivotal clinical studies and those submitted in the regulatory application (e.g. to establish specifications for potency, purity, dissolution and shelf life) are manufactured and tested according to the principles of GMP in order to ensure the reliability of the analytical test results. Deviations and Out of Specification (OOS) test results should be investigated in a timely manner and the results of the investigation summarized in the submission. Justifications with supporting data where necessary should be provided to support the use of the identified lots for setting regulatory specifications for release and stability.

A tabulated summary of batches discussed in the submission to support safety, efficacy, product development, process validation and stability should be provided in the QOS and should include the batch number, strength, manufacturing site, manufacturing process, testing site, batch size, date of manufacture,

API batch number, and use of the batch. This is particularly helpful in situations where the formulation and/or method of manufacture and/or manufacturing site have undergone revisions throughout product or clinical development. Batches used in pivotal clinical trials should be clearly indicated. If any batches have multiple batch numbers (e.g. different batch numbering systems from clinical sites, or manufacturing batch numbers different from packaging batch numbers) the table should incorporate this information, so all batches and their uses can be properly identified.

Number of batches and batch sizes:

It is generally expected that a minimum of three batches of each strength should be manufactured at a minimum of pilot scale from each proposed commercial manufacturing site, and that complete analytical results should be provided for those batches. Executed production documents for these batches should be provided as per R.1.1.

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.

In addition, batch analyses should be provided for batches used in pivotal clinical or bioequivalence studies and batches used for qualification of impurities. Bracketing or matrixing can be applied (e.g. if formulations are a common blend) and if scientifically justified by comparative data and understanding of the process. If matrixing is applied, then batch analyses for a minimum of one batch of each strength should be provided, ensuring that batches are provided from a minimum of two batches of common blend.

For products for which a biowaiver is proposed based on the BCS Based Biowaiver guidance, consult the guidance document referenced below.

Certificates of analysis for pivotal batch(es) should be provided in Module 3 P.5.4 or the regional information section. If certificates of analysis for the release testing of 3 executed batches of each strength are not provided in Module 3, the complete information from the certificates should be provided in tabular format. Tabulated summaries in the QOS should be sufficiently detailed including date and site of testing, date of manufacture of the batch, range, mean and relative standard deviation of individual results for content uniformity and dissolution, results of all tests conducted, quantitative results for all tests ('complies' is not sufficient), RRT and quantity of all unspecified impurities greater than the ICH reporting limit or the Limit of Quantitation (LOQ), as long as the LOQ is less than or equal to ICH reporting limits, and limits of detection where applicable (e.g. when impurities are not detected). Results of additional tests may be provided here or in P.5.6 to justify omission of certain tests from the specification.

References:

ICH Q2, Q3B, Q3C, Q3D, Q6A
Biopharmaceutics Classification System Based Biowaiver

P.5.5 Characterisation of Impurities

Information on the characterisation of impurities should be provided, if not previously provided in "S.3.2 Impurities".

This information would include degradation products (e.g. from interaction of the drug substance with excipients or the container closure system), solvents in the manufacturing process for the drug product, etc.

References:
ICH Q3B, Q3C, Q3D, Q6A, M7

P.5.6 Justification of Specification(s)

Justification for the proposed drug product specification(s) should be provided.

The recommended placement for the overall control strategy is Section P.5.6, preferably in tabular format, and should identify the critical quality attributes (CQAs) of the drug product and indicate the various control points in the manufacturing process (e.g. material attributes and/or process parameters) which contribute to the effective control of each CQA, including whether it is tested in the finished product specification. Justification for tests not considered necessary to include in the specification should be provided (e.g. tests conducted during development or CQAs whose control is assured by a manufacturing process design space). The overall elemental impurity control strategy should be justified based on Q3D.

In vitro Dissolution or Drug Release

A dissolution test is an important performance indicating test and is often used to link changes in the product at various stages of its lifecycle. Its utility as an important test to make key decisions depends on how relevant the test is to product performance and whether it has any discriminatory power. Thus, depending on the level of information the dissolution test could be a simple quality control test used to ensure lot-to-lot similarity, or a surrogate for bioequivalence when an IVIVC is established.

