NOTICE

Our file number: 03-113442-29

Health Canada is pleased to announce the release of the following draft documents for Stakeholder consultation entitled:

1. **Quality Guidance: Applications for Drug Identification Numbers (DINAs) for Pharmaceuticals**, and

2. **Quality Overall Summary - Chemical Entities (Applications for Drug Identification Numbers) (QOS-CE (DINA)).**

Comments on these documents should be submitted no later than **October 1, 2003**. Please cite the appropriate line number(s) when referencing the document. Comments should be directed (preferably in an electronic format) to:

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This and other Guidance documents are available on the [Therapeutic Products Directorate/Biologics and Genetic Therapies Directorate/Marketed Health Products Directorate Website](http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/). The availability of printed copies of guidance documents may be confirmed by consulting the Guidelines and Publications Order Forms (available on the TPD/BGTD/MHPD Website) or by contacting the Publications Coordinator.

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DRAFT GUIDANCE FOR INDUSTRY

Quality Guidance:
Applications for Drug Identification Numbers (DINAs) for Pharmaceuticals

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Health Products and Food Branch
Guidance Document
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Également disponible en français sous le titre : Ligne directrice : Section Qualité des demande d'identification numérique de drogues (DDIN) de produits pharmaceutiques

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FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on how to comply with the policies and governing statutes and regulations. They also serve to provide review and compliance guidance to staff, thereby ensuring that mandates are implemented in a fair, consistent and effective manner.

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 scientific 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 guidances.
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G GENERAL

G.1 Purpose

This document is intended to provide guidance with respect to the Quality (Chemistry and Manufacturing) portion of Applications for Drug Identification Numbers (DINAs) for chemical entities. The purpose of the guidance document is to outline the Quality technical requirements and to assist sponsors in preparing the DINAs to ensure an effective and efficient review process.

This document covers a variety of DINAs and may not be applicable in its entirety for all cases. 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.

G.2 Scope

This guidance document applies to DINAs containing drug substances and their corresponding products of synthetic or semi-synthetic origin (collectively referred to as "chemical entities"), excluding Biotechnological/Biological (Schedule D) and Radiopharmaceutical (Schedule C) drugs, that are filed with Health Canada pursuant to Section C.01.014 of the Food and Drug Regulations, that are not subject to Division C.08 of the Regulations.

Although this guidance document is intended to include those DINAs identified above, differences exist in terms of the data that is to included in these drug submissions at the time of filing as outlined below:

Group A DINAs - Schedule F drugs:

DINAs should include data as outlined in this guidance at the time of filing.

Group B DINAs - non-Schedule F drugs:

The filing expectations for these applications have not changed as a result of the issuance of this guidance. Sponsors of Group B DINAs should continue to file information as outlined in existing Health Canada documents (e.g., Labelling Standards). However, this guidance can be used to provide direction on the various Quality technical requirements and, depending on a risk-based assessment, this data should be made available, upon request (e.g., for sterile products).

G.3 Preamble

Under the provisions of Section C.01.014 of the Food and Drug Regulations, no manufacturer shall sell a drug in dosage form unless a Drug Identification Number (DIN) has been assigned for that drug and the assignment of the number has not been cancelled pursuant to Section C.01.014.6. In the case of a new drug, a New Drug Submission (NDS) or an Abbreviated New Drug Submission (ANDS) is filed pursuant to Division C.08 of the Food and Drug Regulations. When a product is not subject to Division C.08, the application is called an Application for Drug Identification Number (DINA).
The Health Canada guidance document entitled *Preparation of Drug Identification Number Submissions* discusses, in brief, the Quality portion of DINAs. This *Quality (C&M) Guidance for DINAs* supercedes the Quality portion of the *Preparation of Drug Identification Number Submissions* guidance document. However, this guidance document should be read in conjunction with the other general portions of the *Preparation of Drug Identification Number Submissions* as well as other applicable Health Canada guidance documents (e.g., Good Manufacturing Practices (GMP) guidelines).

The structure outlined in this guidance for the Quality portion of DINAs is consistent, to the extent possible, with that used for other types of drug submissions filed in Canada which are based on the format of the International Conference on Harmonization (ICH) *Common Technical Document* (*CTD*). The modular format of the CTD is now being extended to DINAs that are filed with Health Canada. Due to the abbreviated amount of information provided on the drug substance contained in DINAs, it is recognized that the numbering of the *S DRUG SUBSTANCE* portion of this Quality Guidance is not entirely consistent with that of ICH’s CTD. However, the numbering of the *P DRUG PRODUCT* portion of this Quality Guidance more closely mirrors that of ICH’s CTD.

