Health Canada Santé Canada

January 24, 2014

Notice

Our file number: 13-117362-707

Release of the Health Canada *Draft Guidance Document: Quality (Chemistry and Manufacturing): New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs)*

The above referenced document outlines the policy and guidance for industry and staff regarding the regulation of new drugs pursuant to the *Food and Drugs Act* and *Food and Drug Regulations.* This guidance document supersedes the previous version of the ***Draft Guidance for Industry: Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs)*** dated July 18, 2001, as it has been significantly updated in format and content.

Changes in the content of this draft revision include:

1) An update of the guidance document to reference current International Conference on Harmonisation ICH guidance documents.
2) Current interpretation of the *Food and Drug Regulations* as it pertains to New Drugs.
3) Clarification and expansion of the type of information which should be provided in Module 3 of the Common Technical Document (CTD).
4) This guidance document, once finalized and implemented will supersede three existing guidance documents:
    a. *Quality (Chemistry and Manufacturing) Guidance Document: NDSs and ANDSs* (draft, 2001);
    b. *Stability Testing of Existing Drug Substances and Products* (2003);
    c. *Impurities in Existing Drug Substances and Products* (draft, 2005).

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DRAFT GUIDANCE DOCUMENT

Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs)

This guidance document is being distributed for comment purposes only.

Published by authority of the
Minister of Health

Draft Date	2013/09/19

Health Products and Food Branch

Canada

Our mission is to help the people of Canada maintain and improve their health. Health Canada	The Health Products and Food Branch's mandate is to take an integrated approach to the management of the risks and benefits to health related products and food by: • minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and, • promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health. Health Products and Food Branch

Également disponible en français sous le titre : *Ébauche de la Ligne directrice : qualité (chimie et fabrication) : présentations de drogue nouvelle (PDN) et présentations abrégées de drogue nouvelle (PADN)*

FOREWORD

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.

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G GENERAL

G.1 Purpose

As required by Section C.08.002 of the *Food and Drug Regulations*, a new drug submission or an abbreviated new drug submission 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 New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (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 and ANDS to ensure an effective and efficient review 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 products, 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. SNDSs, SANDSs, 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 substances and existing drugs. An existing drug is one that does not contain a new medicinal ingredient (also known as a new active substance), but requires the filing of a New Drug Submission (NDS), an Abbreviated New Drug Submission (ANDS) or a Supplement (e.g., generic products). This would include, for example, submissions for new dosage forms, new strengths, and other changes to approved products.

The scientific and risk-assessment principles outlined in this document are also applicable to other types of applications (e.g. for DIN-A Applications).

G.3 Preamble

Background

The *Common Technical Document - Quality* (CTD-Q) (Module 3) outlines the format of the Quality portion of applications for New Chemical Entities (or new active substances) within the 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 in **bold** following each section title is taken directly from the ICH CTD-Q guideline. The draft Quality (Chemistry and Manufacturing) guidance, 2001, has been updated to incorporate advances in science, ICH regulatory guidance documents and current regional requirements.

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).

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 evaluation 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

guidance documents, principles of applying sound science and risk management to the systematic development of drugs, and current Quality standards and terminologies.

By completing the QOS-CE (NDS/ANDS) template, sponsors share the responsibility for the generation of the Quality evaluation report. Examples of the benefits of using the QOS-CE (NDS/ANDS) template include:

a) improves drug submission quality by ensuring sponsors appraise and systematically present the information by preparing the QOS-CE (NDS/ANDS);

b) provides further guidance on expectations for drug submission content;

c) promotes consistency and quality both in preparation of drug submissions as well as in the subsequent internal reviews, thereby contributing to efficiencies in the overall review process.

d) expedites the review process by enabling Evaluators to spend their time more efficiently on drug submission assessment;

e) provides prompts to summarize information in the QOS-CE (NDS/ANDS) template that is key to Health Canada's decision making.

While both ICH's QOS and Health Canada's QOS-CE (NDS/ANDS) template provide an overview of the information presented in the Quality Module, the latter is meant to define the type and extent of information which is included in the Canadian Quality evaluation report, including regional requirements. Drug submission sponsors are encouraged to complete Health Canada's QOS-CE (NDS/ANDS) template to help ensure an effective and efficient review of drug submissions. It is recommended that the QOS or QOS-CE (NDS/ANDS) be limited to the minimum number pages required to summarize key information (e.g. 40-100 pages).

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.

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.

G.4 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 Evaluator's time in retrieving, reviewing and summarizing data.

In developing Health Canada's QOS-CE (NDS/ANDS) template, a balanced approach was taken for providing sufficient instruction on content of information while accommodating variability in the types of studies and products described in the drug submissions. Essential elements of the minimal approach and the enhanced, Quality by Design approach (as described in ICH's Q8 guideline) and terminologies have been introduced to facilitate an efficient review process.

It is recognised 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, additional modification of table structure or the substitution of a narrative paragraph can also be warranted in certain circumstances. All headings listed in the default sections or tables 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.

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 approved or while the NDS/ANDS review is in progress) and the information has not changed subsequent to that filing, the relevant section should be cross referenced, and so noted in the Introduction to the QOS.. The Introduction should include the names of the cross-referenced drug product and sponsor, date of the Notice of Compliance (if applicable), and submission file 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.

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). A list of applicable Quality guidance documents are provided in the Miscellaneous Section (M) to this guidance document. 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 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) 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. The information that should be provided on the drug product should be as described in this document *Quality Guidance: NDSs and ANDSs*.

d) When filing a response to a request for clarification/additional information from Health Canada (e.g. Request for Clarification (Clarifax), Notice of Non-compliance (NON), Notice of Deficiency (NOD)), sponsors should use the applicable sections of the QOS to summarize new or updated data (e.g. specifications, analytical procedures, stability results) in the response. Generally, an updated QOS should not be submitted as Health Canada uses the first QOS submitted to prepare review reports. However, in the case of an NOD or an extensive NON where the magnitude of deficiency comments warrants the filing of replacement volumes, a refiled/updated QOS can be necessary.

a) In order to facilitate the processing and evaluation of responses to requests for clarification/additional information from Health Canada, all solicited information should be submitted in a question and answer format which is cross-referenced to replacement volumes where appropriate.