Dissolution results should be submitted for all relevant executed batches, including those lots used for pharmacokinetic and bioavailability studies (pivotal clinical lots). Results from pivotal clinical lots should be used as the basis for setting the specification and providing a link to the product's QTPP. Instances where clinical (pivotal) lot has expired (e.g. to justify a post-NOC change), a more recent commercial lot that represents the pivotal lot could be used instead as the reference if concurrent testing with the reference product is required. This should be supported by a justification that the reference lot meets the QTTP; any creep in formulation and/or manufacturing process should also be explained and evidence provided that the changes have not affected the dissolution performance.

The results of studies justifying the choice of in vitro dissolution or drug release conditions (i.e. apparatus, rotation speed, medium) should be provided. This information may be provided elsewhere in the dossier/split between sections P.5.6, P.5.3 and P.2, as appropriate. Appropriate cross-references should be made to these other sections. Data should also be submitted to demonstrate whether the method is sensitive to changes in manufacturing processes and/or changes in grades and/or amounts of critical excipients. The dissolution method should be sensitive to any changes in the product that would result in a change in one or more of the pharmacokinetic parameters. The use of dissolution parameters from a dissolution method included in a pharmacopoeial drug product monograph or from the FDA Recommended Dissolution methods should be justified and the conditions should be shown to be relevant for the drug product under assessment.

Alternatively, the specification can be based on the requirements listed in the guidance document "Biopharmaceutics Classification System Based Biowaiver" or when an IVIVC is established, the specifications can be based on IVIVC-simulated pharmacokinetic data.

For **immediate release** drug products the use of single point test or a dissolution range should be justified based on the solubility and/or biopharmaceutical classification of the drug. For slowly dissolving or low solubility drugs if the time to achieve ≥85% (NLT 80% (Q) according to USP) exceeds 30 minutes, a two-point test should be considered. Dissolution testing and therefore dissolution drug product specifications are formulation and drug product specific tests. Therefore it is the expectation that the specifications be representative of the lots used in the bioequivalence study(ies). Specifications should be representative of the release of the biolot(s), hence it may be necessary to define acceptance criteria which are tighter than those cited within compendial monographs.

Modified-release dosage forms should have a meaningful in vitro release rate (dissolution) test that is used for routine quality control. Preferably this test should possess in vivo - in vitro correlation. Results demonstrating the effect of pH on the dissolution profile should be submitted if appropriate for the type of dosage form. Ideally, the testing conditions should be set to cover the entire time period of expected in vivo release (e.g.12-hour release for B.I. D.) unless a shorter timeframe is justified (e.g. using clinical / bioequivalence/pharmacokinetic studies). At least three time points should be included in the specifications. The first time point should be at the early stage of drug release where about 20-30% is dissolved to ensure the absence of dose dumping. The middle time point should be at about 50% release and the final time point at about 80-85% to demonstrate release of all drug contained in the dosage form. At each test period, upper and lower limits should be set for individual units. A single sided limit (e.g. NLT 85%) is appropriate at the last test point to demonstrate full release of the drug substance. Generally, the range in acceptance criteria at each intermediate test point should not exceed 20% (e.g. ± 10% of the targeted value) without IVIVC or clinical/bioequivalence data to support wider limits.

For **opioids and other drug products** (e.g. modified release products) where inadvertent dose dumping could be potentially fatal to the patient, information on drug release in the presence of alcohol should be provided to demonstrate absence of dose dumping. Typically, this would involve a one-time dissolution study in an aqueous medium containing ethanol (e.g. release in 5%, 20% and 40% aqueous ethanol solutions to represent ethanol consumption).

The method development and validation should not be limited to validation of the method used for quantification (UV, HPLC/UPLC, etc.) but should include the capacity of the method to discriminate between formulation and manufacturing variables and the rationale for the choice of the type of dissolution apparatus, stirrer speed (RPM), volume and pH of the dissolution medium etc. If a surfactant is used, both the choice of surfactant and the concentration should be justified. If a surfactant is justified, the minimum level of surfactant required to reach sink conditions should be selected. The RSD for dissolution at time points beyond the initial time point should be less than 10%. Evidence that the method is discriminatory should also be included in section P.4.3.

Transdermal patch adhesion:

Adhesion of the patch should be tested to assess the patch's adhesive property (also termed a peel test or shear test). It is a numerical value obtained from an in vitro test and is useful to detect any manufacturing anomaly and serves as an index to monitor stability. The in vitro method for testing patch adhesion generally has little correlation with its adhesion property on patients/volunteers. Hence, the proposed patch adhesion numbers in the specification should be linked to the adhesion observed in the clinical studies on patients/volunteers.