Where appropriate, the wording from ICH’s CTD has been repeated and stated in **bold** text, followed by further Health Canada guidance in plain text to assist sponsors in the preparation of DINAs.

### The Quality Overall Summary (QOS):

Since 1995, sponsors of New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) have been providing a comprehensive summary of the Quality information contained in the drug submission. This document provides a summary of the data submitted to Health Canada according to a prescribed format and hence contributes towards a more effective and timely processing of these drug submissions. This template has since been updated according to current Quality standards and terminology, as well as to reflect the developments on the international level.

As the use of this tool has promoted an effective and consistent approach to the review of these drug submissions, it is now being extended to the review process for DINAs. With the implementation of the *Quality Overall Summary - Chemical Entities (Applications for Drug Identification Numbers) (QOS-CE (DINA))*, sponsors share responsibility for the generation of the Quality evaluation report. The objectives of this requirement are two-fold:

(a) expediting the review process by enabling Evaluators to more efficiently spend their time on drug submission assessment; and

(b) improving drug submission quality by way of a more thorough compilation and appraisal of data requirements by sponsors in conjunction with the completion of the QOS-CE (DINA).

The information that follows is intended to provide guidance on the expectations of the various sections of the QOS-CE (DINA) (i.e., the Quality Summary) and the Quality portion of the DINA (i.e., the Quality Module).
G.4 Notes on the Preparation of the Quality Summary and the Quality Module

Sponsors are encouraged to devote the sufficient time necessary to prepare a clear, precise Quality Summary. The filing of an inaccurate or an incomplete Quality Summary will result in greater expenditure of an Evaluator’s time in reviewing and summarizing data.

In developing Health Canada’s Quality Summary template, a balance was needed between providing sufficient instruction regarding the format and content of the submitted information and designing a document that could accommodate variability in the types of studies and products described in these drug submissions. With respect to the latter consideration, it is expected that the tables included in the Quality Summary template may need to be modified (e.g., with data cells being split or joined, as necessary). Additional modification of table structure or the substitution of a narrative paragraph, can also be warranted in certain circumstances in order to best summarize the data.

All titles/parameters listed in the default tables should nonetheless be retained or addressed, regardless of their perceived relevance, unless the subject matter of the entire table does not apply to the drug submission in question.

If portions of the Quality Summary are clearly not relevant 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 Section P.4 if there are not any excipients of human or animal origin used in the manufacture of the drug product). Any portions that are “Not applicable” should not be deleted and should be accompanied by an explanatory note describing the reasons for the inapplicability.

The above practice should not be followed with respect to cross-referenced Drug Master Files (DMFs). DMFs should be identified in the appropriate sections (e.g., S.1). The sections of the Quality Summary should not be deleted. It is the sponsor’s responsibility to submit the relevant non-proprietary information provided by the DMF Holder (e.g., in the Open DMF), obtained in the public domain, and/or developed by the sponsor. For DMF requirements, consult Health Canada’s guidance document Product Master Files (soon to be renamed Drug Master Files). When the sponsor summarizes data obtained from the DMF Holder or the scientific literature, the source of reproduced information should be specified.

The following information is intended to provide assistance to sponsors in preparing the Quality Summary and the Quality Module:

(a) Abbreviations should not be used in the Quality Summary unless initially defined and consistently used (e.g., N/A = Not applicable), or unless they represent well-established scientific abbreviations (e.g., HPLC, UV).

(b) This guidance document makes reference to “Schedule B compendial monographs”, these are compendial monographs that are recognized as official according to Schedule B to the Food and Drugs Act (e.g., USP, Ph.Eur., BP).

(c) When filing a response to a deficiency request from Health Canada (e.g., Request for Clarification (Clarifax)), sponsors should use the applicable sections of the Quality Summary to summarize new or updated data (e.g., specifications, stability results). A refiled/updated Quality Summary should not be submitted.
(d) In order to facilitate the processing and evaluation of responses to deficiency requests from Health Canada, an *electronic version* of the consolidated deficiency comments and responses pertaining to the Quality issues should be provided in a question and answer format.
1 INTRODUCTION

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

Sponsors should provide a contact person’s name, phone number, fax number, and e-mail address for ease of communication.

