

NOTICE

Our file number: 08-134763-687

Health Canada is pleased to announce the release of the guidance document *Quality (Chemistry and Manufacturing) Guidance: Clinical Trial Applications (CTAs) for Pharmaceuticals* and three *Quality Overall Summary – Chemical Entities (Clinical Trial Applications)* templates.

This guidance document supersedes the previous Health Canada draft guidance document *Revised Draft Quality (Chemistry and Manufacturing) Guidance: Clinical Trial Applications (CTAs) for Pharmaceuticals* dated 2008/04/08. These new templates supersede the current *Quality Overall Summary – Chemical Entities (Clinical Trial Applications – Phase I) (QOS-CE (CTA – Phase I))* and *Quality Overall Summary – Chemical Entities (Clinical Trial Applications – Phase II/III) (QOS-CE (CTA – Phase II/III))* templates.

Scope and Application

The changes made to the guidance document and templates affect all new Phase I, Phase II and Phase III Clinical Trial Applications and corresponding Clinical Trial Application – Amendments (CTA-A) and Notifications filed with the Therapeutic Products Directorate. Quality requirements for Clinical Trial Applications for Bioavailability/Bioequivalence studies are outside the scope of these documents.

Consultation Process

The revised draft guidance document was released for comment on April 20th, 2008 for a period of 60 days. A total of 135 comments were submitted on topics varying from GMP requirements for early phase Clinical Trial Applications to clarification on the type of information requested in the new templates. A copy of the tabulated summary of comments is available to stakeholders upon request.

Health Canada's experience with the new guidance document and templates has been positive, with an increase in the quality of submissions (measured in terms of the number of comments and requests for clarification sent) without significant increases in review time.

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Final Changes to the Guidance Document

Based on feedback from stakeholders on the revised draft guidance document dated 2008/04/08 and internal discussions, several changes have been made to the final version of the guidance document. First, the language throughout the guidance document has been changed to allow for more flexibility in the information required for Clinical Trial Applications. Secondly, in sections where the language was unclear with respect to requirements at each phase, the guidance has been modified to outline Health Canada's expectations.

Changes to the *Quality Overall Summary – Chemical Entities Templates*

Phase I and Phase II QOS – Minor revisions have been made to maintain consistent language across all three templates.

Phase II QOS – Several changes have been made in the final version of the Phase III template. The two most important changes are the removal of Section 2.3.S.2.6 (Manufacturing Process Development) and formatting changes in Section 2.3.P.2 (Pharmaceutical Development). In response to stakeholder feedback on the revised Phase III template, other revisions have been made which are intended to eliminate the duplicate reporting of any information and simplify the submission process.

Next Steps and Implementation

Sponsors should not submit Quality (Chemistry and Manufacturing) updates for previously approved Clinical Trial Applications for the purpose of satisfying the new requirements of the guidance document and templates.

With respect to Phase II and Phase III Clinical Trial Applications, sponsors are now requested to submit brief descriptions of the analytical procedures and tabulated summaries of the validation of those procedures. Detailed descriptions of the step-by-step analytical procedures and complete validation reports should not be submitted for Clinical Trial Applications. Quality (Chemistry and Manufacturing) updates should not be filed for analytical procedures unless the changes made to the method directly affect the specifications of the drug substance or drug product.

Sponsors are strongly encouraged to file Clinical Trial Applications according to the *Quality Overall Summary – Chemical Entities* templates at this time. After June 1st, 2009, sponsors will be notified at the time of screening that submission in formats other than the Quality Overall Summary may lead to comments and requests for clarification at the time of review. Alternate approaches should be discussed with the screening and review divisions prior to filing to avoid any potential delays in the review of the Clinical Trial Application.

The appropriate administrative changes have been made to the guidance document *Guidance for Clinical Trial Sponsors: Clinical Trial Applications*.

Contacts

Questions or additional clarifications about the guidance document or *Quality Overall Summary* templates should be directed to:

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GUIDANCE DOCUMENT

Quality (Chemistry and Manufacturing) Guidance: Clinical Trial Applications (CTAs) for Pharmaceuticals

Published by authority of the
Minister of Health

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|----------------|------------|
| Date Adopted | 2008/11/12 |
| Effective Date | 2009/06/01 |

Health Products and Food Branch

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Également disponible en français sous le titre : Ligne directrice en matière de qualité (chimie et fabrication) : demandes d'essais cliniques (DEC) pour les produits pharmaceutiques

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 document, 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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1. INTRODUCTION

1.1 Policy Objectives

To assist submission sponsors in preparing Clinical Trial Applications (CTAs) filed with Health Canada by outlining the Quality (chemistry and manufacturing) technical requirements for CTAs pursuant to Division C.05 of the *Food and Drug Regulations*.

1.2 Policy Statements

The scope and detail of information submitted in support of the Quality portion of a Clinical Trial Application should enable Health Canada to make an adequate assessment of the characteristics of the drug substance and the drug product.

