Health Canada Santé Canada

August 8, 2011

Notice

Our file number: 11-113839-2

Re: Revised Draft Guidance Document: *Preparation of Drug Submissions and Applications in the Common Technical Document (CTD) Format*

Health Canada is pleased to announce the release of the revised draft *Guidance for Industry: Preparation of Drug Submissions and Applications in the Common Technical Document (CTD) Format* for a 60-day comment period. Once final, it will replace the 2003 *Draft Guidance for Industry: Preparation of New Drug Submissions in the CTD Format.*

This guidance document will assist sponsors in the preparation of drug submissions and applications in the Common Technical Document (CTD) format developed by the International Conference on Harmonisation (ICH). It defines the regional requirements of submissions in CTD format, found in Modules 1 and 3.

Noteworthy updates include:

- Extensive revisions made to the Canadian Module 1 format, allowing for the CTD format to be used for all submission and application types filed over a product's lifecycle, for example:
    - Post-authorization commitment tracking table;
    - Clinical Trial Applications and their amendments are now included in the proposed Module 1;
    - Regional Clinical information;
    - the addition of Module 3.2.R.4 for Yearly Biological Product Reports, submitted to the Biologics and Genetic Therapies Directorate only; and
    - Addition of clarification has been added to Module 5 regarding the placement of Periodic Safety Update Reports (PSUR).

In conjunction with this initiative, it should be noted that the *Guidance for Industry: Creation of the Canadian Module 1 eCTD Backbone File* and the *Document Type Definition (DTD) for the Canadian Module 1* are being updated and are targeted to be published in Winter 2011. This will allow for the transition of eCTD submissions to the proposed Module 1 format.

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Comments provided to Health Canada should be submitted no later than October 7, 2011 in order to allow sufficient time for their assessment.

Comments should be submitted electronically and directed to**:**

Submission and Information Policy Division (SIPD)
Therapeutic Products Directorate
Health Canada
Finance Building 2,
Address Locator 0201A1
101 Tunney's Pasture Driveway
Ottawa, Ontario
K1A 0K9

Telephone: 613-957-3123
Fax: 613-941-0825
Email: eReview@hc-sc.gc.ca

Health Canada Santé Canada

REVISED DRAFT GUIDANCE DOCUMENT

Preparation of Drug Submissions and Applications in the Common Technical Document (CTD) Format

This guidance document is being distributed for comment purposes only.

Published by authority of the
Minister of Health

Draft Date	2011/07/08

Canada

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

Également disponible en français sous le titre : Ébauche révisée de la ligne directrice : Preparation des présentations et des demandes de drogues en format Common Technical Document (CTD)

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 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

The *Common Technical Document for Registration of Pharmaceuticals for Human Use* (International Conference on Harmonisation [ICH] Topic M4) was adopted by Health Canada, in 2003, for use in the preparation of drug submissions and applications.

The Common Technical Document (CTD) provides a globally harmonised format that is accepted in many regions, avoiding the need to compile different registration dossiers for different regulatory authorities. It is organized into five modules. Module 1 is region specific, while Modules 2, 3, 4, and 5 are intended to be common for all regions. A regional component is included in Module 3. The review of information provided in a well structured submission will improve the efficiency of the screening and review of a submission.

This guidance document has been updated to facilitate the use of a common format for submission filings and management of information over the lifecycle of a product. Once finalized, this guidance document will supersede the 2003 *Draft Guidance for Industry: Preparation of New Drug Submissions in the CTD Format* and all other references to the layout of Modules 1 and/or 3.2.R, where extensive changes have been made to provide placeholders for regional documents throughout the lifecycle of the product.

It is important to note that the implementation and use of the CTD represents a work in progress, and it is expected that future refinements of this guidance will continue to be necessary as a result of experience gained. Amendments will also be undertaken as a result of the migration to and implementation of the eCTD.

1.1 Policy Objective

To facilitate the preparation of a drug submission or application, pursuant to Part C of the *Food and Drug Regulations,* in the CTD format.

1.2 Policy Statement

The *Food and Drug Regulations* provides regulatory requirements for the approval and sale of drugs in Canada and prohibits the sale of drugs unless the manufacturer has filed a submission that is satisfactory to the Minister. Although the Regulations do not define format requirements, Health Canada has adopted the CTD format within the Canadian registration framework. This guidance document, once finalised, is to be used in the preparation of drug submissions and applications for human use filed to Health Canada.

1.3 Scope and Application

This guidance document applies to the preparation of all drug submissions and applications for human use, filed pursuant to the *Food and Drug Regulations*, including Clinical Trial Applications (CTA), their amendments (CTA-A) and Drug Master Files (DMF).