References:

ICH Q3D, Q6A
Biopharmaceutics Classification System Based Biowaiver

P.6 Reference Standards or Materials

Information on the reference standards or reference materials used for testing of the drug product should be provided, if not previously provided in "S.5 Reference Standards or Materials".

P.7 Container Closure System

A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. Specifications should be provided from both the vendor and drug product manufacturer. However, if the two are identical, then the drug product manufacturer's specifications should be provided in conjunction with confirmation that they are identical to those from the vendor. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

Certificates of compliance, if relevant, can be provided from either the vendor or drug product manufacturer.

For functional secondary packaging components, the amount of additional information which should be provided depends on the purpose of the container. For minor functional secondary packaging components (e.g. cartons where the product is light sensitive), only a brief description should be provided.

Suitability information (e.g. qualification data) should be provided in P.2.

Provide a description and specifications for the packaging components that:

a. come in direct contact with the dosage form (container, closure (e.g. rubber stoppers), liner, desiccant);
b. are used as a protective barrier to help ensure stability or sterility (e.g. nitrogen headspace);
c. are used for drug delivery (e.g. syringe, dropper, measuring cup);
d. are necessary to ensure drug product quality during transportation;

If a Master File (MF) is filed with Health Canada and cross-referenced for certain proprietary information (e.g. composition), provide the MF number assigned by Health Canada.

If processing agents (e.g. silicone for stoppers) are applied by the vendor then they should be listed in this section rather than P.3.2 or 3.3. Include all proposed market containers as well as sample packs for physicians and containers used for bulk storage.

The information for the container closure system depends on the dosage form and route of administration. The following table outlines the general recommendations for routine testing for various dosage forms. For additional testing required to qualify a container closure system see section P.2.

Table 5: General recommendations for routine testing

Specifications for routine testing	Oral and Topical	Inhalation	Sterile Products (including Ophthalmics)
Name, physical description, dimensions (e.g. thickness)	✓	✓	✓
Specific identification tests (e.g. IR) for components that come in direct contact with the dosage form or are primary packaging components	✓	✓	✓
Performance characteristics necessary for product delivery	✓ (if applicable)	✓	✓
✓ The checkmark represents tests that should be included routinely in the container closure component specifications.			

Results of extractable/leachable studies should be provided for components in contact with aqueous solutions. The tests should investigate the aqueous (and other applicable solvents) extraction of the plastic to characterize or determine the presence of impurities or extractables. If possible, the extraction media should also include the drug vehicle to be used. Testing should meet the requirements of the USP General Chapters <87/88> Biological Reactivity, and the Health Canada guides, Pharmaceutical Quality of Aqueous Solutions or Pharmaceutical Quality of Inhalation and Nasal Products Guidance as applicable for the intended dosage form. Additional results from extraction and/or leachable studies may be warranted depending on the characteristics of the drug product and the primary components of the container closure system (e.g. risk of glass delamination).

References:

Pharmaceutical Quality of Aqueous Solutions

Pharmaceutical Quality of Inhalation and Nasal Products Guidance

USP <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems

USP <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery systems

P.8 Stability

As outlined in ICH's Q1A guidance document, the purpose of stability testing is to provide evidence on how the quality of a drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a shelf life for the drug product and recommended storage conditions.

References:

ICH Q1A, Q1B, Q1C, Q1D, Q1E

P.8.1 Stability Summary and Conclusions

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions with respect to storage conditions and shelf life, and, if applicable, in-use storage conditions and shelf life.

Stress testing:

As outlined in ICH's 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 and observe 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).

Representative chromatograms of stress studies showing 10-20% degradation of the API should be submitted.

Accelerated and long term testing:

The conditions for stability testing of drug products are outlined in ICH's Q1A guidance document. The following storage conditions and minimum data at the time of submission are recommended by ICH's Q1A guidance document for the Primary Batches. Other storage conditions can be proposed based on the proposed labelled storage conditions (e.g. 8 - 15°C). It is recommended that alternate storage conditions are based on evaluation of mean kinetic temperature over the labelled storage range.