The information provided in the Quality portion of a Clinical Trial Application should reflect the information available for a drug at each clinical trial phase. Consequently, sponsors should use the appropriate Quality Overall Summary template when submitting information in support of a CTA.

1.3 Scope and Application

This guidance document applies to Clinical Trial Applications (CTAs) containing drug substances and their corresponding products of synthetic or semi-synthetic origin, excluding Biotechnological/Biological (Schedule D) and Radiopharmaceutical (Schedule C) drugs, that are filed with Health Canada pursuant to Division C.05 of the *Food and Drug Regulations*. Note that this document does not provide guidance on the quality requirements of Clinical Trial Applications - Bioavailability Studies.

The scope of this guidance document includes Phases I, II and III of clinical trials. Sponsors are expected to submit progressively more detailed Quality information through subsequent clinical trial phases. Not all requirements outlined in this guidance document are applicable to all trial phases. Alternate approaches to the principles and practices described in this document may be acceptable, provided they are supported by adequate scientific justification. Sponsors are advised to discuss, in advance, alternate approaches used in support of their drug submission to avoid rejection or withdrawal of the drug submission.

Depending on the phase of clinical trial development, the applicable Quality Overall Summary template for Pharmaceuticals would be:

- (a) Quality Overall Summary - Chemical Entities (Clinical Trial Applications - Phase I) (*QOS-CE (CTA - Phase I)*);

- (b) Quality Overall Summary - Chemical Entities (Clinical Trial Applications - Phase II) (QOS-CE (CTA - Phase II));
- (c) Quality Overall Summary - Chemical Entities (Clinical Trial Applications - Phase III) (QOS-CE (CTA - Phase III));

For combination protocols (e.g. Phase I/II or II/III protocols), sponsors should submit Quality data according to the requirements of the highest phase.

For further information on the filing requirements of Clinical Trial Application-Amendments and Notifications, sponsors should consult Health Canada's *Guidance for Clinical Trial Sponsors: Clinical Trial Applications*.

1.4 Background

A revised draft guidance document was released for stakeholder comment in April, 2008, along with three new Quality Overall Summary (Clinical Trial Applications) templates. Based on comments received from internal discussions and stakeholders, this document, as well as three new Quality Overall Summary templates, have been finalized.

2. GUIDANCE FOR IMPLEMENTATION

2.1 General Information

Abbreviations should not be used in the Quality Overall 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, etc.).

References in this guidance document to "Schedule B compendial monographs" imply those compendial monographs listed under Schedule B of the *Food and Drugs Act*.

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 Overall Summary to summarize only new or updated data (e.g., specifications, stability results, etc.). An updated/annotated QOS, highlighting the changes made in response, may also be submitted.

To accommodate variability in the types of studies and products described in these drug submissions, the tables included in the Quality Overall Summary-Chemical Entities (Clinical Trial Applications) template may be modified as necessary (e.g., with data cells being split or joined). Additional modification of table structure or the substitution of a narrative paragraph may be warranted in certain circumstances in order to best present the data. If scanned images

are incorporated into the document (e.g., synthetic schemes, molecular structures), sponsors should ensure that a low resolution is used to avoid files that are excessively large. 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.

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 may be provided in a question and answer format in either WordPerfect® or Microsoft Word® format in addition to/in lieu of the paper copy.

Sponsors of Clinical Trial Applications may cross-reference all Quality information to previously approved CTAs **provided they are of the same or higher phase** (e.g. Phase III CTAs cannot be fully cross-referenced to Phase II CTAs but may be cross-referenced to approved Phase III CTAs), with the exception of the drug product batch analysis for Phase I and Phase II Clinical Trial Applications.

The structure of these templates for the Quality portion of Clinical Trial Applications is consistent with that used for New Drug Submissions (NDS) and Abbreviated New Drug Submissions (A/NDS) filed in Canada. This approach is intended to facilitate the subsequent preparation of drug submission information and is consistent with Health Canada's focus on a life-cycle approach for regulating drugs. A QOS prepared in accordance with **either** the ICH CTD-Q guidance or according to Health Canada's QOS-CE (CTA) templates will be considered acceptable on filing.

For ease of reference, the remainder of this guidance document follows the structure of the Quality Overall Summary templates.

I INTRODUCTION

I (a) Excerpt from Protocol Synopsis

To aid in the Quality evaluation, an excerpt from the Protocol Synopsis from the Clinical Module should be inserted. Sponsors are encouraged to consult Health Canada's *Guidance for Clinical Trial Sponsors: Clinical Trial Applications* for guidance notes on the preparation of the Protocol Synopsis. The following information should be provided for the proposed clinical trial:

- Trial Title, Phase, and Number
- Trial Objectives
- Study Design & Duration

- Number of Centres
- Sample Size/Patient Population (Target population)
- Drug Formulation
- Dosage Regimen and Concomitant Medication

I (b) Comparator Products

If a comparator drug product is used, the proprietary name of the drug product, non-proprietary name or common name of the drug substance, company name, country from which the clinical supplies were obtained (as well as the market status in that country), dosage form(s) and strength(s) should be listed.