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, packaging, storage, shelf life, and commitments). Most important, it serves as a valuable knowledge management tool and a

reference document to track the changes in the Quality information in the drug product during its lifecycle. It is a useful document for both the sponsor and the regulator. 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, it is preferable that the proposed CPID-CE be submitted with the submission, as it helps the review division in planning and allocating the required resources for an efficient review process. For post-approval changes (e.g. Supplements), the CPID-CE should be completed in its entirety regardless of the proposed changes including information on all dosage forms, and be provided at the time of filing. It is acknowledged that when filing a submission for a post-approval change, the updated CPID-CE may include changes that did not need prior approval by Health Canada (e.g. Annual Notification). An annotated version highlighting changes is considered useful in distinguishing changes proposed in the S(A)NDS versus those made and submitted as Annual Notifications. Health Canada's position is that data supporting these changes have been generated and evaluated by the company prior to their implementation and that the data are available for Health Canada's review on request.

MODULE 2.3: QUALITY OVERALL SUMMARY (QOS)

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 may provide other introductory information, such as a contact person's name, phone number, fax number, and e-mail address for ease of communication. The introductory information can also include other salient points of the drug submission (e.g. filing and marketing status and brand name in other jurisdictions, cross-referenced drug product, date of the Notice of Compliance (if applicable), submission number and control numbers).

S DRUG SUBSTANCE

In this guidance, the term "active pharmaceutical ingredient" (API) (as defined in C.01A.001(1) of the Regulations) and the term "drug substance" should be considered interchangeable and refer to the API used as raw (input) material in the fabrication 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) as the medicinal ingredient contained in the drug product, which should be identified on product labelling in accordance with C.01.004(1)(c).

Drug Master Files (DMFs)

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 Drug Master File (DMF) directly with Health Canada. The supplier would then be considered the DMF Owner. This DMF 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 DMF Owner or Canadian Agent (i.e., via a letter of access). Copies of letters of access should be provided in Module 1. If a Canadian Agent is used by the DMF Owner, a letter from the DMF Owner should be submitted allowing the agent to act on their behalf, rather than the letter being written by the Canadian Agent.

It is the sponsor's responsibility to submit the relevant non-proprietary information provided by the DMF Owner (e.g. from the Sponsor's ("Open Part" of DMF), obtained in the public domain, and/or developed by the sponsor. For recommendations on the content of DMFs, Health Canada's guidance document entitled *Drug Master Files* (DMFs) should be consulted. When the sponsor summarizes data obtained from the DMF Owner (or from published scientific literature), the source of the reproduced information should be clearly identified.

The drug submission sponsor should ensure that the information included in the DMF is up to date and that the DMF has been received by Health Canada. Consult HC guidance on DMFs for further information.

With respect to information on the Drug Substance, the sponsor should be able to provide most of the information, except for certain proprietary information, e.g. as found in Module 3.2.S.2 for the Drug Substance. It is the responsibility of the sponsor to obtain all other information from the supplier of the drug substance and include this in the drug submission. The information from the Sponsor's ("Open") DMF should be provided in various sections of the drug submission and summarized in the QOS.

Regardless of the information provided by the supplier of the drug substance, the manufacturer of the dosage form is responsible for ensuring that acceptable specifications and properly validated analytical procedures for the drug substance are developed and for providing the results of batch analyses.

References:
Drug Master Files

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

Health Canada encourages the filing of CEPs when they are available. An appropriately referenced CEP will expedite the review 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 the Health Canada 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 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 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. Additional details should be provided in 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 physical and chemical properties of the drug substance such as the physical description, solubilities in common solvents (e.g. including those used in the manufacturing process, analytical methods or for cleaning), quantitative aqueous pH solubility profile (e.g. water, pH 1.2 to 6.8, dose/solubility volume), polymorphism, pH and pKa values, UV absorption maxima and molar absorptivity, melting point, 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.

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.

Solubility/quantitative aqueous pH solubility profile:

Information on the solubility of the drug substance in a number of common solvents (e.g. water, alcohols, buffers, solvents used for manufacturing) should be provided. Information on the solubility over the physiological range, pH 1.2-6.8, should also be provided to determine the Dose/Solubility volume ratio where applicable (e.g. solid orals). If this information is not readily available (e.g. literature references, 'Open' DMF), it should be generated in-house. Phrases such as "sparingly soluble" or "freely soluble" should be avoided.

The dose/solubility volume is calculated based on the minimum concentration of the drug [in milligram/millilitre (mg/mL)], in the highest dosage strength, 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. This drug would be considered a low solubility drug as its dose/solubility volume is 400 mL (400 mg/1.0 mg/mL).

Biopharmaceutics Classification System (BCS) information:

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

References:

ICH Q6A
Biopharmaceutics Classification System Based Biowaiver

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 fabrication and testing of the drug substance or key 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 release testing sites for all Drug Substances are required to have Good Manufacturing Practices (GMP) compliance ratings issued by Health Canada. GMP requirements for sites involved in Drug Substance manufacturing may change depending amendments to the *Food and Drug Regulations*.

Drug substances that need special handling and/or precautions during handling due to their inherent nature (e.g. antibiotics, cytotoxic materials) should be identified.

If a DMF is filed with Health Canada and cross-referenced for certain proprietary information (e.g. sections Modules S 2.2, S 2.3, S 2.4, and S 2.6), the DMF number assigned by Health Canada should be provided.

Where applicable (e.g. the manufacture of sterile drug substances, testing facilities), information relating to GMP compliance ratings issued by Health Canada should be provided in Module 1.

Good Manufacturing Practices requirements for the manufacture of Drug Substances come into effect on November, 8 2013. Information relating to the GMP status of facilities involved in the manufacture of non-sterile drug substances should be provided in Module 1.