The CTD format is the expected format for all drug submissions and applications including drug/device combinations where the primary mechanism of action is drug-related. For cases where the combination product is classified as a device, the use of the CTD format for the drug component is encouraged. For medical devices, please see *Summary Technical Document for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices* (STED), developed by the Global Harmonization Task Force (GHTF).

2 GUIDANCE FOR IMPLEMENTATION

This document outlines the CTD format for the submission of information in relation to drugs for human use, which is filed over the lifecycle of that product in Canada. **Table 1** below provides an overview of the presentation of the drug submission or application, outlining the modular structure and main headings, which should be used.

For a New Drug Submission (NDS), if no information is available or required under a specific heading, that section or subsection should be marked as "not applicable" or "not relevant" while retaining the section title and numbering. If necessary, a justification for the absence of information should be provided. It is not necessary, however, to include subsection headings when an entire section is designated as "not applicable".

For submission types other than a NDS, if no information is provided under a specific heading, that section or subsection of the submission or application should be omitted and the section title and numbering should be retained. A rationale for the absence of information should be provided in a note to reviewer, as necessary.

The CTD Guidance indicates *where and how* available information is to be presented; however, it is not intended to indicate *what* is actually required. Therefore, when preparing a submission or application, it is necessary to consult relevant Health Canada guidance documents (including adopted ICH guidelines) on technical (data) requirements. Applicants are advised to consult the Health Canada website for the latest updates on guidance documents.

This guidance is intended to be used in conjunction with the most recent version of the following documents:

- ICH CTD guidelines and the corresponding *Questions and Answers* documents on the ICH website;

- The accompanying Health Canada *Notice* for supplementary and/or interim guidance; and

- Related Health Canada guidance documents and notices on Quality and comparative bioavailability information.

For additional guidance, the applicant should consult the appropriate review Bureau in the Therapeutic Products Directorate (TPD) or the Office of Regulatory Affairs in the Biologics and Genetic Therapies Directorate (BGTD).

Table 1: Presentation of Information in the Common Technical Document (CTD) Format

Module Number	Title and Main Section Headings	Cross-Reference to Modules	Binder/ Label colour	Number of Paper Copies
1	**Administrative and Product Information**	2, 3 and 5	Red	1*
1.0	Correspondence			
1.1	Table of Contents (Modules 1 to 5)			
1.2	Administrative Information			
1.3	Product Information			
1.4	Health Canada Summaries			
1.5	Environmental Assessment Statement			
1.6	Regional Clinical Information			
1.7	Clinical Trial Application (CTA) and Clinical Trial Application-Amendment (CTA-A) Specific Requirements			
1.A	Appendix			
2	**Common Technical Document (CTD) Summaries**		Yellow	1*
2.1	CTD Table of Contents (Modules 2 to 5)	2 to 5		
2.2	CTD Introduction	2 to 5		
2.3	Quality Overall Summary	3		
2.4	Nonclinical Overview	2 and 4		
2.5	Clinical Overview	2 and 5		
2.6	Nonclinical Written and Tabulated Summaries	2 and 4		
2.7	Clinical Summary	5		
3	**Quality**		Blue	1*
3.1	Table of Contents of Module 3			
3.2	Body of Data			
3.3	Literature References			
4	**Nonclinical Study Reports**		Green	1
4.1	Table of Contents of Module 4			
4.2	Study Reports			
4.3	Literature References			
5	**Clinical Study Reports**		Black	1
5.1	Table of Contents of Module 5			
5.2	Tabular Listing of All Clinical Studies			
5.3	Clinical Study Reports			
5.4	Literature References			

* For combination products that require a joint review an additional copy of Modules 1, 2, and 3 is required.

3 STRUCTURE OF DRUG SUBMISSIONS AND APPLICATIONS IN THE COMMON TECHNICAL DOCUMENT (CTD) FORMAT

3.1 Module 1: Administrative and Product Information

Module 1 identifies placeholders, defined by the numerical items listed in the Module 1 Table of Contents (ToC), for all administrative and product information documentation.

Module 1.0 Correspondence

All correspondence-related documents submitted to Health Canada are to be placed in Module 1.0 unless otherwise indicated. Scientific information is not to be included in this Module.

Module 1.0.1 Cover Letter

Any data being submitted to Health Canada should be accompanied by a cover letter. The cover letter should clearly state what is being submitted, including reference to the request letter (if applicable) and a brief description of the package. For example, if a Periodic Safety Update Report (PSUR) is to be submitted, one of the following types should be indicated in the cover letter:

- Requested AD HOC PSUR - submitted as a one-time submissions request;
- Voluntary PSUR - unsolicited submission;
- Requested Periodic PSUR 0 requested by Health Canada, for example (e.g.) Risk Management Plan (RMP) follow-up or post-authorization commitment;
- PSUR-C (confirmatory) - submitted to support the fulfilment of a Notice of Compliance with Conditions (NOC/c).