Preferably, the comparator product should be obtained from the Canadian market. For comparator drug products not obtained from the Canadian market, where the results of the clinical trial are intended to be used in support of a New Drug Submission (NDS) or Abbreviated New Drug Submission (ANDS), the sponsor should be aware that additional information may be requested *at the NDS stage* (e.g., comparative *in vivo* or *in vitro* studies between the Canadian marketed product and the comparator product may be required).

For Phase I, II and III CTAs, additional information (other than that identified above) is not necessary for comparator products obtained from the markets of ICH regions, Switzerland, and Australia. For comparator products obtained outside these regions, Quality (Chemistry and Manufacturing) information should be provided.

For Phase IV CTAs, sponsors should consult Health Canada's *Canadian Reference Product* policy for requirements for reference products obtained outside the Canadian market.

If the comparator drug product is modified in any way in order to blind the trial (e.g., grinding of tablets, encapsulation of tablets), results of an *in vitro* study (e.g., comparative dissolution profiles for solid dosage forms) comparing the unchanged and the modified product should be submitted. For sterile products that are repackaged for blinding purposes, it should be demonstrated that sterility is maintained.

I (c) Note on Cross-Referenced Submissions

Sponsors should provide the Control Number and File Number for the submissions or sections being cross-referenced in support of the current application.

S DRUG SUBSTANCE

Some of the information included under the “S Drug Substance” section may not be available to the sponsor of the Clinical Trial Application. 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).

The sponsor should be able to provide most of the information on the drug substance, except possibly the proprietary information found in the closed part of the Drug Master File (e.g. sections S.2.2, S.2.4 and S.2.6 (see below)). 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 Open part of the DMF should be included in the Quality Overall Summary.

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 DMFs, see Health Canada’s guidance document on filing and referencing of Drug Master Files.

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), British Approved Name (BAN)); and
- (f) Chemical Abstracts Service (CAS) registry number.

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. For drug substances existing as salts, the molecular mass of the free base should also be provided.

S 1.3 General Properties

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

Give the physical and chemical properties of the drug substance such as the physical description, solubilities (e.g. aqueous/nonaqueous solubility profile, pH-dependent solubility profile), polymorphism, particle size distribution, pH and pKa values. Other characteristics could include UV absorption maxima and molar absorptivity, melting point, refractive index (for a liquid), hygroscopicity, partition coefficient, etc.. This list is by no means exhaustive, but provides an indication as to the type of information that could be included.

Physical Description:

The description should include appearance, colour, and physical state.

Solubilities:

The solubility should be provided in a number of common solvents (e.g. water, alcohols, etc.) as well as the solubilities over the physiological pH range (pH 1 to 8) in at least 3 buffered media. Phrases such as “sparingly soluble” or “freely soluble” should be quantitatively defined or a literature reference can be provided (e.g., “as per USP”). If this information is not readily available, it should be generated in-house.

S 2 Manufacture

If a Drug Master File is filed with Health Canada and is cross-referenced for certain proprietary information (e.g., section S.2.2), provide the DMF number assigned by Health Canada and a copy of the Letter of Access. Sponsors should ensure that the DMF has been registered with Health Canada and that a DMF number has been assigned to the file. For existing Drug Master Files, it should be ensured that the information included in the DMF is up to date (e.g., updated every two years) and that the data has been received by Health Canada. If a Canadian agent is used by the DMF Holder, a letter *from the DMF Holder* should be submitted allowing the agent to act on their behalf, rather than the letter coming from the Canadian agent.

For further information on the requirements for DMFs, see Health Canada's current guidance document on filing and referencing of Drug Master Files.

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, packaging, labelling, testing, importing, storage, and distribution of the drug substance used in the clinical studies. 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 office(s).

S 2.2 Description of Manufacturing Process and Process Controls

The manufacturing process description should be progressively more detailed from Phase I to Phase III. Sponsors are expected to provide a flow diagram, accompanied by a narrative description (Phase II and Phase III only), summarizing the synthetic process of the drug substance. Drug substances which are milled/micronized should be indicated as such. A summary of the expectations at each phase is provided below.

For drug substances which are manufactured as sterile substances, a complete description of the method of sterilization should be provided. Controls in place to maintain sterility during transportation and storage should also be summarized.

Phase I Clinical Trial Applications

A flow diagram of the synthetic process(es) should be provided that includes chemical structures and configurations of starting materials, intermediates and the drug substance. In addition, all reagents (including chemical formulae), solvents and catalysts should be specified in the flow diagram.