References:
ICH Q7A
Good Manufacturing Practices (GMP) Guidelines
Drug Master Files (DMFs)

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 molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and drug substance reflecting stereochemistry, and identifies operating conditions and solvents.

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 critical steps, process controls, yield, equipment and process parameters (e.g. temperature, pressure, pH, time).

Alternate processes (including those used for reprocessing) 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 3.2.S.2.5.

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

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 can 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.

Starting material:

A starting material is proposed by the applicant and approved by Health Canada. The selection of a particular compound as the starting material for synthesis and its specifications should be justified. ICH Q7 defines the point from which GMP requirements apply to the synthetic process in some jurisdictions.

ICH Q11 describes the general principles to be considered when selecting starting materials. While Health Canada accepts these principles, it does not preclude the necessity to provide information on the route of synthesis of the starting material in order to fully characterize the impurity profile and to justify specifications for the starting material or drug substance. The information which should be provided to Health Canada should permit the complete evaluation of the safety and quality of the drug substance. In many cases, the information provided on the route of synthesis may precede the ICH Q7 starting material by several steps in the synthetic process. The level of detail required in the manufacturing description depends on the criticality 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. For commercially available starting materials, the complexity of the starting material will determine the level of detail to be provided when describing the route of synthesis of the starting material.

In general, the starting material for chemical synthesis of a drug substance should:

- be a synthetic precursor where multiple synthetic steps separate the starting material from the final drug substance,
- be a significant structural fragment which is incorporated into the drug substance, but not an intermediate which differs by only one functional group/component from the final product unless that intermediate is a drug substance in itself and hence fully controlled and manufactured under GMPs for APIs,
- be a well characterised, isolated and purified substance with structure fully elucidated,
- have well defined specifications which include one or more specific identity tests, and tests and limits for potency, specified and unspecified impurities and total impurities.

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

Each branch of a convergent drug substance manufacturing process begins with one or more starting materials.

Information on the route of synthesis and purification of the drug substance should be provided (e.g. in S.2.6) in a manner that allows the assessment of the fate and purging of all potential

impurities, including regioisomeric and stereoisomeric impurities, toxic (including genotoxic) impurities, residual solvents and residues of catalysts in the starting material**.**

This information may include:

- A flow chart and brief narrative description of the synthesis with all the reagents, solvents, and intermediates specified.

- Potential for the presence of adventitious agents, including viral and bacterial agents, residual proteins and TSE agents should be discussed.

- From the API starting material onwards, complete details of the process are necessary, and these should include quantities of raw materials, description of equipment, 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.

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, 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). All processing steps after harvesting should be well documented (e.g. drying equipment and time, treatment of plant material (e.g. solvent extraction, pesticides)). It may be necessary to include limits for residues resulting from such treatment in the drug substance specification. Discussion, which may include supporting data, should be provided to demonstrate absence of toxic metals and radioactivity.

Micronized/milled Drug substances

Micronization or milling may be a critical step for certain drug substances, e.g. for poorly soluble drug substance used in a tablet or powder inhalers or to ensure process capability. In such instances, the type of equipment and critical process parameters (equipment setting, and operating conditions) necessary to produce lots with consistent particle size distribution should be described.

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.

References:
ICH Q7, Q8, Q11

S.2.3 Control of Materials

Materials used in the manufacture of the drug substance (e.g. raw materials, 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 specifications for the materials used in the synthesis, fermentation, extraction, isolation, and purification steps should be provided in the drug submission. If recovered materials (i.e. solvents, intermediates) are used, the details of purification and the specifications for the recovered materials should be provided or confirmation that the specifications are identical to those used for the fresh material and justification of the suitability of these specifications should be provided.

Specifications for starting materials should include tests and acceptance criteria for appearance, identity, purity, and potency, where applicable. Well-defined controls of potential impurities should be included. Special consideration should be given to potential isomeric impurities and genotoxic 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 Bovine Spongiform Encephalopathy (BSE)/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 BSE/TSE affected country/area, or data should be provided demonstrating that the material is not at risk of transmitting BSE/TSE (e.g. an EDQM Certificate of Suitability).

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

S.2.4 Controls of Critical Steps and Intermediates

Critical Steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in S2.2 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.

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 potency, where applicable. Well-defined controls of potential impurities should be included. Special consideration should be given to potential isomeric impurities and genotoxic impurities, particularly those that could be carried through the synthesis to the drug substance.

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 consistently rapid and complete).

In-process drug

A drug substance is considered be an in-process drug if it is mixed with any material or mixture of materials that must undergo further processing to become the drug in dosage form. If this activity is performed by the drug substance manufacturer/supplier as part of the raw material used in a drug product, then it is subject to the GMPs for manufacture of drug products (C.02 of the Food and Drug Regulations) and the expiry date of the drug product should be assigned based on the date of manufacture of the in-process drug. Any exception to this practice (e.g. inability to isolate the drug substance in a pure and stable form) should be justified.

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.

It is expected that the manufacturing processes for all drug substances, including any justified alternate manufacturing processes, should be validated before commercial distribution of the resulting drug product.

For non-sterile drug substances results of process validation studies are not normally included in the 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 of 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. 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 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 or polymorphic form of the drug substance used during development compared to the drug substance used in the commercial product should be discussed.

References:
ICH Q3A, Q8, Q11

S.3 Characterisation

S.3.1 Elucidation of Structure and other Characteristics

Confirmation of structure based on e.g. synthetic route and spectral analyses should be provided. Information such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs should also be included.

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). The drug submission should include copies of the spectra, peak assignments, and a detailed interpretation of the data.

For drugs with a compendial reference standard, it is generally sufficient to provide copies of the IR and UV spectra of the drug substance from the proposed suppliers run concomitantly with 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, NMR, MS). See section S 5 for further details on References Standards or Materials.

To establish pharmaceutical equivalence (e.g. in an ANDS), include a summary of any comparative studies performed.