The cover letter should not contain any scientific information. The Question and Answer (Q and A) responses from Health Canada issued correspondence and the Note to Reviewer are assigned a specific location (1.0.4 and 1.0.7) and should not be included in the cover letter.

Any cross-referenced submission or application should be clearly stated in the cover letter, and the following information should be included:

- Submission or application type;
- control number;
- brand name;
- manufacturer / applicant's name;
- Central Registry (CR) file number;

- date the submission or application was approved.

Module 1.0.2 Life Cycle Management (LCM) Table

The Life Cycle Management (LCM) Table is a specific requirement for filing a submission or application in electronic Common Technical Document (eCTD) format, and should be placed in this section.

Module 1.0.3 Copy of Health Canada Issued Correspondence

A Copy of all Health Canada issued correspondence should be placed in this section, which includes (but are not limited to) the following:

- Clarifax (during screening or review);
- Notice of Deficiency (NOD);
- Notice of Non-Compliance (NON);
- Not Satisfactory Notice (NSN);
- Post-Notice of Compliance Letters (Post-NOC);
- No Objection Letter (NOL) comments;
- Screening Deficiency Notice (SDN).

Module 1.0.4 Health Canada Solicited Information

Solicited information is defined as information requested by Health Canada. Responses to these requests are to be provided in Question and Answer format, and placed in this section. The answers should summarise the response and cross-reference the supporting data that is to be placed in the appropriate Module of the submission or application. **No data** is to be provided in this section.

Module 1.0.5 Meeting Information

Any meeting related information and documentation, with the exception of Pipeline and Reconsideration meetings, are to be placed in this section. This includes (but is not limited to) the following:

- meeting information package;
- proposed meeting agenda;
- presentation slides;
- meeting minutes.

Module 1.0.6 Request for Reconsideration Documentation

Any documentation required as part of the Request for Reconsideration process is to be placed in this section.

Module 1.0.7 General Note to Reviewer

The Note to Reviewer should be used to facilitate the review. These comments are **NOT** to be included in the cover letter.

Notes relating to the entire submission or application (e.g., advising that the product is referred to by a foreign trade name throughout the submission or application) should be placed in this section.

Notes relating to a specific section of the submission or application should be placed at the beginning of each pertinent section. For example, this note can be used to identify changes in a section and/or document.

Module 1.1 Table of Contents (ToC)

The Table of Contents (ToC) for the entire submission or application should be placed in this section. It should list all documents included in Modules 1-5.

Module 1.2 Administrative Information

Module 1.2.1 Application Forms

Completed and signed application forms should be placed in this section.

Module 1.2.2 Fee Forms

Completed fee forms should be placed in this section.

Module 1.2.3 Certification and Attestation Forms

Completed and signed forms are to be placed in this section. These include, but are not limited to, the following:

- Submission Certification Form
  - Required as per section C.08.005.1 of the *Food and Drug Regulations*. The use of company letterhead is preferred. Please see the Health Canada website for an example of appropriate wording.

316 - To be signed and dated by the senior executive officer of the manufacturer in
317 Canada and the medical or scientific director of the manufacturer. If the
318 submission certification or any significant part of the certification was prepared
319 by an agent authorized by the manufacturer, the submission certification must
320 also be signed by that agent.
321 - Responses to Screening Deficiency Notices, Notices of Noncompliance and
322 Notices of Deficiency should include a revised submission certificate signed
323 and dated as described above.
324 • Letter of Attestation
325 - To be included for any submission or application that includes both paper and
326 electronic versions of information, confirming that the content contained in the
327 electronic submission or application is identical to the paper-based submission.
328 • Submission Disclosure Form (BGTD only)
329 • Certification of Electronic Signature (placeholder)
330 • Changes in Manufacturer's Name and/or Product Name Administrative Changes -
331 Certification Form
332 • Attestation of Pristine Product Monograph
333 • Product Monograph Translation Certification Form
334 • Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform
335 Encephalopathy (TSE) Attestation Form
336 • Certification of Suitability to the Monographs of the European Pharmacopoeia
337 (CEP) issued by the European Directorate for the Quality of Medicines and
338 Healthcare (EDQM)
339 • Application Certification Form
340 • Statement of Commitment for Drug Master Files (DMF)
341
342 Module 1.2.4 Intellectual Property Information
343
344 Module 1.2.4.1 Patent Information
345
346 As per the *Patented Medicines (Notice of Compliance) Regulations* (*PM (NOC)*
347 *Regulations*), an applicant (that is [i.e.] first person) who files or who has filed a new
348 drug submission or a supplement to a new drug submission may submit a patent list
349 in relation to the submission or supplement for addition to the Patent Register by
350 filing a Form IV: Patent List within the time limits and according to the conditions
351 set out in section 4 of the *PM (NOC) Regulations*.
352
353 A second person (i.e. subsequent entrant) must address all patents listed on the Patent
354 Register for the Canadian reference product used to establish bioequivalence for the
355 second person's submission by filing a Form V: Declaration Re: Patent List as per