Phase II Clinical Trial Applications

In addition to the flow chart, a stepwise narrative description of the drug substance manufacturing process should be provided. The use of all reagents, solvents, catalysts and auxiliary materials should be summarized in the manufacturing process description. Relevant process controls should be indicated where critical steps in the synthesis have been identified.

The description of the manufacturing process at Phase II should be sufficiently detailed to address quality and safety concerns without being overly restrictive to process optimization.

For non-standard or novel manufacturing processes or technologies, a higher level of detail in the narrative description, addressing critical process controls and safety concerns, should be provided at Phase II.

Phase III Clinical Trial Applications

A detailed flow chart and narrative process description should be provided. The detailed description provided at Phase III should include critical steps identified in the process and relevant process controls (e.g. reaction times, pH, temperatures, etc.), including all purification steps.

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) composition of media;
- (c) precursors;
- (d) additional details on how the reaction conditions are controlled (e.g., times, temperatures, rates of aeration, etc.); and
- (e) name and composition of preservatives.

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. It may be necessary to include limits for residues resulting from such treatments in the drug substance specification. Absence of toxic metals and radioactivity may also have to be confirmed.

S 2.3 Control of Materials

Drug substances or materials used in the synthesis which are of animal origin should be free of Bovine Spongiform Encephalopathy (BSE) / Transmissible Spongiform Encephalopathy (TSE) and an attestation confirming this should be provided either as an Attachment or directly within the QOS, if applicable.

Phase II and Phase III Clinical Trial Applications

Sponsors should provide details of the starting materials for the synthesis of the drug substance. The level of detail expected concerning controls on starting materials for synthesis increases as synthetic steps get closer to the final drug substance. Generally, the “starting material for synthesis” is:

- a synthetic precursor one or more synthetic steps prior to the final intermediate
- a well-characterised, isolated and purified substance with the structure fully elucidated
- controlled by 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 and esters (or similar derivatives) of the drug substance, and the racemate of a single enantiomeric drug substance, are not considered final intermediates.

For starting materials which are commercially purchased, the source and a copy of the provisional specifications is typically considered acceptable. For “starting materials for synthesis” which are manufactured in-house, a copy of the flow chart and provisional specifications for the starting material should be provided.

S 2.4 Controls of Critical Steps and Intermediates

[Information in this section not required for Phase I or Phase II Clinical Trial Applications]

Phase III Clinical Trial Applications

Provide a summary of critical steps identified in the synthesis and the tests and tentative acceptance criteria for their control. In-process controls or provisional specifications for isolated intermediates may be summarized here.

S 3 Characterisation

S 3.1 Elucidation of Structure and other Characteristics

For all Clinical Trial Applications

Confirmation of structure based on synthetic route and spectral analyses should be provided. Copies of the actual spectra are not required for Clinical Trial Applications, but should be available upon request.

The Quality Overall Summary should include a list of the studies performed and a conclusion from the studies (e.g., if the results support the proposed structure, spectral interpretations).

The studies carried out to elucidate and/or confirm the chemical structure of New Chemical Entities normally includes elemental analysis, Infrared (IR), Ultraviolet (UV), Nuclear Magnetic Resonance (NMR), X-ray diffraction (XRD) and Mass Spectra (MS) studies.

When a drug substance is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the clinical studies.

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.

If the drug substance is a single isomer or a fixed ratio of isomers, provide the rationale for this decision. For existing drugs (e.g., generics), include a summary of any comparative studies performed.

For drug substances that contain an asymmetric centre, where there has not been any information provided regarding the manufacture of the starting material through which it has been introduced, a summary of results of a study should be submitted demonstrating that the material exists as a racemic mixture (e.g., specific optical rotation).

It is recognized that some drugs (e.g., certain antibiotics, enzymes, and peptides) present difficulties with respect to structural investigation. In such cases, more emphasis should be placed on the purification and the specification for the drug substance. If a drug substance consists of more than one component, the physicochemical characterization of the components and their ratio should be submitted.

If, based on the structure of the drug substance, there is not a potential for isomerism, it may be sufficient to include a statement to this effect.

Polymorphism:

If the potential for polymorphism is a concern, sponsors are expected to provide a summary of investigations of the drug substance, recrystallized from several solvents, to determine if the drug substance exists in more than one crystalline form. 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 that the desired polymorph is the one obtained.

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 of the drug product. Particle size can also be important in dosage form performance (such as inhalation products), achieving uniformity of content in low-dose tablets, desired smoothness in ophthalmic preparations, and stability of suspensions.

If particle size is deemed relevant to the performance of the drug product, results from several development batches should be provided, and appropriate controls on particle size distribution included in the specifications.

S 3.2 Impurities

The tables in the Quality Overall Summary template can be used to summarize the names, structures, and origin of the impurities. 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”, etc.). It should also be indicated if the impurity is a metabolite of the drug substance.

Results of the impurity investigation should be provided. 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.

Phase I Clinical Trial Applications

The structure (or other identifier, if not structurally characterized) as well as the origin should be included in the drug substance impurity table.