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

It is recognized that some drugs (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), the physicochemical characterization of the components and their ratio should be submitted.

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 mesoisomer.

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:

If the potential for polymorphism is a concern, 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.

In-Situ Conversion:

Where investigation of the drug product reveals that the physical (e.g. polymorphic or pseudopolymorphic) 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 both forms - the API and medicinal ingredient contained in the drug product.

Particle size distribution:

For poorly soluble drug substances, the particle size distribution of the material 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. 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), results from an investigation of several (at least three) 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). 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).

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

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. 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 in synthesis should be identified.

Justification of Proposed Acceptance Criteria:

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 reviewed 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 >0.1%, ID threshold >0.5%, qualification threshold >1.0%), although different thresholds (either higher or lower) may be considered appropriate 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 (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).

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 is some latitude for these types of drug substances (e.g. a limit of NMT 0.20% for unspecified impurities may be appropriate, 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 may be presented. A limit equivalent to the level found in the Canadian Reference Product would be considered supportive provided there are no other reasons that would indicate otherwise (e.g. no genotoxic structural alerts).

The basis for setting the acceptance criteria for the impurities should be provided. This is established by considering the identification and qualification thresholds for drug-related impurities (e.g. related substances) and the concentration limits for process-related impurities (e.g. residual solvents) as per the applicable ICH guidance document (e.g. Q3A, Q3C). 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 are also 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, and comparative 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.

Qualifying limits for specified impurities is normally based on the levels found in the nonclinical and clinical batches at the time the studies were conducted, rather than levels observed on stability or levels found in subsequent batches manufactured according to the proposed commercial process. Impurity levels in the drug product can also be presented for comparative batches (e.g. for a comparative purity study of a generic product against the Canadian Reference Product).

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). The use of a tabulated summary of drug substance batch numbers, levels of impurities and study reference numbers for qualifying studies is strongly encouraged.

Genotoxic impurities:

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

Summarization of data in the QOS:

The QOS should summarise the data on potential and actual impurities arising from the synthesis, manufacture and/or degradation, and should summarise the basis for setting the acceptance criteria for individual and total impurities. It should also summarise 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 state how the proposed impurity limits are qualified. If a complete description of impurities is included in this section, Sections S.4.4 Batch Analyses and S.4.5 Justification of specifications should refer back to this section for relevant information on impurities.

References:

ICH Q3A, Q3C, Q6A
ICH M7

Stereochemical Issues in Chiral Drug Development

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 approved by regulatory authorities as conditions of approval.

Signed and dated 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 specification should be dated and signed by authorized personnel (i.e., the person in charge of the Quality Control department or designate). Electronic signatures are also considered acceptable if certified in accordance with an acceptable standard (e.g. FDA's 21CFR, Part 11). The specifications should include tests, acceptance criteria, and reference to analytical methods, and a version number. The specification reference number, version, and date should be provided for version control purposes.

Specifications can comply with one of 4 types of standards. Regardless of the standard claimed, the specifications must be acceptable to the Minister.

- Professed Standard (e.g. where no prescribed or compendial standard exists),
- Prescribed Standard (e.g. Canadian Standard Drugs in Part C, Division 6 of the *Food and Drug Regulations*),
- Compendial Standard as per Schedule B of the Food and Drugs Act (e.g. USP, Ph.Eur., BP), or a
- Manufacturer's or House Standard (e.g. differs in some respect to an existing compendial standard).

Although a Schedule B compendial monograph may exist, a sponsor can choose to use a Manufacturer's Standard which indicates that the material may differ in some respect from the

compendial standard. However, according to section C.01.011 (4) of the *Food and Drug Regulations*, no person shall use a manufacturer's standard for a drug that provides (a) a lesser degree of purity than the highest degree of purity and (b) a greater variance in potency than the least variation in potency, provided for that drug in any publication mentioned in Schedule B to the *Act*. Therefore, if a manufacturer's standard is used, the controls on purity (e.g. limits on specified identified impurities and total impurities) and potency should be at least as stringent as the most stringent of those limits listed in any of the Schedule B compendial monographs. If a solvated form of the drug substance is used other than that declared in a compendial monograph, the standard would be professed.

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, criteria should be incorporated into the drug substance specification to 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 not required for drug substances that are highly soluble, although potential impact of polymorphism on manufacturability and stability should be considered. Justification for the exclusion of controls for polymorphism for poorly soluble drug substances should be provided. 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.

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, IR, UV, HPLC, 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, Q6A
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S.4.2 Analytical Procedures

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

Copies of the in-house analytical procedures for routine testing should be provided. Copies of historical analytical procedures that have been used during drug development, but are not intended for routine testing purposes, should be provided either in S.4.4 (for batch analyses) or S.7.3 (for stability testing), whichever 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 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. 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, provided the response factors (RF) of those impurities are sufficiently close to that of the drug substance (e.g. 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 may still be acceptable to use the drug substance, 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 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 the limit for unspecified impurities. In accordance with the USP General Chapter on Chromatography and Health Canada's guidance document *Acceptable Methods*, 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 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
Acceptable Methods (available by emailing bps_enquiries@.hc-sc.gc.ca)
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.

Copies of the validation reports for the analytical procedures employed for routine testing should be provided in S4.3. Copies of validation reports for historical analytical procedures that have been used during drug development but are not intended for routine testing purposes, and a summary of differences between these historical analytical procedures and those proposed for routine analysis, should be provided in either Sections S.4.4 (for batch analyses) or S.7.3 (for stability testing), whichever is applicable.

Different sources of the same drug substance can contain impurities and degradation products that were not considered during the development of the monograph and the extent of studies required 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 may need to 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 potency or for specified impurities), equivalence of the House and compendial methods should be demonstrated. This could be accomplished by performing replicate analyses of two samples by both methods and providing comparative results from the study. Alternate approaches to demonstrating equivalency of analytical procedures may be considered acceptable, if scientifically justified.