S DRUG SUBSTANCE

Some of the information included under the “S Drug Substance” section may not be available to the sponsor for the DINA. If such is the case, the supplier of the drug substance can file a Drug Master File directly with Health Canada. The supplier would then be considered the DMF Holder. This DMF will be held in strict confidence and will be used in support of the drug submission only upon receipt of written authorization from the supplier/DMF Holder of the drug substance (i.e., via a letter of access).

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 by the manufacturer’s facilities and for providing the results of batch analyses performed at the manufacturer's facilities.

For further information on the requirements for Drug Master Files, see Health Canada’s guidance document Product Master Files (soon to be renamed Drug Master Files).

S.1 Manufacture

The name, address, and responsibility of each manufacturer/supplier, including those involved in the manufacturing and testing, should be provided.

This includes the facilities involved in the fabrication, packaging, labelling, testing, importing, storage, and distribution of the drug substance. 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 production or manufacturing site(s) involved, rather than the administrative offices.

Descriptions of the manufacturing process and process controls do not need to be submitted. However, the sponsor should be able to provide a letter of access to refer to the drug substance manufacturer’s Drug Master File (DMF), if requested.
S.2 Control of the Drug Substance

S.2.1 Specification

The specification for the drug substance should be provided.

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.

A copy of the drug substance specification from the company responsible for release testing should be provided in the drug submission, dated and signed by authorized personnel (i.e., the person in charge of the Quality Control department). The specification reference number, version, and date should be provided for version control purposes. The standard declared by the sponsor could be a Schedule B compendial standard (e.g., USP, Ph.Eur., BP), Manufacturer’s or House Standard, Prescribed Standard (e.g., Canadian Standard Drugs in Division C.06 of the Food and Drug Regulations), or a Professed 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 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 and potency should be at least as tight as the most stringent of those listed in the Schedule B compendial monographs.

If the drug submission is for a non-official drug (e.g., where neither a Prescribed nor a Schedule B compendial standard exists), a professed standard is used and the product labelling for such products does not carry any standard.

The following universal tests are considered generally applicable to all drug substances:

(a) Description (e.g., physical form, colour);
(b) Identification (should be specific for the drug substance);
(c) Assay (should be specific, stability-indicating);
(d) Impurities (individual and total related impurities, residual solvents).
In addition to the universal tests indicated above, further specific tests could be included in the specification depending on the nature of the drug substance. Some of these tests include, but not limited to, the following:

(a) physicochemical properties;

(b) particle size;

(c) polymorphic forms;

(d) tests for chiral drug substances;

(e) water content;

(f) inorganic impurities;

(g) microbial limits.

With respect to completing the QOS-CE (DINA), the sponsor should either (whichever is applicable):

(a) For Schedule B standards, provide attestation that the specification for the drug substance complies with the above stated Schedule B monograph; or

(b) For non-Schedule B standards or for specifications that contain additional tests to the Schedule B monograph, provide a summary of the specification.

The specification can be summarized according to Health Canada’s Quality Summary 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.

Drug substances of animal origin should be free of Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalopathy (TSE) and a letter of attestation confirming this should be included with the drug submission.

S.2.2 Analytical Procedures and S.2.3 Validation of Analytical Procedures

Copies of compendial analytical procedures do not need to be submitted. However, the sponsor should ensure that compendial procedures are properly validated to be used for their drug substance (e.g., for potential impurities that are not listed in the compendial monograph).

For non-compendial analytical procedures, copies of the test methods and validation reports should be included in the drug submission. The test methods should be validated according to the applicable Health Canada and/or ICH guidance documents (e.g., Acceptable Methods, Text on Validation of Analytical Procedures (Q2A), Validation of Analytical Procedures: Methodology (Q2B)).
S.2.4 Batch Analyses

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

This would include information such as batch number, batch size, date and site of production on relevant drug substance batches used to establish the specification(s) and evaluate consistency in manufacturing.

Analytical results, tested by the manufacturer/supplier and by the company responsible for release testing, should be provided from at least two batches from each proposed manufacturer of the drug substance. Copies of the certificates of analyses for these batches should be provided in the drug submission and the company responsible for generating the testing results should be identified.

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., as in individual and total impurity tests and potency tests), it should be ensured that actual numerical results are provided rather than vague statements such as “within limits” or “conforms”. A discussion and justification should be provided for any incomplete analyses (e.g., results not tested according to the proposed specification).