Phase II and III Clinical Trial Applications

The impurity name (or identifier), structure (if characterized) and origin should be provided in the table for all specified impurities.

Impurity levels for previously manufactured nonclinical and clinical batches may also be summarized within this section.

S 4 Control of the Drug Substance

S 4.1 Specification

[Information in this section not required for Phase I Clinical Trial Applications]

A summary of the specification for the drug substance should be provided. The specification is a list of tests, references to analytical procedures, and acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. This includes tests for description, identification, purity, and potency as well as other tests specific to the drug substance.

The specification can be summarized according to the table in the Quality Overall Summary template including the Tests, Method Types (including Source), and Acceptance Criteria. The Method Type should indicate the kind of analytical procedure used (e.g., visual, IR, UV, HPLC, laser diffraction, etc.) and Source refers to the origin of the analytical procedure (e.g., USP, Ph.Eur., BP, House, etc.).

Phase II Clinical Trial Applications

Specifications are considered interim as they are based on a limited number of development batches. A higher degree of flexibility will be allowed in specifications with sufficient scientific justification (refer to Section S.4.5 - *Justification of Specification*).

Phase III Clinical Trial Applications

Specifications are expected to be re-assessed prior to the Phase III application and reflect those intended for the marketing application, based on additional manufacturing experience and stability information.

S 4.2 Analytical Procedures

[Information in this section is not required for Phase I Clinical Trial Applications]

Phase II and III Clinical Trial Applications

A brief description of the analytical methods used for the drug substance should be provided for all tests included in the drug substance specifications (e.g. method type, column size, etc.). Detailed descriptions of the step-by-step analytical procedures should not be submitted for Clinical Trial Applications, but should be available upon request.

Unless modified, it is not necessary to provide descriptions of Schedule B compendial analytical procedures.

S 4.3 Validation of Analytical Procedures

[Information in this section not required for Phase I Clinical Trial Applications]

Phase II and III Clinical Trial Applications

The suitability of the analytical methods and a tabulated summary of the validation carried out should be provided (e.g. results or values for specificity, linearity, range, accuracy, precision, intermediate precision, limit of detection and limit of quantitation, where applicable). Complete validation reports should not be provided for Clinical Trial Applications.

For substances which comply with a Schedule B monograph, reference to the monograph will be considered sufficient.

S 4.4 Batch Analyses

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

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “All tests meet specifications”. This could 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”. When reporting the analytical results it is important that the method used for each test be identified (including Type and Source).

Batch analysis results for the drug substance may be provided in either the Quality Overall Summary or by providing a copy of the Certificate of Analysis. The batch number, batch sizes, and dates and sites of production should be stated for all batches.

Phase I Clinical Trial Applications

Analytical results from the batch(es) to be used in the proposed clinical trial should be provided.

Phase II Clinical Trial Applications

Analytical results from the batch(es) to be used in the proposed clinical trial should be provided. If batch analysis from the actual batches to be used in the proposed study are not available at the time of filing, results from representative batches of drug substance may be provided as

supporting data, with a commitment that the batch analysis for the specific lot to be used in that protocol will be submitted prior to dosing.

Phase III Clinical Trial Applications

Analytical results from the batch(es) to be used in the proposed clinical trial, or batches representative thereof, should be provided.

Note: For the purpose of this guidance document, a “representative batch” is defined as a batch of drug substance or drug product that is manufactured using the same formulation (for the drug product), method of manufacture and equipment, specifications and the same container closure system as the proposed clinical batch, with a similar batch size. All subsequent references in this guidance document to “representative batch” should be interpreted per this definition.

S 4.5 Justification of Specification

[Information in this section is not required for Phase I Clinical Trial Applications]

The sponsor should ensure the specification includes all the tests and acceptance criteria appropriate for the drug substance, and that reasonable limits for impurities and residual solvents have been established. Acceptance criteria should be based on manufacturing experience, stability data and safety considerations.

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.

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.

S 7 Stability

S 7.1 Stability Summary and Conclusions

The types of studies conducted, protocols used, and the results of the studies should be summarized.

The tables in the Quality Overall Summary template can be used to summarize the information on the batches used in the stability studies. Full long term stability data is not required at the time of filing, provided some preliminary stability data is available on representative batches together with a commitment that the stability of the clinical trial samples or representative batches will be monitored according to the stability protocol until the re-test period has been established.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “All tests meet specifications”. This could 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”.

Available long-term and accelerated stability data for the drug substance should be provided at each stage of development to support its storage (conditions and re-test period) and use in the manufacture of the drug product.

The proposed storage conditions and re-test period (or shelf life, as appropriate) for the drug substance should be reported.

Stress testing:

Stress testing of the drug substance can help identify the likely degradation products, which can in turn help establish the degradation pathways, the intrinsic stability of the molecule and validate the stability-indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of drug product being developed.