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 impurity method, a summary of the results for specificity, linearity, range, accuracy, precision (repeatability, intermediate precision), LOD, LOQ, robustness). 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 templates available from Health Canada are used for summarizing analytical validation data. 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
Acceptable Methods

S.4.4 Batch Analyses

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

A tabulated summary of batch number, batch size, date and site of production, and specific use including clinical/pre-clinical study numbers, the testing site, etc. should be provided for relevant drug substance batches. Analytical results should be provided for those batches used in nonclinical, clinical, comparative bioavailability, pharmaceutical equivalence, and stability studies, including batches manufactured at pilot scale ($1/10^{th}$ commercial scale) and, if available, production scale. The number of batches should be sufficient to support the specification(s) and evaluate 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, while preferred, need not be provided, however, a tabulated summary should be sufficiently detailed including range, mean and relative standard deviation of

individual results, results of all tests conducted regardless of whether they are in the currently proposed specifications, quantitative results for all tests ('complies' is not sufficient), RRT and quantity of all unspecified impurities, limits of detection where applicable (e.g. when impurities are not detected).

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, potency, residual solvents), it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms". Even if impurities, including individual unspecified impurities, are not detected, the summary should include these impurities with a statement they are not detected and the LOD if 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.

A summary of analytical procedures and validation information for those procedures not previously summarized in S.4.2 and S.4.3 (e.g. historical analytical procedures) should be provided.

References:
ICH Q3A, Q3C, Q6A
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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, evolution of tests, analytical procedures, acceptance criteria, and any differences from 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.

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.

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 do not need to be repeated here, although a cross-reference to their location should be provided.

References:
ICH Q3A, Q3C, Q6A, Q11
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S.5 Reference Standards or Materials

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

Reference standard

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, potency tests).

Primary reference standards can be obtained from official sources such 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. IR, UV, NMR, MS). All data supporting structure elucidation, strength and purity should be submitted. A certificate of analysis should also be submitted with purity 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 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 copies of certificates of analyses should be provided.

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

References:
Q6A
Acceptable Methods

S.6 Container Closure System

A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification (and drawings with critical dimensions, where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

For non-functional secondary packaging components (e.g. those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information 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 CFR or EEC Regulations for food safe materials.

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 re-test 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, it is believed that the recommendations also should be applied to applications for existing drugs (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.

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.

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. Mass balance can be used to demonstrate that methods are stability indicating and all degradation products are detected by the methodology.

The table in Health Canada's QOS-CE (NDS/ANDS) template can be used to summarize the results from the stress testing. 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. potency, 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).

Accelerated and long term testing:

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

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

General case:

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

To support alternate 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. If the route of manufacture or process conditions are changed, then results for at least 2 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 approved one.

In exceptional cases, information available in the public domain may be sufficient to establish an appropriate re-test 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.

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 re-test period:

The proposed storage conditions should normally include a temperature range (e.g. upper and lower temperature limits) and re-test 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), the following storage recommendation would generally be considered acceptable:

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

Based on the results of the stability evaluation, additional storage precautions may be warranted (e.g. "Protect from light", "Protect from moisture"). Precautionary statements should not be a substitute for selecting the appropriate 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 re-tested 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 re-test period.

Monitoring of transportation

For a drug substance posing a higher risk (e.g. sterile drug substance or a drug substance requiring stringent storage conditions) a transportation study is recommended to support the use of proposed packaging and handling until the drug substance is ready to be used for the manufacture of the drug product.

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 re-test 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 shelf life. The long term stability studies for the Commitment Batches should be conducted through the proposed shelf life/re-test period (and the accelerated studies for six months, if relevant) on at least three production batches.

The stability protocol for Commitment batches should include, but is not limited to:

(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 batches or 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 re-test 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 mg, 10 mg, and 20 mg) each debossed with the markings "XXX". The two higher strengths include a vertical 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 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), including the total weight or measure of the dosage unit.

This should include all components used in the manufacturing process, regardless if they appear in the final drug product (e.g. solvents, nitrogen, silicone for stoppers). If the drug product is formulated using a salt or solvate and the strength is declared as 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 or manufacturing excesses should be clearly indicated (e.g. "Formulated with 2% overage of the drug substance to compensate for manufacturing losses.").

The components should be identified 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)").

The qualitative composition should be provided for all proprietary components or blends (e.g. capsule shells, colouring blends, imprinting inks). This information is used for product labelling purposes. Reference to a Drug Master File can be provided for the actual *quantitative* composition.

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 Table 1 of the Guidance Document "Bioequivalence of Proportional Formulations") that it could have 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 guidance 'Bioequivalence of Proportional Formulations', then justification should be provided for the proposed variation (e.g. granule size distribution, tablet hardness, dissolution).

The use of alternative excipients in a formulation is generally not considered acceptable without data to demonstrate that the quality and performance of the drug product has not changed. Use of different grades or ranges for excipients quantities are generally not accepted unless supported by in-vitro and if necessary in-vivo data. Adjustment of a filler to account for as-is-assay of the active 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 reviewed and approved in connection with another drug submission with Health Canada, information on the diluents should be provided in a separate Drug Product ("P") portion, 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 P7 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. Potential *critical quality attributes* (CQAs)* of the drug product should be identified.

Typical quality attributes and process parameters vary for different dosage forms. Some of 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.

Usage instructions found in the Dosage and Administration part of the Product Monograph need to be supported by adequate data (e.g. in-use periods, compatibility with co-administered substances/diluents, scored tablets, sprinkling studies to support sprinkling content of capsules on food, dispersion in liquid, use of a feeding tube, storage of admixtures, etc.). For existing drugs, e.g. generics, the dosage and administration section should be the same as that of the Canadian Reference Product.

References:
ICH Q6A, Q8
Validation Guidelines for Pharmaceutical Dosage Forms (including product specifc validation guidelines)

* The definitions of these terms can be found in the ICH guidance Q8.

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 combination products, the compatibility of drug substances with each other should be discussed.