section 5 of the *PM (NOC) Regulations*. Documents relating to the Notice of Allegation, including proof of service and the Acknowledgement and Certification of Receipt of Information and Material form, are also to be placed in this section.

Module 1.2.4.2 Data Protection Information

C.08.004.1 of the *Food and Drug Regulations* provides a term of data protection to manufacturers of innovative drugs during which the Minister shall not approve a subsequent entry submission submitted for a new drug on the basis of a comparison between the new drug and the innovative drug. The term of data protection is effective from the date of the issuance of the Notice of Compliance (NOC) and extends to eight years (eight and one-half years if relevant paediatric clinical trial data is submitted). Innovative manufacturers may place information that supports the eligibility of their innovative drug for data protection in this section.

Module 1.2.5 Compliance and Site Information

Module 1.2.5.1 Clinical Trial Site Information Forms (CTSI)

Completed Clinical Trial Site Information Forms (CTSI) must be provided in this section for each proposed clinical trial site.

Module 1.2.5.2 Establishment Licensing (EL)

Establishment Licensing (EL) information should be placed in this section.

Module 1.2.5.3 Good Clinical Practices (GCP)

Good Clinical Practices (GCP) related documentation should be placed in this section.

Module 1.2.5.4 Good Laboratory Practices (GLP)

A statement of GLP compliance consistent with the Organisation for Economic Co-operation and Development's (OECD) *Principles of Good Laboratory Practice (GLP)* should be placed in this section.

Module 1.2.5.5 Good Manufacturing Practices (GMP)

Good Manufacturing Practices (GMP) compliance information should be placed in this section. This may include the Certificate of Compliance (COC) issued by the

Health Products and Food Branch Inspectorate (HPFBI) when the foreign GMP rating is accepted for a foreign site under a Mutual Recognition Agreement (MRA).

Module 1.2.5.6 Good Pharmacovigilance Practices (GPP)

Good Pharmacovigilance Practices (GPP) related documentation should be placed in this section.

Module 1.2.5.7 Other Compliance and Site Information Documents

Any other regulatory compliance and site-related information which is not currently covered under Module 1.2.5.1-1.2.5.6 should be placed in this section.

Module 1.2.6 Authorization for Sharing Information

Letters authorizing Health Canada to share information regarding the submission with other regulatory authorities (or vice versa), and/or to access other (third party) drug submissions and applications, DMF and Site Reference Files (SRF) should be provided in this section.

Module 1.2.7 International Information

Information on the product application, approved indications and marketing status in other countries/regions should be provided in this section. Depending upon the status this may include, but not be limited to, the following:

- International registration, review and/or marketing status, including date of filing, approval of product or supplemental changes in other jurisdictions, information regarding the withdrawal, stop of sale and/or market recall;
- Regulatory GMP compliance and EL status issued by other jurisdictions, including Date of last GMP and/or pre-approval inspection, and any observation-related information;
- Foreign refusals;
- Foreign clinical trial status;
- International Birth Date of the product and for all approved indications;
- Confirmation of filing or the date(s) of approval or withdrawal;
- Foreign review reports, including Question and Answer (Q and A) documents (**upon request only**);
- Meeting minutes from other jurisdictions (**upon request only**).

Module 1.2.8 Post-Authorization Information

The following information should be included in this section:

- Market Notification Forms
  - As per part C.01.014.3 of the *Food and Drugs Regulations*, companies are required to notify Health Canada of a drug being sold.
  - For labels see section 1.3.2
- Post-Authorization Commitments
  - The commitment tracking table, as detailed in Appendix C should be provided here.
  - Data supplied in response to these commitments are to be placed in appropriate sections throughout Modules 1-5.
  - For NOC/c related documents, see Module 1.6.4.
- Notices of Change (Level III) forms
  - *Post-Notice of Compliance (NOC) Changes: Notices of Change (Level III) Forms* are to be placed in this section.
- Notice of Decision and Summary Basis of Decision
  - All revisions of the Notice of Decision and Summary Basis of Decision documents are to be placed in this section.

Module 1.2.9 Other Administrative Information

This section is for any administrative information that does not have a designated location in the CTD format. This section should **NOT** contain any scientific information.