Stability information from accelerated and long term testing should be provided on at least three primary batches of each strength manufactured and packaged in each type of container closure system proposed for marketing. Two of the three batches should be at least pilot scale batches, and the third one can be smaller, if justified. 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).

For batches that are smaller than pilot scale, the chemistry of degradation and performance indicating tests (e.g. dissolution) should be scale independent. The small scale batch may be a development batch manufactured in a non-GMP research plant, provided it is representative of the impurity profile and functional characteristics of the larger batches.

Refer to section S.7.1 for additional information on reporting stability information.

Table 6: General case for stability studies of the drug product

Study	Storage Condition	Minimum Time Period Covered by Data at Submission
Long term	25°C ± 2°C / 60% RH ± 5% RH	12 months (6 months for existing drugs)
Intermediate	30°C ± 2°C / 65% RH ± 5% RH	6 months (if applicable)
Accelerated	40°C ± 2°C / 75% RH ± 5% RH	6 months

When "significant change" occurs at any time during testing over the 6 month period at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition. See ICH's Q1A guidance document for definition of "significant change".

Changes to a product after opening should be assessed for multiple-dose sterile products and for products where the labelling indicates a specific in-use period (this information may also be provided in P.2.6). 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). 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.

The information on the stability studies should include details such as storage conditions, strength, batch number, batch size, type of container closure system (including use of desiccants), orientation for liquid dosage forms (e.g. upright, inverted), and completed (and proposed) test intervals. Data should be summarized in tabular format for all batches/strengths/container closure systems which exhibit similar stability profiles. This should include ranges of analytical results and/or relevant results for justifying the proposed shelf life (e.g. maximum values for each timepoint if an increasing trend is observed for impurities).

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "All tests meet specifications". Any trends that were observed or statistical analysis performed should be discussed.

Monitoring of transportation

For a drug product posing a higher risk (e.g. sterile drug product or a drug product where a humidity sensitive intermediate is transported prior to final packaging), a transportation study is recommended to support the proposed strategy for shipping and handling of the drug product. The transportation study should be adequate to support conclusions regarding selection of appropriate packaging materials, mode(s) of transportation, necessary controls on shipping conditions (e.g. temperature and humidity), maintenance of sterility, and shelf-life. The study protocol should take into account the nature of the drug product, local conditions, modes of transportation, and any seasonal variations experienced, as well as describe any special handling instructions. When warranted, either the results of a transportation study or a protocol and a commitment to complete the study prior to marketing the drug product should be provided.

Proposed storage conditions and shelf life:

The proposed storage conditions with suitable tolerances (e.g. a temperature range with upper and lower criteria) representative of temperature conditions for which supporting data is provided as well as the shelf

life for the drug product should be stated. If more than one packaging format is available with different storage conditions and/or shelf-life the container closure system should be included.

When the drug product has been shown to be stable (e.g. under the ICH conditions with long term studies at 25°C ± 2°C/60% RH ± 5% RH and accelerated studies at 40°C ± 2°C/75% RH ± 5% RH) without any adverse trends, the following storage recommendation would generally be considered acceptable:

- "Store at room temperature (15°C to 30°C)".

If any adverse trends are observed, other storage recommendations may be warranted (e.g. "Store at room temperature (15°C to 25°C)").

Open ended storage conditions such as "Store below 30°C" (i.e. without mentioning store at room temperature) should not be used, unless stability data have been provided to demonstrate stability under refrigerated and frozen conditions. Stability data from studies conducted at temperatures below 15°C should be included for drug products which may be susceptible to precipitation or low temperature induced changes (e.g. solutions, suspensions and solid dispersions).

Based on the assessment of the stability data, other storage precautions should be assessed and precautionary statements added to the labelling if warranted (e.g. "Protect from light", "Protect from moisture", "Store in the overwrap provided"). Precautionary statements should not be a substitute for selecting the appropriate container closure system.

If justified, at the time of the application for market authorization the real time data generated under long term storage conditions can be extrapolated according to ICH Q1E to extend the shelf life period.

References:

ICH Q1B, Q1C, Q1D, Q1E
Guidelines for Temperature control of Drug Products during Storage and Transportation

P.8.2 Post-approval Stability Protocol and Stability Commitment

The post-approval stability protocol and stability commitment should be provided.