S.3 Stability

In accordance with Section of C.02.027 of the Regulations, every distributor referred to in paragraph C.01A.003(b) and importer shall establish the period of time during which each drug in the package in which it is sold comply with the specifications.

The stability data in the proposed container closure system should be available upon request. The proposed storage conditions and re-test period (or shelf life, as appropriate) should be provided.

The re-test period is the period of time during which the drug substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given drug product, provided that the drug substance has been stored under the defined conditions. After this 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 (e.g., within 30 days). If re-tested, the batch does not receive the period of time established for the re-test period. A batch of drug substance can be retested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification. 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.

Re-test periods are generally one or two years. A re-test period longer than two years should be fully supported by the results from stability studies conducted under the conditions recommended by Health Canada’s/ICH’s Stability Testing of New Drug Substances and Products (Q1A) guidance document.
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:

(a) Description of the dosage form;

The description of the dosage form should include the physical description, strength, release mechanism, as well as any other distinguishable characteristics (e.g., “The proposed drug product is available as an oval, immediate-release, aqueous film-coated tablet in a 100 mg strength. The product includes a vertical score line to facilitate the breaking of the tablets.”).

(b) 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, including a statement of 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, silicon for stoppers). If the drug product is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g., “1 mg of active ingredient base = 1.075 mg active ingredient hydrochloride”). All overages should be clearly indicated (e.g., “Contains 2% 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)”).

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 provided.

(e) Description of accompanying reconstitution diluent(s); and

For drug products supplied with reconstitution diluent(s) 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 diluent(s) should be provided in a separate Drug Product (“P”) portion, as appropriate.
(d) Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.

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

P.2 Pharmaceutical Development

For drug submissions containing in vivo studies (pivotal clinical, comparative bioequivalence), a discussion should be provided of any differences in the formulations and manufacturing process for the batches used in these studies and the formulation and manufacturing process described in P.3.

For drug submissions containing comparative in-vitro studies (e.g., dissolution for solid oral products) and/or physicochemical testing (e.g., to support the absence of a comparative bioequivalence study for an aqueous solution subsequent entry product), a discussion of the results should be provided.

P.3 Manufacture

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, storage, 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 Establishment License (EL) and/or Good Manufacturing Practice (GMP) compliance rating status should be provided.

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 including a statement of the total weight or measure of the batch. This 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 drug product is formulated using an active moiety, then the composition for the
active ingredient should be clearly indicated (e.g., “1 mg of active ingredient base = 1.075 mg active
ingredient hydrochloride”). All 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 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. In-process tests performed at critical steps during the manufacturing process should be included
(e.g., particle size, moisture content, homogeneity, average weight/weight variation, hardness, friability,
disintegration, weight gain during coating, pH, specific gravity, viscosity, fill volume, leak test, as applicable
to dosage form).

Proposals for the reprocessing of materials should be justified.

Copies of the drug product master production documents should be provided for each commercial batch
size and manufacturing site.

Copies of the executed production documents should be provided for at least one pilot scale batch of each
strength and be 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. The executed production documents should
also be provided for the batches used in the pivotal clinical and/or comparative bioavailability studies (if
applicable). Any notations made by operators on the executed production documents should be clearly
legible.

### P.3.4 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).

The following information should be provided:

(a) a copy of the process validation protocol, specific to this drug product, which identifies the critical
equipment and process parameters that can affect the quality of the drug product and defines
testing parameters, sampling plans, analytical procedures, and acceptance criteria;
(b) confirmation that three consecutive, production-scale batches of this drug product will be
subjected to prospective validation in accordance with Health Canada’s Validation Guidelines
for Pharmaceutical Dosage Forms and Cleaning Validation Guidelines;

(c) if the process validation studies have already been conducted (e.g., as for sterile products), a copy
of process validation report should be submitted in lieu of (a) and (b) above, a summary of these
process validation studies should also be provided.

The manufacture of sterile drugs needs a well-controlled manufacturing area (e.g., a strictly controlled
environment, highly reliable procedures, and numerous in-process controls). A detailed description of
these conditions, procedures, and controls should be provided, together with actual copies of the following
standard operating procedures:

(a) washing, treatment, sterilizing, and depyrogenating of containers, closures, and equipment;
(b) filtration of solutions;
(c) lyophilization process;
(d) leaker test of filled and sealed ampoules;
(e) final inspection of the product; and
(f) sterilization cycle.