S 7.2 Stability Protocol and Stability Commitment

If full long-term stability data supporting the re-test period is not available at the time of filing, provide a commitment that the stability of the clinical trial samples, or batches considered representative thereof, will be monitored according to the stability protocol. A summary of the stability protocol (in tabular format, summarizing frequency of testing, tests to be conducted, etc.) should be provided.

S 7.3 Stability Data

Results of the stability studies (e.g., long-term studies, accelerated studies, stress conditions, etc.) should be presented in an appropriate format.

The actual stability results (i.e., raw data) used to support the clinical trial should be provided as a separate Attachment. 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”.

Phase II and III Clinical Trial Applications

In cases where analytical procedures are only used in stability studies (i.e. stability-indicating assay method) and were not summarized in 2.3.S.4, a brief description of the analytical procedure as well as a tabulated summary of validation information should be provided per the instructions in Sections S.4.2 and S.4.3.

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:

- (a) 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 oval, round, immediate-release, aqueous film-coated tablet in three strengths (5 mg, 10 mg, and 20 mg).”).

- (b) Composition, i.e., list of all components of the dosage form, their amount on a per unit basis (including overages, if any) 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, etc.) 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. 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 active pharmaceutical ingredient to compensate for manufacturing losses.”).

The components should be declared by their proper or common names, Quality standards (e.g., USP, Ph.Eur., House, etc.) and, if applicable, their grades (e.g., “Microcrystalline Cellulose NF (PH 102)”). The function of each component (e.g., diluent/filler, binder, disintegrant, lubricant, glidant, granulating solvent, coating agent, antimicrobial preservative, etc.) should also be stated.

The qualitative composition should be provided for all proprietary components or blends (e.g., capsule shells, colouring blends, imprinting inks, etc.).

- (c) Description of reconstitution diluent(s), if applicable;

List all reconstitution solvents/diluents to be used in the proposed clinical study.

If the reconstitution solvent/diluent is manufactured in-house, a separate drug product section (e.g. Sections P.1-P.8) should be completed for the chemistry and manufacturing information for the reconstitution solvent/diluent.

- (d) Type of container closure system used for accompanying reconstitution diluent, if applicable:

A brief description of the container closure system(s) used for the accompanying reconstitution diluent should be provided, if applicable (for commercially-purchased diluents, provide information only if the primary packaging has been changed);

- (e) Qualitative list of the components of the placebo samples used in the clinical trials, if different from the components listed in P.1(b)

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. Additionally, this section should identify and describe

the formulation and process attributes (critical parameters) that may influence batch reproducibility, product performance and drug product quality.

Where sterile, reconstituted products are to be further diluted, compatibility should be demonstrated with all potential diluents over the range of dilution. These studies, including tests for purity, potency, sub-visible particulate matter, pH, etc., should preferably be conducted on aged samples. Where the type of container is not specified, compatibility should be demonstrated in suitable containers. If one or more containers are identified, compatibility of admixtures should be demonstrated only in the specified containers.

Phase I Clinical Trial Applications

This section should only be completed for sterile products. Summaries of compatibility studies with diluents and containers should be included in this section.

Phase II and III Clinical Trial Applications

To the extent possible, information pertaining to the following aspects of pharmaceutical development should be submitted:

- (a) The compatibility of the drug substance with excipients listed in P.1 should be discussed. For combination products, a summary of investigations of the compatibility of the drug substances with each other should be provided.
- (b) 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 earlier clinical formulations and the formulation (i.e., composition) described in P.1 should be discussed, if applicable.
- (c) The selection of the manufacturing process described in P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilisation should be explained and justified.
- (d) 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 labelling.

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. Sponsors should ensure that the DMF has been registered with Health Canada and that a DMF number has been assigned to the file. For existing Drug Master Files, it should be ensured that the information included in the DMF is up to date (e.g., updated every two years) and that the data has been received by Health Canada. A copy of the Letter of Access should be provided as an Attachment. If a Canadian agent is used by the DMF Holder, a letter *from the DMF Holder* should be submitted allowing the agent to act on their behalf, rather than the letter coming from the Canadian agent.

For further information on the requirements for DMFs, see Health Canada's current guidance document on filing and referencing of Drug Master Files.

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 for the batches used in the clinical studies. 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 office(s).

An attestation should be provided in the Quality Overall Summary or as an Attachment confirming that the drug product to be used in the Canadian study was manufactured according to Good Manufacturing Practices.

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. 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 active pharmaceutical ingredient to compensate for manufacturing losses.”). Batch formula tables should be representative of the lots intended for use in the proposed clinical trial.

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

P 3.3 Description of Manufacturing Process and Process Controls

The manufacturing process description should be progressively more detailed from Phase I to Phase III. Sponsors are expected to provide a flow diagram, accompanied by a narrative description (Phase II and Phase III only), summarizing the manufacturing process of the drug product. The level of detail expected at each phase of Clinical Trial Application is outlined below.