Module 1.3 Product Information

Module 1.3.1 Product Monograph

A copy of the non-annotated (clean) and annotated Product Monograph are to be placed in this section.

The text of the annotated copy at the time of filing should be cross-referenced to supporting information and study findings reported in Module 2 documents and, when submitted, the Bioequivalence Summary (Module 1.4.2). Applicants may also choose to include references to related information in Modules 3 to 5, as appropriate.

Within the sections of the annotated Product Monograph, the text should also be cross-referenced by number to the *References or Selected Bibliography* section at the end of the Product Monograph.

Articles from publications listed in the References section should be cited in accordance with the current edition of the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*, International Committee of Medical Journals Editors (ICMJE). When reference is made to a publication not provided in Modules 2 - 5, copies of the reference material should be provided in this section.

When revisions are requested during the course of the review, an annotated version of the revised Product Monograph is required. The annotations should reflect all changes made.

Module 1.3.2 Inner and Outer Labels

All inner and outer labels should be provided in this section, including those submitted with the Market Notification.

This should include the labels for all strengths, dosage forms and reconstitution diluents. Typewritten or other draft label copy is acceptable for review purposes.

When additional revisions are requested during the course of the review, an annotated version of the revised label is required. The annotations should reflect all changes made.

Module 1.3.3 Non-Canadian Labelling

If the drug product has been marketed outside Canada, the applicant is encouraged to supply the monograph or package inserts approved in other jurisdictions, clearly identifying them by country or region.

Module 1.3.4 Investigator's Brochure (IB)

Investigator's Brochure for CTA and CTA-As should be placed in this section.

Module 1.3.5 Reference Product Labelling

The Product Monograph for Canadian Reference Products is to be placed in this section.

Module 1.3.6 Certified Product Information Document (CPID)

A copy of the non-annotated (clean) and annotated CPID are to be placed in this section. The text of the annotated copy at the time of filing should be cross-referenced to the corresponding sections of Module 3, while any further revisions should reflect all changes that have been made, including Level III changes. The clean version should not contain any cross-referencing.

Module 1.3.7 Look alike/Sound alike Assessments (LA/SA)

The assessments are to be placed in this section.

Module 1.3.8 Pharmacovigilance Information

Module 1.3.8.1 Pharmacovigilance Plan
Pharmacovigilance plans or their equivalent are to be placed in this section.

Module 1.3.8.2 Risk Management Plan (RMP)
Risk management plans or their equivalent are to be placed in this section.

Module 1.3.8.3 Risk Communications
Risk Communications are to be placed in this section.

Module 1.3.8.4 Other Pharmacovigilance Information
Any other pharmacovigilance information should be placed in this section.

Module 1.4 Health Canada Summaries

Module 1.4.1 Protocol Safety and Efficacy Assessment Template - Clinical Trial Application (PSEAT-CTA)

The completed Protocol Safety and Efficacy Assessment Template - Clinical Trial Application (PSEAT-CTA) should be placed in this section.

Module 1.4.2 Comprehensive Summary: Bioequivalence

The completed Comprehensive Summary: Bioequivalence (CS-BE) for all *pivotal* comparative bioavailability (bioequivalence) studies should be placed in this section.

Module 1.4.3 Multidisciplinary Tabular Summaries

This section is a placeholder for tables that contain information that is applicable to more than one discipline.

Module 1.5 Environmental Assessment Statement

This section is for the Environmental Assessment Statement, required for new substances in products regulated under the *Food and Drug Act* as per the New Substances Notification Regulations (NSN) of the *Canadian Environmental Protection Act* (CEPA).

Module 1.6 Regional Clinical Information

Module 1.6.1 Comparative Bioavailability Information

Specific requirements for *pivotal* comparative bioavailability (bioequivalence) studies should be placed in this section. These specific requirements include, but are not limited to:

- Canadian Reference Product (CRP) Confirmation;
- Requests for waivers and justification statements;
- Verification of potency of the Test and Reference products (Certificates of Analysis);
- Bioavailability/Bioequivalence (BA/BE) data sets (required for all types of *pivotal* comparative bioavailability (bioequivalence) studies.

Module 1.6.2 Company Safety Core Data Sheets

Company Safety Core Data Sheets should be placed in this section.

Module 1.6.3 Priority Review Requests

All documents related to a Priority Review Request, including the cover letter, should be placed in this section only.

Module 1.6.4 Notice of Compliance with Conditions (NOC/c)

All documentation relating to an NOC/c is to be placed in this section only. These documents include, but are not limited to, the following:

- Letter of undertaking;
- Qualifying Notice;
- Dear Health Care Professional (DHCP) Letters;
- Product Specific Fact Sheets.