When available long term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, or stability data submitted is on pilot scale batches, a commitment should be made to continue the stability studies for primary batches in order to firmly establish the shelf life. If the primary batches are not commercial scale, a commitment should be provided that commercial size production batches will be studied post-approval. These batches would normally be the process validation batches. The long term stability studies for the Commitment Batches should be conducted through the proposed shelf life, and for six months under accelerated conditions on at least three production batches of each strength.

A Continuing (i.e. ongoing) Stability Program is a requirement of Division 2 of the *Food and Drug Regulations* (GMPs) and is implemented to ensure on-going compliance with the authorised shelf life specifications. A minimum of one batch of each strength, if manufactured that year, in each type of container closure system and from each commercial manufacturing site is placed in the continuing stability program each year. If no batches are manufactured during the year, the first batch manufactured in the subsequent year should be placed on stability.

The stability protocols for the Commitment Batches and Continuing (i.e. ongoing) Batches should include, but not limited to:

a. Number of batches per strength and batch sizes;
b. Tests and acceptance criteria;
c. Container closure system(s);
d. Testing frequency; and
e. Storage conditions (and tolerances) of samples.

Bracketing and matrixing can be applied if justified. Any differences in the stability protocols used for the primary batches and those proposed for the Commitment Batches or Continuing Batches should be scientifically justified.

P.8.3 Stability Data

Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included.

The summary presented in the QOS should include data presented in a way that it illustrates the stability conclusions (e.g. only highest and lowest values recorded in summary, or values that best represent the data and trends, highest levels of impurity recorded for all batches at the latest timepoint) and discussion on the stability trends. If appropriate, data from different batches or formats can be combined in a single data to illustrate conclusions. Only data representative of the stability of the product should be summarized.

Information on characterisation of impurities is located in P.5.5.

The actual stability results (i.e. raw data) used to support the proposed shelf life should be provided in Module 3 of the drug submission and tabulated by batch and timepoint. For quantitative tests (e.g. individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms".

All impurities observed above the reporting threshold should be reported and identified by name if known, or by retention time or applicable code if unknown.

A Appendices

A.1 Facilities and Equipment

Not applicable (i.e. not a Biotech product)

A.2 Adventitious Agents Safety Evaluation

Information assessing the risk with respect to potential contamination with adventitious agents should be provided in this section.

For non-viral adventitious agents:

Detailed information should be provided on the avoidance and control of non-viral adventitious agents (e.g. transmissible spongiform encephalopathy agents, bacteria, mycoplasma, fungi). This information can include for example, certification and or testing of raw materials and excipients and control of the production process as appropriate for the material, process and agent.

Potential contamination with mycotoxins should be considered for fermentation products from fungi.

For excipients of human or animal origin (e.g. glycerin, gelatin), information should be provided. This information could include certification from a recognized regulatory authority (e.g. EDQM Certificate of Suitability) or appropriate information on source (e.g. species, country of origin, tissue) and processing that minimizes the risk of transmission.

A.3 Excipients

For excipient(s) used for the first time in Canada (novel excipients) in a drug product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided in this section or in a cross-referenced MF in the CTD format.

If the excipient has been used in products marketed in other jurisdictions, this information can be submitted as a supporting justification for the use.

R Regional Information

R.1 Production Documentation

R.1.1 Executed Production Documents

Documents for a minimum of 2 batches including 1 batch for each proposed strength should be provided. Copies of the executed production documents (English or French original or translated) for the drug product should be provided for the batches used in the pivotal clinical and/or comparative bioavailability studies. Any notations made by operators on the executed production documents should be clearly legible. When there are multiple pivotal batches (i.e. 2 or more), executed production documentation submitted can be limited to 1 pivotal batch per strength as long as executed documents are provided for a minimum of 2 batches that cover the range of strengths. When 2 or more pivotal batches have been manufactured and a suitable matrixing/bracketing approach is proposed, a minimum of 2 pivotal executed batches per product should be provided and executed documents from a minimum of the highest and lowest strength per manufacturing site should be included. When a batch of a strength which has not been used for a pivotal study is submitted, the executed document for the primary stability batch should be submitted.

The documentation submitted for executed batches should be for products manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. 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.

Generally, executed documents for one batch of each strength should be provided. Representative documentation from each commercial manufacturing site should be provided. Bracketing or matrixing is acceptable, if scientifically justified.

Executed packaging records are not required for non-sterile products. For sterile products, only the primary packaging executed packaging records are required.