The sterilization process used to destroy or remove microorganisms is probably the single most important
process in the manufacture of parenteral drugs. The process can make use of moist heat (e.g., steam),
dry heat, filtration, gaseous sterilization (e.g., ethylene oxide), or radiation. It should be noted that 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.

The sterilization process should be described in detail, and evidence should be provided to confirm that it
will produce a sterile product with a high degree of reliability and that the physical and chemical properties
as well as the safety of the drug product will not be affected. Details such as F₀ range, temperature
range, and peak dwell time for a drug product and the container closure should be provided. Although
standard autoclaving cycles of 121°C, 15 minutes or more, would not need a detailed rationale; such
justifications should be provided for reduced temperature cycles or elevated temperature cycles with
shortened exposure times. If ethylene oxide is used, studies and acceptance criteria should control the
levels of residual ethylene oxide and related compounds.

Filters used should be validated with respect to pore size, compatibility with the product, absence of
extractables and lack of adsorption of the drug substance or any of the components.
P.4 Control of Excipients

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, etc.).

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 for the excipient should be provided.

Testing for microbial requirements should be at least as stringent as those specified in the corresponding USP monograph should one exist (e.g., as for Magnesium Stearate). Excipients derived from natural sources should have appropriate microbial tests and limits.

If additional purification is undertaken on commercially available excipients, details of the process of purification and modified specifications should be submitted.

Copies of analytical procedures and validation reports for non-compendial procedures should be provided.

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). 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 gelatin for use in pharmaceuticals, a letter of access from the proposed supplier should be provided to their Drug Master File, which is registered with Health Canada. Furthermore, confirmation should be included with a letter of attestation that the gelatin used is free of Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalopathy (TSE).

For proprietary components (e.g., capsule shells, colouring blends, imprinting inks), a copy of a letter of access addressed to Health Canada should be provided allowing access to the supplier’s Drug Master File which should have been registered with Health Canada.

A confirmation 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.

1 Refer to Health Canada’s Therapeutic Products Compliance Guide
P.5 Control of Drug Product

P.5.1 Specification(s)

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

A specification is defined as 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 product should conform to be considered acceptable for its intended use. “Conformance to specifications” means that the drug product, 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.

A copy of the drug product specification(s) from the sponsor (as well from the company responsible for release testing, if different from the sponsor) should be provided, dated and signed by authorized personnel (i.e., the person in charge of the Quality Control department). The specification reference number, version, and date should be provided for version control purposes. The standard declared by the sponsor could be a Schedule B compendial standard (e.g., USP, BP), Manufacturer’s or House Standard, Prescribed Standard (e.g., Canadian Standard Drugs in Division C.06 of the Food and Drug Regulations), or a Professed 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 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 and potency should be at least as tight as the most stringent of those listed in the Schedule B compendial monographs.

If the drug submission is for a non-official drug (e.g., where neither a Prescribed nor a Schedule B compendial standard exists), a professed standard is used and the product labelling for such products does not carry any standard.

The specification can be summarized according to Health Canada’s Quality Summary 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(s). The Method Type should indicate the kind of analytical procedure used (e.g., visual, IR, UV, HPLC); the Source refers to the origin of the analytical procedure (e.g., USP, BP, House); and the Code Number/Version/Date should be provided for version control purposes.

The following universal tests are considered generally applicable to all drug products:

(a) Description (e.g., physical form, colour);

(b) Identification (should be specific for the drug substance);
(c) Assay (should be specific, stability-indicating);

(d) Impurities (individual and total degradation products, residual solvents).

In addition to the universal tests indicated above, further specific tests should be included in the specification depending on the nature of the drug product. Some of these tests include, but not limited to, the following:

<table>
<thead>
<tr>
<th>Drug Product</th>
<th>Additional Suggested Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid oral products</td>
<td>dissolution, disintegration, hardness/friability, uniformity of dosage units, water content, microbial limits</td>
</tr>
<tr>
<td>Liquid oral products</td>
<td>uniformity of dosage units, pH, microbial limits, antimicrobial preservative content, antioxidant preservative content, extractables, alcohol content, dissolution, particle size distribution, redispersibility (for oral suspensions), rheological properties (for viscous solutions or suspensions), reconstitution time (for dry powder products that require reconstitution), water content (for oral products requiring reconstitution)</td>
</tr>
<tr>
<td>Parenteral products</td>
<td>uniformity of dosage units, pH, sterility, endotoxins/pyrogens, particulate matter, water content (for non-aqueous parenterals, and for parenteral products for reconstitution), antimicrobial preservative content, antioxidant preservative content, extractables, functionality of the delivery system, osmolarity (when the tonicity of a product is declared in its labelling), particle size distribution, redispersibility (for injectable suspensions), reconstitution time (for parenteral products which require reconstitution)</td>
</tr>
<tr>
<td>Modified-release products</td>
<td>a meaningful drug-release method</td>
</tr>
<tr>
<td>Inhalation and nasal products</td>
<td>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</td>
</tr>
<tr>
<td>Suppositories</td>
<td>uniformity of dosage units, melting point</td>
</tr>
<tr>
<td>Transdermal products</td>
<td>peel or shear force, mean weight per unit area, dissolution</td>
</tr>
</tbody>
</table>

**P.5.2 Analytical Procedures and P.5.3 Validation of Analytical Procedures**

Copies of compendial analytical procedures do not need to be submitted. However, the sponsor should ensure that compendial procedures are properly validated to be used for their drug product (e.g., for potential degradation products not listed in the compendial monograph).
For non-compendial analytical procedures, copies of the test methods and validation reports should be included in the drug submission. The test methods should be validated according to the applicable Health Canada and/or ICH guidance documents (e.g., Acceptable Methods, Text on Validation of Analytical Procedures (Q2A), Validation of Analytical Procedures: Methodology (Q2B)).

**P.5.4 Batch Analyses**

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

This would include information such as strength, batch number, batch size, date and site of production on relevant drug product batches used to establish the specification(s) and evaluate consistency in manufacturing.

Analytical results, tested by the company responsible for release testing, should be provided from at least two batches from each proposed manufacturer of the drug product. Copies of the certificates of analyses for these batches should be provided in the drug submission and the company responsible for generating the testing results should be identified.

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., as in individual and total impurity tests and potency tests), it should be ensured that actual numerical results are provided rather than vague statements such as “within limits” or “conforms”. A discussion and justification should be provided for any incomplete analyses (e.g., results not tested according to the proposed specification).

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 dosage form) 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 (i.e., manually split by hand). 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. 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.5.5 Characterisation of 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 manufacture of the drug product and/or degradation. The tables in Health Canada’s Quality Summary 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., “potential by-product due to rearrangement of the drug substance”). It should also be indicated if the impurity is a metabolite of the drug substance.

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., degradation products) and the concentration limits for process-related impurities (e.g., residual solvents) as per the Health Canada/ICH guidance documents (e.g., *Impurities in New Drug Products (Q3B), Impurities: Guideline for Residual Solvents (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. For drugs available in multiple dosage forms and strengths, having different MDD values, it is imperative that the thresholds and corresponding controls for each of the presentations be considered to ensure that the risks posed by impurities have been addressed. This is normally achieved by using the highest potential daily MDD, rather than the maintenance dose. For parenteral products, the maximum hourly dose of the drug substance should also be included.

### P.6 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).

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.

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;

The tables in Health Canada’s Quality Summary template can be used to summarize the above information.

The information for the container closure system depends on the dosage form and route of administration. The following table outlines the general recommendations for the various dosage forms. Some of this highlighted information can be performed on a one-time basis to establish the suitability of the container closure system (e.g., as outlined under “Qualification of Components”):
## Specifications for routine testing:

<table>
<thead>
<tr>
<th></th>
<th>Solid Oral Products</th>
<th>Oral Liquid and Topical Products</th>
<th>Sterile Products (including Ophthalmics)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Name, physical description, dimensions (e.g., thickness)</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>- Specific identification tests (e.g., IR) for components that come in direct contact with the dosage form</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

## Qualification of components:

<table>
<thead>
<tr>
<th></th>
<th>Solid Oral Products</th>
<th>Oral Liquid and Topical Products</th>
<th>Sterile Products (including Ophthalmics)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Composition and drawings for all components (including cap liners, coatings for metal tubes, elastomers, adhesives, silicon)</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>- Description of any additional treatments*</td>
<td>x</td>
<td>x</td>
<td>x (sterilization and depyrogenation of the components)</td>
</tr>
<tr>
<td>- USP &lt;661&gt; Containers</td>
<td>x</td>
<td>x</td>
<td>x (includes USP &lt;87&gt;/&lt;88&gt; tests)</td>
</tr>
<tr>
<td>- USP &lt;671&gt; Containers - Permeation</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>- USP &lt;381&gt; Elastomeric Closures for Injections</td>
<td>--</td>
<td>--</td>
<td>x (includes USP &lt;87&gt;/&lt;88&gt; tests)</td>
</tr>
</tbody>
</table>