For sterile products, a complete narrative description of the manufacturing process should also be submitted *regardless of the clinical trial phase*. Furthermore, details of sterilization and lyophilization (if applicable) procedures should be provided for all Clinical Trial Applications.

Phase I Clinical Trial Applications

A flow chart of the manufacturing process should be provided clearly indicating the order of addition of components and a summary of unit operations (e.g. blending, screening, etc.).

Phase II Clinical Trial Applications

A flow chart and narrative description of the manufacturing process should be provided. Detailed summaries of process controls (e.g. blending times, end-points for drying operations, etc.) are not required, with the exception of the sieve/screen size for immediate-release solid oral dosage forms.

The description of the manufacturing process at Phase II should be sufficient to fully describe the process without being restrictive to continuing process development and optimisation.

For non-standard or novel manufacturing processes or technologies, a higher level of detail in the narrative description which addresses critical process controls, and safety and bioavailability concerns, should be provided at Phase II.

Phase III Clinical Trial Applications

A flow chart and a detailed narrative description of the process should be provided. A summary of in-process controls and process parameters (e.g. mixing/blending time, temperature, pH for preparations of solutions) should be provided. The critical steps, process controls, intermediate tests and final product controls should be identified and described in additional detail. Equipment should, at least, be identified by type (e.g., tumble blender, in-line homogeniser) and working capacity, where relevant.

P 3.4 Controls of Critical Steps and Intermediates

[Information in this section not required for Phase I or Phase II Clinical Trial Applications]

Phase III Clinical Trial Applications

To the extent possible at the time of submission, sponsors should provide information on the following:

Critical Steps: Tests and tentative acceptance criteria for controls on the critical steps in the drug product manufacturing process, where identified.

Intermediates: Information on the quality and provisional controls on intermediates isolated during the process, where relevant.

P 4 Control of Excipients

P 4.1 Specifications

This includes the specifications for all excipients, including those that do not appear in the final drug product (e.g., solvents). 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 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 specifications for the excipient should be provided.

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 Drug Regulations*.

For excipients which are filed with Health Canada as a DMF, a Letter of Access should be provided as an Attachment. For more information, please refer to Health Canada's current guidance document on filing and referencing of Drug Master Files.

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).

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, supporting data should be provided which confirms that the gelatin is free of Bovine Spongiform Encephalopathy (BSE) / Transmissible Spongiform Encephalopathy (TSE). If the supplier of the gelatin has a DMF registered with Health Canada, a Letter of Access should be provided.

Supporting information for excipients of human or animal origin should be provided as a separate Attachment.

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 should be provided, with cross-references to supporting safety data (nonclinical and/or clinical) using the relevant sections of the Quality Overall Summary according to the drug substance and/or drug product format.

P 5 Control of Drug Product

P 5.1 Specification(s)

[Information in this section is not required for Phase I Clinical Trial Applications]

A summary of the specification(s) for the drug product should be provided. The specification is a list of tests, references to analytical procedures, and acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. This includes tests for description, identification, purity, and potency as well as other tests specific to the dosage form.

The specification(s) can be summarized according to Health Canada's Quality Overall Summary template including the Tests, Method Types, Sources, and Acceptance Criteria. The Method Type should indicate the kind of analytical procedure used (e.g., visual, IR, UV, HPLC, etc.) and the Source refers to the origin of the analytical procedure (e.g., USP, BP, House, etc.).

Phase II Clinical Trial Applications

Specifications are considered interim as they are based on a limited number of development batches. A higher degree of flexibility will be allowed in specifications with sufficient scientific justification (Please refer to Section P.5.6 - *Justification of Specification*).

Phase III Clinical Trial Applications

Specifications are expected to be re-assessed prior to the Phase III submission and reflect those intended for the marketing application, based on additional manufacturing experience and stability information.

P 5.2 Analytical Procedures

[Information in this section is not required for Phase I Clinical Trial Applications]

Phase II and III Clinical Trial Applications

A brief description of the analytical methods used for the drug product should be provided for all tests included in the drug product specifications (e.g. reverse-phase HPLC, GC, etc.). Detailed descriptions of the step-by-step analytical procedures should not be submitted for Clinical Trial Applications, although this information should be available upon request.

Unless modified, it is not necessary to provide a copy of Schedule B compendial procedures.

P 5.3 Validation of Analytical Procedures

[Information in this section is not required for Phase I Clinical Trial Applications]

Phase II and III Clinical Trial Applications

Suitability of the analytical methods and a tabulated summary of the validation information should be provided (i.e. results or values for specificity, linearity, range, accuracy, precision, robustness, limit of detection and limit of quantitation, where applicable). Complete validation reports should not be submitted for Clinical Trial Applications, although this information should be available upon request.

For substances which comply with a Schedule B monograph, reference to the monograph will be considered sufficient for all Clinical Trial Applications.