Module 1.7 Clinical Trial Application (CTA) and Clinical Trial Application- Amendment (CTA-A) Specific Requirements

Module 1.7.1 Submission Rationale/Brief Summary

The Submission Rationale/Brief Summary for BGTD products are to be placed in this section.

Module 1.7.2 Study Protocol

All required copies of the Study Protocol are to be placed in this section.

Module 1.7.3 Informed Consent Forms

The Informed Consent Forms are to be placed in this section.

Module 1.7.4 Canadian Research Ethics Board (REB) Refusals

Canadian Research Ethics Board (REB) refusals are to be placed in this section.

Module 1.7.5 Information on Prior-related Applications

Information on prior-related applications is to be placed in this section.

Module 1.A Appendix

Module 1.A.1 Electronic Review Documents

All electronic media submitted to support the drug submission or application should be placed in this section.

3.2 Module 2: Common Technical Document (CTD) Summaries

Please consult the ICH M4 Guidelines.

3.3 Module 3: Quality

Please consult the ICH M4Q Guidelines.

Module 3.2.R Regional Information

To complete the regional section of Module 3 the applicant should refer to the appropriate Health Canada CTD Quality guidance documents.

Module 3.2.R.1 Production Documentation

Module 3.2.R.2 Medical Devices

Module 3.2.R.3 Lot Release Documentation - BGTD

Module 3.2.R.4 Yearly Biologic Product Report (YBPR)-BGTD Only

The Yearly Biologic Product Report (YBPR), provided for BGTD only, is to be placed in this section.

3.4 Module 4: Nonclinical Study Reports

The applicant should refer to the ICH M4S guidelines, as well as the appropriate Health Canada guidance documents to complete this module.

3.5 Module 5: Clinical Study Reports

The applicant should refer to the ICH M4E guideline under *Module 5: Clinical Study Reports*, and the ICH E3 guideline, *Structure and Content of Clinical Study Reports.*

In addition, the applicant should note the following in relation to cited modules of the CTD:

Module 5.3.1.2 Comparative Bioavailability (BA) / Bioequivalence (BE) Study Reports

The technical requirements for *pivotal* comparative bioavailability (bioequivalence) studies are provided in the Health Canada *Guidance for Industry: Preparation of Comparative Bioavailability Information for Drug Submissions in the CTD Format*.

Module 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

The technical requirements for *pivotal* comparative bioavailability (bioequivalence) studies are provided in the Health Canada *Guidance for Industry: Preparation of Comparative Bioavailability Information for Drug Submissions in the CTD Format*.

Module 5.3.6 Post Marketing Experience

Periodic Safety Update Reports (PSUR) should be placed in this section.

Module 5.3.7 Case Report Forms (CRF) and Individual Patient Listings

As per Section C.08.005.1(a) of the Food and Drug Regulations, Case Report Forms (CRF) are required for any deaths, serious adverse reactions, unexpected adverse reactions, and for all subjects who were unable to complete the study. All other CRFs, as outlined in the ICH Guideline *Structure and Content of Clinical Study Reports* (E3), should be provided upon request only.

All CRFs provided should be placed in this section, indexed by study and in the same order that the clinical study reports were provided in the submission. All CRFs are to be provided in electronic format only.

4 PRESENTATION OF SUBMISSIONS AND APPLICATIONS

This section describes the physical specifications for submitting paper submissions and applications in CTD format. The paper format is to serve as the official Central Registry (legal) copy for paper-based submissions and applications.

4.1 Organization and Identification of Submission and Application Volumes

- The submission or application should be bound in three-ring binders.
- Binders should be colour-coded as specified in **Table 1**. Alternatively, labels on the spines as well as on the cover are to be colour-coded as indicated.
- The binder labels on the spine and the front cover should include the following information:
  - trade (brand) name of the drug product;
  - name of the manufacturer;
  - proper or common and code names;
  - sequential number, starting at Volume 1 for each module;
  - The volume number for that binder, out of the total number of volumes for that module, the section(s) contained within each volume, and the date of submission or application (month and year), should also be specified on the label.

For example, the label on a blue-coloured binder (Volume 1 of Module 3: Quality), would read as follows:

Drug Product "ABC"
Applicant/Manufacturer "XYZ"
Volume 1 of 63
3.1-3.2.S.2.3
Month/year

Note: In the case of NCs containing small amounts of information it is recommended, where possible, that all modules of the submission or application be provided in one (black) binder.

4.2 Organization, Presentation and Identification of Information within Submissions and Applications

Information within the CTD is organized into a series of structured documents which are in turn organized into modules. The M4 guidance *Organisation of the Common Technical Document* and ICH General *Questions and Answers* provides the definition of a document and guidance on

ToC formatting, cross-referencing within the CTD and for document pagination, segregation and section numbering.