High Risk Products:

Documentation for at least one commercial size lot should be submitted (see P 2.3).

Post-NOC Changes:

Information on Post-NOC changes that require executed batch records are addressed in the Post-NOC Changes guidance document.

R.1.2 Master Production Documents (MPDs)

Copies of the drug product MPDs should be provided for each proposed strength, commercial batch size, and manufacturing site.

The details in the master production documents should include, but are not limited to, the following:

a. The name and batch number of the product;
b. Dates and times of commencement, of significant intermediate stages and of completion of production;
c. precautions necessary to ensure product quality (e.g. temperature and humidity control, maximum holding times, total processing time);
d. dispensing, processing and packaging sections with relevant material and operational details;
e. relevant calculations (e.g. if the amount of drug substance is adjusted based on the potency results or on the anhydrous basis);
f. identification of all equipment by type and working capacity (if applicable);
g. process parameters (e.g. mixing time, mixing speed, milling screen size, processing temperature range, tablet machine speed, vial filling speed);
h. list of in-process tests (e.g. appearance, pH, assay, blend uniformity, viscosity, particle size distribution, LOD, weight variation, hardness, disintegration time, weight gain during coating, leaker test, minimum fill, clarity, bioburden, filter integrity test, 100% visual inspection);
i. Notes on special problems including details, for any deviation from the Manufacturing Formula and Processing Instructions;
j. sampling plan with regard to the steps where sampling should be done (e.g. drying, lubrication, compression):
k. number of samples that should be tested (e.g. blend drawn using a sampling thief from x number of different parts of the blender);
    i. frequency of testing (e.g. weight variation every x minutes during compression or capsule filling);
l. theoretical yield and provision for the actual yield.

Where any of this information is included in a SOP, MPDs should clearly reference the SOP by name, number or code. Where documents are updated frequently, a reference to the current version of the document can be made rather than including a specific version number.

For sterile products, instructions for cleaning, sterilization, and if relevant, depyrogenation procedures for equipment and primary container closure system components should be provided in the MPDs or in referenced SOPs. If the production instructions or critical control parameters are present in SOPs, the SOP should be provided. Examples of SOPs which should be provided are:

- Procedures which contain Bubble Point test parameters (acceptance criteria)
- Aseptic Filtration of Bulk Solution (e.g. specification of filling speed, filters used)
- Procedures for aseptic filling, stoppering, lyophilization or autoclave loading and operation parameters, unloading, sealing
- Procedure for dispensing of Raw Materials (if this contains formulation information)
- Procedures for operation of critical equipment (e.g. blending vessels, 100% visual testing where the Acceptable Quality Levels are listed in the SOP).

A brief summary of SOP titles listed in production documents should be provided in the submission, and if requested by the assessor, the SOP should be available.

R.2 Medical Devices

Combination products are classified as either medical devices or drugs according to the principal mechanism of action by which the claimed effect to purpose is achieved. Those combination products that have been classified as devices include drug coated devices such as catheters, pacemaker leads, drug impregnated

devices. Those that have been classified as drugs include prefilled syringes, transdermal patches, peritoneal dialysis solutions, implants whose primary purpose is to release a drug. For those combination products classified as drugs, relevant product information should be provided as per this guidance. Where the device forms part of the primary packaging (i.e. is in contact with the product during storage) it should be described under P.7.

If relevant, for novel medical devices used to deliver the dosage form that are external to the drug product (e.g. inhalation devices) a description, details of the composition and specifications should be provided. Data to demonstrate suitability of the administration device should also be provided. If the device is provided with the drug product, it should be described in the CPID-CE.

R.3 Acceptable Compendial Monographs

The compendial monographs listed in this section are recognized as official according to Schedule B to the *Food and Drugs Act*.

The most recent editions, including all errata, supplements, revisions and addenda, of the following standards:

European Pharmacopoeia (Ph.Eur.)
Pharmacopée française (Ph.F.)
Pharmacopoeia Internationalis (Ph.I.)
The British Pharmacopoeia (B.P.)
The Canadian Formulary (C.F.)
The National Formulary (N.F.)
The Pharmaceutical Codex: Principles and Practices of Pharmaceuticals The United States Pharmacopoeia

Footnote

1. The abbreviation S(A)NDS refers to either an SNDS or an SANDS.