P 5.4 Batch Analyses

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

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “All tests meet specifications”. This could 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”. When reporting the analytical results it is important that the method used be identified (including Type and Source).

Batch analysis results for the drug product may be provided in either the Quality Overall Summary or by providing a copy of the Certificate of Analysis. In all cases, the batch numbers, batch sizes, dates and sites of production, and input drug substance batches should be provided.

Phase I Clinical Trial Applications

Analytical results from the batch(es) to be used in the proposed clinical trial should be provided.

Phase II Clinical Trial Applications

Analytical results from the batch(es) to be used in the proposed clinical trial should be provided. If batch analysis from the actual batches to be used in the proposed study are not available at the time of filing, results from representative batches of drug product may be provided as supporting data with a commitment that the batch analysis for the specific lot(s) to be used in that protocol will be submitted prior to dosing.

Phase III Clinical Trial Applications

Analytical results from the batch(es) to be used in the proposed clinical trial, or batch(es) considered representative thereof, should be provided.

P 5.5 Characterisation of Impurities

Information on the characterisation of impurities should be provided, if not previously summarized in Section S.3.2 - *Impurities*.

This information includes 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.. The tables in the Quality Overall Summary template in section S.3.2 can be used to summarize this information.

This section may also be used to report any new impurities found in the drug product during stress testing (e.g. photostability testing).

P 5.6 Justification of Specification(s)

[Information in this section is not required for Phase I Clinical Trial Applications.]

The sponsor should ensure the specification(s) includes all the tests and acceptance criteria appropriate for the drug product, and that reasonable limits for degradation products have been established. Acceptance criteria should be based on manufacturing experience, stability data, and safety considerations. For impurities/degradation products which are unique to the drug product, acceptance criteria should be supported by appropriate toxicology and safety studies.

P 7 Container Closure System

A description of the container closure system(s) to be used in the clinical trial should be provided, including the materials of construction for each packaging component. This includes packaging components that:

- a) are product contact surfaces
- 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

For sterile products, details of the washing, sterilization and depyrogenation should be submitted in this section.

For dosage forms that have a higher potential for interaction between filling and container closure system (e.g. parenteral, ophthalmic products, oral solutions), additional detail may be required.

P 8 Stability***P 8.1 Stability Summary and Conclusions***

The types of studies conducted, protocols used, and the results of the studies should be summarized.

The tables in the Quality Overall Summary template can be used to summarize the information on the batches used in the stability studies. Full long term stability data is not required at the time of filing, provided some preliminary stability data is available on representative batches together with a commitment that the stability of the clinical trial samples (or representative batches) will be monitored according to the stability protocol until the shelf-life of the drug product has been established with confidence.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “All tests meet specifications”. This could 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”.

For sterile products, sterility should be reported at the beginning and end of shelf life. During development it is expected that sterility will be monitored on a routine basis (e.g. annual basis) until the shelf life has been determined with confidence. For parenteral products, sub-visible particulate matter should be reported at every test interval until a shelf life has been established. Bacterial endotoxins need only be reported at the initial test interval.

For drug products which are reconstituted or diluted prior to administration, stability and compatibility studies covering the entire in-use period should be provided. Furthermore, for products which are diluted or reconstituted into a secondary container closure system (i.e., infusion kit), compatibility data should be submitted to support in-use conditions in that specific container closure.

Available long-term and accelerated stability data should be provided for the drug product at each stage of development to support its storage conditions and shelf-life.

Stress testing:

For certain drug products, stress testing of dosage forms may be appropriate to assess the potential for changes in physical and/or chemical properties of the drug product. The nature of the stress testing will depend on the type of drug product being developed.

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 provided. Alternative storage conditions may be acceptable with supporting scientific data.

Based on the results of the stability evaluation, other storage precautions may be warranted (e.g., “Do not refrigerate”, “Protect from light”, “Protect from moisture”).

P 8.2 Stability Protocol and Stability Commitment

If full long term stability data supporting the proposed shelf life is not available at the time of filing, provide a commitment that the stability of the clinical trial samples, or samples considered representative of the clinical batches, will be monitored throughout the duration of the clinical trial. A summary of the stability protocol (e.g. tabular format, summarizing frequency of testing, tests to be conducted, etc.) should be provided.

P 8.3 Stability Data

Results of the stability studies (e.g. long-term and accelerated studies) should be presented in an appropriate format.

The actual stability results (i.e., raw data) used to support the clinical trial should be provided as an Attachment. 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”.

Phase II and III Clinical Trial Applications

In cases where analytical procedures are only used in stability studies (i.e. stability-indicating assay method) and were not previously summarized, details of the analytical procedure as well as a tabulated summary of validation information should be provided per the instructions in Section P.5.2 and P.5.3.

A Attachments

A list of Attachments should be provided (e.g., actual stability results (raw data), specifications for non-Schedule B compendial excipients, letters of access to Drug Master Files, letters of attestation of BSE/TSE-free material, etc.).