Literature references should be cited in accordance with the current edition of the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals,* International Committee of Medical Journals Editors (ICMJE).

Acronyms and abbreviations should be defined the first time they are used in each module.

Module 1 does not need to be paginated in full, but pagination within documents is useful. It is not necessary to include a header or footer on Module 1 documents, except where already an integral part of the document, (e.g. the Certified Product Information Document (CPID) template), or to paginate Module 1 forms or labels.

4.3 Language

Information in the submission or application should be recorded in either English or French. Material in a different language should be accompanied by an English or French translation with the possible exception of Case Report Forms (consult the appropriate Bureau (TPD) or the Office of Regulatory Affairs (BGTD) first).

4.4 Legibility and Font Size

Text and tables should be prepared using margins that allow the document to be printed on 8.5 x 11 inch paper. The left-hand margin should be sufficiently large that information is not obscured by the method of binding. Font sizes for text, tables, flow diagrams and floor maps should be of a style and size that are large enough to be easily legible, even after photocopying. Times New Roman, 12-point font is recommended for narrative text.

5 APPENDICES

APPENDIX A: CANADIAN MODULE 1

Module #	Module Title
1	**Administrative and Product Information**
1.0	**Correspondence**
1.0.1	Cover letter
1.0.2	Life Cycle Management Table (LCM)
1.0.3	Copy of Health Canada issued correspondence
1.0.4	Health Canada Solicited Information
1.0.5	Meeting Information

1.0.6	Request for Reconsideration Documentation
1.0.7	General Note to Reviewer
1.1	**Table of Contents (ToC)**
1.2	**Administrative Information**
1.2.1	Application Forms
1.2.2	Fee Forms
1.2.3	Certification and Attestation Forms
1.2.4	Intellectual Property Information
1.2.4.1	Patent Information
1.2.4.2	Data Protection Information
1.2.5	Compliance and Site Information
1.2.5.1	Clinical Trial Site Information Form (CTSI)
1.2.5.2	Establishment Licensing (EL)
1.2.5.3	Good Clinical Practices (GCP)
1.2.5.4	Good Laboratory Practices (GLP)
1.2.5.5	Good Manufacturing Practices (GMP)
1.2.5.6	Good Pharmacovigilance Practices (GPP)
1.2.5.7	Other Compliance and Site Information Documents
1.2.6	Authorization for Sharing Information
1.2.7	International Information
1.2.8	Post- Authorization Information
1.2.9	Other Administrative Information
1.3	**Product Information**
1.3.1	Product Monograph
1.3.2	Inner and Outer Labels
1.3.3	Non-Canadian Labelling
1.3.4	Investigator's Brochure
1.3.5	Reference Product Labelling
1.3.6	Certified Product Information Document (CPID)
1.3.7	Look-alike/Sound-alike Assessment (LA/SA)
1.3.8	Pharmacovigilance Information
1.3.8.1	Pharmacovigilance Plan
1.3.8.2	Risk Management Plan (RMP)
1.3.8.3	Risk Communications
1.3.8.4	Other Pharmacovigilance Information
1.4	**Health Canada Summaries**
1.4.1	Protocol Safety and Efficacy Assessment Template – Clinical Trial Application (PSEAT-CTA)
1.4.2	Comprehensive Summary : Bioequivalence
1.4.3	Multidisciplinary Tabular Summaries

1.5	**Environmental Assessment Statement**
1.6	**Regional Clinical Information**
1.6.1	Comparative Bioavailability Information
1.6.2	Company Core Data Sheets
1.6.3	Priority Review Requests
1.6.4	Notice of Compliance with Conditions (NOC/c)
1.7	**Clinical Trial Application (CTA) and Clinical Trial Application-Amendment (CTA-A) Specific Requirements**
1.7.1	Submission Rationale/Brief Summary (BGTD only)
1.7.2	Study Protocol
1.7.3	Informed Consent Forms
1.7.4	Canadian Research Ethics Board (REB) Refusals
1.7.5	Information on Prior-related Applications
1.A	**Appendix**
1.A.1	Electronic Review Package