* e.g., coating of tubes, siliconization of rubber stoppers, sulphur treatment of ampoules/vials

Information should be submitted if information does not need to be submitted

Comparative studies can be necessary for changes in components (e.g., comparative delivery study (droplet size) for a change in supplier of dropper tips).

The information on the composition should be available to Health Canada either in the drug submission or in a Drug Master File. Refer to Health Canada’s guidance document Product Master Files (soon to be renamed Drug Master Files) for filing requirements for Type II DMFs (packaging materials).

### P.7 Stability

In accordance with Section of C.02.027 of the Regulations, every distributor referred to in paragraph C.01A.003(b) and importer shall establish the period of time during which each drug in the package in which it is sold comply with the specifications.
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.

### P.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, for example, conclusions with respect to storage conditions and shelf life, and, if applicable, in-use storage conditions and shelf life.

Data from stability studies should be provided on at least two batches of the drug product. The batches should be of the same formulation and packaged in the same container closure system as proposed for marketing. The manufacturing process used for these batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing. One of the two batches should be at least pilot scale batches (e.g., 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 and the second one can be smaller, if justified (e.g., for solid oral dosage forms, a smaller batch is generally 25,000 or 50,000 dosage units).

Bracketing and matrixing can be applied, if scientifically justified.

The following storage conditions and minimum data at the time of drug submission are recommended:

<table>
<thead>
<tr>
<th>Study</th>
<th>Storage Condition</th>
<th>Minimum Time Period Covered by Data at Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long term</td>
<td>25°C ± 2°C/60% RH ± 5% RH</td>
<td>6 months</td>
</tr>
<tr>
<td>Accelerated</td>
<td>40°C ± 2°C/75% RH ± 5% RH</td>
<td>3 months</td>
</tr>
</tbody>
</table>

RH = relative humidity

Updated stability data to support the proposed shelf life should be available upon request. For long term studies, the frequency of testing should be sufficient to establish the stability profile of the drug product (e.g., 0, 3, 6, 9, 12, 18, 24, 36 months). At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 1, 2, 3 months) is recommended.

The information summarized on the stability studies should include details such as storage conditions, strength, batch number, batch size, container closure system, and completed (and 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., 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”.

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 provided.
If the results from the stability studies demonstrate that the drug product is acceptable in the general case (e.g., 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 are examples of acceptable storage statements:

"Store between 15°C - 30°C"
"Store at Room Temperature (15°C to 30°C)"
"Store at 25°C, with excursions permitted to 15°C - 30°C".

Based on the results of the stability evaluation, other storage precautions may be warranted (e.g., "Protect from light", "Protect from moisture").

Limited extrapolation of the real time data from the long term storage condition beyond the observed range to extend the shelf life can be undertaken at approval time, if justified.

For further information, Health Canada guidance documents (e.g., Stability Testing of New Drug Substances and Products and Stability Testing of Existing Drug Substance and Products) should be consulted.

### P.7.2 Post-approval Stability Protocol and Stability Commitment

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

In accordance with Section C.02.028 of the Regulations, every distributor referred to in paragraph C.01A.003(b) and importer shall monitor, by means of a continuing program, the stability of the drug in the package in which it is sold.

A Continuing Stability Programme is implemented to ensure compliance with the approved shelf life specifications. A minimum of one batch of every strength of the drug product is enrolled into the continuing stability programme each year. Bracketing and matrixing can be applied, if scientifically justified.

The stability protocols for the 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.

Any differences in the stability protocols used for the primary batches (i.e., those to support the drug submission) and those proposed for the Continuing Batches should be scientifically justified.
P.7.3 Stability Data

The actual stability results (i.e., raw data) used to support the proposed shelf life should be provided in the drug submission. 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”.

M MISCELLANEOUS

M.1 Labelling

Provide copies of the container label(s) (and prescribing information or a package insert, where applicable).

Refer to Health Canada’s guidance document Labelling of Drugs for Human Use for further details.