Specific attributes (CQAs) of the drug substance that can impact on manufacturability should be identified. (e.g. sensitivity to light, heat or moisture).

An API may be converted to a different chemical or physical form (e.g. in situ conversion of free base to salt, change of polymorphic form) during the drug product manufacturing process. Such a conversion could be 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. 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, as the medicinal ingredient contained in the final dosage form.

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

The Food and Drug Regulations allow a drug submission to be submitted as an ANDS if the product meets the requirements for "pharmaceutical equivalence" as per Section C.08.001.1 of the Food and Drug Regulations. Among the criteria to establish pharmaceutical equivalence, the product must contain an identical medicinal ingredient to the Canadian reference product. To determine this, the guidance document "Identical Medicinal Ingredients" should be consulted. A submission failing to meet the requirements should be submitted as an NDS.

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

Potential toxicity of drug substance (e.g. antibiotics, cytotoxic agents, hormones) should be identified and precautions to segregate and/or dedicate the handling of the drug product to prevent cross-contamination (over and above routine GMP requirements) should be described in P3.3b.

Reference:
Identical Medicinal Ingredients 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 for control of critical ingredients (e.g. viscosity of a rate controlling excipient).

Where relevant, compatibility study results (e.g. compatibility of a primary or secondary amine with lactose) should be included to justify the choice of excipients.

As absorption enhancers 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).

A certification should be provided that none of the excipients which appear in the drug product are prohibited for use in drugs by the Canadian *Food and Drugs Act and Regulations* (e.g. colouring agents).

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 differences between clinical formulations and the formulation (i.e., composition) described in P1 should be discussed. Results from comparative *in vitro* studies (e.g. dissolution) or comparative *in vivo* studies (e.g. bioequivalence) should be discussed, when appropriate.

Ideally formulation development should use a systematic 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 including transdermal patches, liposomal, microemulsion, depot injection). The rationale should be linked to the QTPP and CQAs.

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

For products where a biowaiver is supported by an in-vitro in-vivo correlation (IVIVC), IVIVC-simulated pharmacokinetic data should be provided in Module 5.

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

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 generally not acceptable. However, if the overage is required to make up for loss in manufacturing process (e.g. loss during vacuum transfer) or to fill void space (e.g. excess coating solution to fill the pipes) it should be presented along with justification 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, the results of a study should be provided testing the uniformity of dosage units of the manually-split tablet halves. 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 10 randomly selected whole tablets. As an illustrative example, the number of units (i.e., the splits) would be 20 halves for bisected tablets or 40 quarters for quadrisected tablets. At least one batch of each strength should be tested. Ideally, the study should cover a range of the hardness values. 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 USP General Chapter <905> Uniformity of Dosage Units for whole tablets. Testing according to the criteria in the European Pharmacopoeia General Chapter 0478 would also be considered acceptable.

For modified release products with a score line, equivalent rates of release should be demonstrated for the split halves vs. the whole tablet. If immediate or modified release products cannot be split or should not be split a score line should not be 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.

P.2.3 Manufacturing Process Development

The selection and optimisation of the manufacturing process described in P3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified. Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in P3.3 that can influence the performance of the product should be discussed.

In accordance with C.08.002(2)(m) and C.08.002.1(2)(d) of the Food & 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 scientific rationale using the principles of risk management for the choice of the manufacturing, filling, and packaging processes 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 during the manufacturing process should be discussed (e.g. protection from heat, light or moisture, controls during wet granulation).

For drug products developed using an enhanced Quality by Design approach, 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 Testing, omission of drug product specification test for impurity(ies).)
c) discuss the role of QbD in the overall control strategy (e.g. to support real time release (RTR) 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 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.

Environment controls necessary during the manufacturing process such as reduced lighting, temperature and humidity control and inert atmosphere should be evaluated.

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 critical process parameters that are linked to CQAs of the drug product (e.g. the rate of addition of granulating fluid, massing time, granulation end point, and drying end point (LOD) which determine the quality of the granules). The equipment should be identified 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 SUPAC class but different SUPAC subclass, 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 manufacturing process for higher risk products should be chosen carefully. In such instances 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 has a Narrow Therapeutic Index, or is a critical dose drug and the drug product is not a solution.
2) Strength (low dose): When the 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).

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, etc.

Sterile products

For sterile products, terminal steam sterilization, when practical, is considered to be the method of choice to ensure sterility of the final drug product. Therefore, scientific justification for selecting any other method of sterilization should be provided.

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 F_0 range, temperature range and peak dwell time for a drug product and the container closure 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, studies and acceptance criteria should 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, compatibility with the product, extractables and leachables and adsorption of the drug substance or any of the formulation components.

Minimum product rinse volumes should be established.

Containment and prevention of cross-contamination:

Steps taken to minimise the risks due to inadvertent cross-contamination should be discussed for drug products that need special handling, containment and/or precautions during handling due to their inherent nature (e.g. antibiotic, hormones, extremely toxic compounds) or to prevent microbial and particulate contamination (e.g. sterile products).

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.

	Oral and Topical Products	**Inhalation Products**	**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	√	√	√
Tests for reproducibility of dose delivery (or packaging materials responsible for delivery of a dose)	√ (if applicable)	√	Drop size (ophthalmics)
Composition and drawings for all components (including cap liners, coatings for metal tubes, elastomers, adhesives, silicon, etc.)	√	√	√

Description of any additional treatments[1]	√	√	√ (sterilization and depyrogenation of the components)
USP <661> Containers	√	√	√ (includes USP <87> / <88> /<1031> tests)
USP <671> Containers - Permeation	√	√	√
USP <381> Elastomeric Closures for Injections	--	--	√ (includes USP <87> / <88> tests)
Additional tests	2	2	2

√ 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)

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 Drug Master File. Refer to Health Canada's guidance document *Drug Master Files* for filing requirements for Type II DMF's (packaging materials).

References:
Pharmaceutical Quality of Aqueous Solutions
Drug Master Files

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 and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. 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 preferably 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 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). Where the labelling specifies co-administration with other drugs, compatibility should be demonstrated with respect to the principal drug as well as the co-administered drug (i.e., in addition to other aforementioned parameters for the mixture, the assay and degradation levels of each co-administered drug should be reported).

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 reference product to adequately qualify the impurity and other limits proposed in the drug product specification(s).

P.3 Manufacture

If a Drug Master File (DMF) is filed with Health Canada and cross-referenced for certain proprietary information, provide the DMF 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 and testing should be provided.

This includes the facilities involved in the fabrication, packaging, labelling, testing, importing and distribution of the drug product. If certain companies are responsible only for specific steps (e.g. manufacturing of an intermediate), this should be indicated. 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 Canadian Inspectorate 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, and a reference to their quality standards.

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, nitrogen, silicon for stoppers). If the amount of active ingredient is adjusted (e.g. based on the potency 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)).

The Master Formula should be written to provide not less than 100% of label claim unless overages have been adequately justified. All manufacturing overages should be clearly indicated (e.g. “Contains 5 kg overage of the drug substance to compensate for manufacturing losses.”).

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, that represents the sequence of steps undertaken and the scale of production should also be provided. 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.

Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced or filed in this section (P 3.3).

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. The proposed commercial batch sizes should be stated (See section R 1 for the discussion on production scale). 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 can 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.

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. 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.

Validated hold times should be included. Unless clearly stated and authorized, the start of manufacturing (for purposes of establishing product shelf life) is defined as the first date of processing of the drug substance, regardless of whether a drug product intermediate is manufactured at another facility. Unless data are available to support longer hold times, the time

from start of manufacture to the end of packaging (or end of sterilization for a terminally sterilized product) should generally not be more than 30 days for stable solid drug products (or 24 hours for liquids).

Proposals for reprocessing of failed batches will not be evaluated during the pre-market review and should not be submitted. Any reprocessing of batches is authorized on a case-by-case basis by the regional Inspectorate only. If routine reprocessing of materials is expected (e.g. recirculation of fines), then this should be submitted as part of the manufacturing process with relevant supporting data.

For sterile products, the sterilization cycle should be described where contract manufacturers are used for sterilization of packaging components.

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.

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

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; (iv) *transdermal patches:* assay of drug-adhesive mixture, weight per area of coated patch without backing, adhesion strength; (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; (viii) *parenterals:* appearance, clarity, fill volume/weight, pH, filter integrity tests, particulate matter.

Weight variation controls:

The industrial 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 – 4 %
- Individual tablet weight: target weight ± 5%

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 (e.g. ±7.5% for individual weight) is only 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. an orally disintegrating tablet that is difficult to manufacture.

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.

The following information should be provided:

a) A copy of the process validation protocol or validation report specific to this 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 this 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 depyrogenating of containers, closures, and equipment.
c) Filtration of solutions.
d) The lyophilization process.
e) Assessment of potential interruptions during sterilization cycle.

f) The integrity test of filled and sealed container closures.
g) Final inspection of the product.

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 those that do not appear in the final drug product (e.g. solvents, nitrogen, silicon 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.

Testing should be at least as stringent as specified in the Schedule B compendia monograph should one or more exist. Excipients derived from natural sources should have appropriate microbial tests and limits.

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 P4.6 or cross-referenced to the Drug 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
Acceptable Methods

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.

Copies of analytical validation information should be submitted for novel test methods. 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 the templates available from Health Canada are used for summarizing analytical validation data.

Reference Guidances:
ICH Q2
Acceptable Methods

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, 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 kept on file) should be provide 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.

For gelatin and other high risk excipients a Certificate of Suitability should be provided. Alternatively, the relevant information from the proposed supplier should be provided in a Drug Master File, which is registered with Health Canada.

Reference Guidances:
ICH Q5A, Q5D, Q6B

P.4.6 Novel Excipients

For excipient(s) used for the first time 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 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.

If toxicological information is submitted to support a novel excipient or daily exposure of excipient, a summary of studies found in Module 4 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 may be necessary in certain cases in order to ensure that shelf life acceptance criteria are met throughout the labelled shelf life of the drug product.

Refer to S.4.1 for detailed information about types of standards which can be declared. Although a Schedule B compendial monograph may exist, a sponsor can choose to use a Manufacturer's Standard which indicates that the material may differ in some respect from the compendial standard. However, according to section C.01.011 of the *Food and Drug Regulations*, no person shall use a manufacturer's standard for a drug that provides (a) a lesser degree of purity than the highest degree of purity and (b) a greater variance in potency than the least variation in potency, provided for that drug in any publication mentioned in Schedule B to the *Act*. Therefore, if a manufacturer's standard is used, the controls on purity (e.g. limits on specified degradation products) and potency should be as tight as the most stringent of those listed in the Schedule B compendial monographs.

A copy of the signed and dated 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).

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.

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.
Transdermals	Peel or shear force, mean weight per unit area, *in vitro* drug release, monitoring for crystal growth.

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

References:
ICH Q3B, Q3C, Q6A

P.5.2 Analytical Procedures

The 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.

Professed or House methods:

Copies of the house analytical procedures used during the drug development (if used to support testing results in the drug submission) as well as those proposed for routine testing should be provided.

The system suitability tests (SSTs) are an integral part of chromatographic analytical procedures. At a minimum, HPLC and GC assay methods should include a SST for repeatability. For HPLC 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 and Health Canada's guidance document Acceptable Methods, the repeatability test should include an acceptable number of replicate injections (i.e., five or six).

For purposes of summarizing analytical methods and validation in the QOS, tables in electronic format are available from Health Canada (email bps_enquiries@hc-sc.gc.ca).

References:
ICH Q2
Acceptable Methods

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 duplicate analyses of one sample by both methods and providing the results from the study.

As outlined in Health Canada's guidance document *Acceptable Methods*, 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.

References:
ICH Q2
Acceptable Methods

P.5.4 Batch Analyses

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

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

Number of batches:

It is generally expected that a minimum of two batches of each strength should be manufactured at a minimum of pilot scale ($1/10^{th}$ commercial scale) from each proposed commercial manufacturing site, and that complete analytical results should be provided for those batches. 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, a minimum of one commercial scale batch should be manufactured. See P2.3 for further guidance on when batch analyses should be of batches manufactured at a commercial scale.

Certificates of analysis need not be provided, however, the tabulated summary should be sufficiently detailed including range, mean and relative standard deviation of individual results for content uniformity and dissolution, results of all tests conducted regardless of whether they are in the currently proposed specifications, quantitative results for all tests ('complies' is not sufficient), RRT and quantity of all unspecified impurities, limits of detection where applicable (e.g. when impurities are not detected).

References:
ICH Q3B, Q3C, Q6A

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, Q6A

P.5.6 Justification of Specification(s)

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

The overall control strategy should be described in P.5.6, preferably in tabular format, and should identify the 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).

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 in-vitro in-vivo correlation (IVIVC) is established.

Dissolution results should be submitted for several lots of each strength, 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 (apparatus, rotation speed, medium) should be provided. 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 product under review.

Alternatively, 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 poorly water soluble drugs if the time to achieve ≥85% (NLT 80% (Q) according to USP) exceeds 30 minutes, a two-point test should be considered.

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% or ± 10% of the targeted value.

For **opioids and other drug 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 4%, 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 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.

Transdermal patch adhesion:

Adhesion of the patch should be tested to evaluate 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 Q6A

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. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

For non-functional secondary packaging components (e.g. those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

Suitability information 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, 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;

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

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.

General recommendations for routine testing

	Oral and Topical	Inhalation	Sterile Products (including Ophthalmics)
Specifications for routine testing:			
Name, physical description, dimensions (e.g. thickness)	√	√	√
Specific identification tests (e.g. IR) for components that come in direct contact with the dosage form	√	√	√
Performance characteristics necessary for product delivery	√ (if applicable)	√	√

√ - The checkmark represents tests that should be included routinely in the container closure component specifications.

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 summarised. 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.

Stress studies to demonstrate degradation of the drug product should include evaluation of the mass-balance.

Additional stress testing of certain types of dosage forms may be appropriate (e.g. cyclic freeze-thaw studies for liquids, semi-solids and transdermal patches).

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.

For new drugs, stability information from accelerated and long term testing should be provided on at least three batches of each strength manufactured at a minimum of pilot scale in each type of container closure system proposed for marketing. For existing drugs (e.g. generics), stability information from accelerated and long term testing should be provided on at least three batches of each strength manufactured at a minimum of pilot scale (or 2 pilot scale batches and one small scale batch) in each type of container closure system proposed for marketing. Bracketing and matrixing can be applied, if scientifically justified.

If justified, one of the batches submitted can be smaller than pilot scale. The chemistry of degradation and performance indicating tests (e.g. dissolution) should be scale independent.

General case:

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. 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 beyond 28 days should be justified with experimental data).

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), 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.

Proposed storage conditions and shelf life:

The proposed storage conditions with suitable tolerances (e.g. a temperature range with upper and lower criteria) and 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), the following storage recommendation would generally be considered acceptable:

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

Health Canada discourages the use of open ended storage conditions such as "Store below 30°C" unless stability data have been provided to demonstrate stability under refrigerated and frozen conditions.

Based on the results of the stability evaluation, other storage precautions may be warranted (e.g. "Protect from light", "Protect from moisture", "Store in the overwrap provided"). This information should be consistent with the labelling. 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

P.8.2 Post-approval Stability Protocol and Stability Commitment

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

Commitment batches are an ICH requirement. 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, commercial size batches should 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. On-going) Stability Program* is a requirement of Division 2 of the Food and Drug Regulations (GMP) and is implemented to ensure on-going compliance with the approved shelf life specifications. A minimum of one batch of each strength in each type of packaging and from each commercial manufacturing site is placed in the continuing stability programme each year.

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.

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. For quantitative tests (e.g. individual and total degradation product tests and potency tests), it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms". Where applicable, representative chromatograms of the oldest samples, particularly chromatograms for determination of degradation products, should be provided.

For quantitative tests (e.g. as in individual and total degradation product tests and potency 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 know, 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 according to the drug substance and/or drug product 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

Copies of the executed production documents (English or French original or translated) 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.

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.

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 guidance document (2011).

R.1.2 Master Production Documents

Copies of the drug product master production documents 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) special handling provisions relevant to the drug substance (e.g. antibiotics, teratogenic substances);
b) precautions necessary to ensure product quality (e.g. temperature and humidity control, maximum holding times);
c) dispensing, processing and packaging sections with relevant material and operational details;
d) relevant calculations (e.g. if the amount of drug substance is adjusted based on the

potency results or on the anhydrous basis);
e) identification of all equipment by type and working capacity;
f) process parameters (e.g. mixing time, mixing speed, milling screen size, processing temperature range, tablet machine speed);
g) list of in-process tests (e.g. appearance, pH, potency, blend uniformity, viscosity, particle size distribution, LOD, weight variation, hardness, disintegration time, weight gain during coating, leaker test, minimum fill, clarity);
h) sampling plan with regard to the steps where sampling should be done (e.g. drying, lubrication, compression):
    i. number of samples that should be tested (e.g. blend drawn using a sampling thief from x number of different parts of the blender);
    ii. frequency of testing (e.g. weight variation every x minutes during compression or capsule filling);
i) theoretical yield and provision for the actual yield.

Where any of this information is included in a SOP, master production documents 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 packaging components should be provided in the master production documents or by reference to SOPs.

A brief summary of SOPs should be provided in the submission, and if requested by the reviewer the SOP should be available.

R 2 Medical Devices

Combination products are be 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, complete 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 may also be required. If the device is provided with the drug product, it should be described in the CPID-CE.