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APPENDIX B: CORRELATION OF ORIGINAL VERSUS PROPOSED MODULE 1

Original		Proposed	
Module #	**Module Title**	**Module #**	**Module Title**
1	**Administrative Information and Prescribing Information**	**1**	**Administrative and Product Information**
		1.0	**Correspondence**
		1.0.1	Cover letter
		1.0.2	Life Cycle Management Table
		1.0.3	Copy of Health Canada issued correspondence
		1.0.4	Health Canada Solicited Information
		1.0.5	Meeting Information
		1.0.6	Request for Reconsideration Documentation
		1.0.7	General Note to Reviewer
1.1	**Table of Contents**	**1.1**	**Table of Contents**
1.2	**Application Information**	**1.2**	**Administrative Information**
1.2.1	Drug Submission Application Form (HC-SC 3011)	1.2.1	Application Forms
1.2.2	Drug Submission Fee Application Form	1.2.2	Fee Forms
1.2.3	Submission Certification Form	1.2.3	Certification and Attestation Forms
1.2.4	Patent Information	1.2.4	Intellectual Property Information
		1.2.4.1	Patent Information
		1.2.4.2	Data Protection Information
1.2.5	GMP and Establishment Licensing (EL) Information	1.2.5	Compliance and Site Information
		1.2.5.1	Clinical Trial Site Information Form
		1.2.5.2	Establishment Licensing
		1.2.5.3	Good Clinical Practices
		1.2.5.4	Good Laboratory Practices
		1.2.5.5	Good Manufacturing Practices
		1.2.5.6	Good Pharmacovigilance Practices
		1.2.5.7	Other Compliance and Site Information Documents
1.2.6	Letter of Access	1.2.6	Authorization for Sharing Information
1.2.7	International Registration Status 1	2.7	International Information

Original		Proposed	
1.2.8 Other	Application Information	1.2.8	Post- Authorization Information
		1.2.9	Other Administrative Information
1.3	**Product Labelling**	**1.3**	**Product Information**
1.3.1	Product Monograph	1.3.1	Product Monograph
1.3.2	Inner and Outer Labels	1.3.2	Inner and Outer Labels
1.3.3	Non-Canadian Package Inserts	1.3.3	Non-Canadian Labelling
		1.3.4	Investigator's Brochure
		1.3.5	Reference Product Labelling
		1.3.6	Certified Product Information Document (CPID)
		1.3.7	Look-alike/Sound-alike Assessment (LA/SA)
		1.3.8	Pharmacovigilance Information
		1.3.8.1	Pharmacovigilance Plan
		1.3.8.2	Risk Management Plan (RMP)
		1.3.8.3	Risk Communications
		1.3.8.4	Other Pharmacovigilance Information
1.4	**Health Canada Summaries**	**1.4**	**Health Canada Summaries**
1.4.1	Certified Product Information Document (CPID)	1.4.1	Protocol Safety and Efficacy Assessment Template – Clinical Trial Application (PSEAT-CTA)
1.4.2 Com	prehensive Summary: BioEquivalence	1.4.2	Comprehensive Summary : Bioequivalence
		1.4.3	Multidisciplinary Tabular Summaries
1.5	**Environmental Assessment Statement**	1.5	**Environmental Assessment Statement**
1.6	**Electronic Review Documents**	**1.6**	**Regional Clinical Information**
		1.6.1	Comparative Bioavailability Information
		1.6.2	Company Core Data Sheets
		1.6.3	Priority Review Requests
		1.6.4	Notice of Compliance with Conditions(NOC/c)
		1.7	**Clinical Trial Application (CTA) and Clinical Trial Application-Amendment (CTA-A) Specific Requirements**
		1.7.1	Submission Rationale/Brief

Original		Proposed	
			Summary (BGTD only)
		1.7.2	Study Protocol
		1.7.3	Informed Consent Forms
		1.7.4	Canadian Research Ethics Board (REB) Refusals
		1.7.5	Information on Prior-related Applications
		1.A	**Appendices**
		1.A.1	Electronic Review Package

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APPENDIX C: POST-AUTHORIZATION COMMITMENTS

Commitments are periodically made by the sponsors to provide additional information to Health Canada in order to further support the approved submission or application.

Submissions and applications with Post-Authorization commitments that are not subject to the NOC/c policy, either because they do not meet the requirements or because they are Level II changes, should be tracked.

Some examples include (but are not limited to) the following:

- additional stability data;
- periodic updates of ongoing trials or surveillance programs;
- risk management studies (e.g. phase IV, pharmacoepidemiological, drug utilization studies).

To track the status of outstanding commitments over the Lifecycle of the product, the following table should be included in section 1.2.8 Post- Authorization Information.

Summary of Commitment	**Date of No Objection Letter/ Notice of Compliance**	**Control #**	**Submission date of Outstanding Information**	**Date of commitment closure by Health Canada**

Once the commitment has been closed off by Health Canada, it should remain in the table for at least one subsequent submission or application and for a minimum of one year, after which it can be removed.

6 REFERENCES

6.1 Health Canada References

The latest versions of these and other Health Canada guidance documents, policies, templates and forms that should be consulted during the preparation of a drug submission or application can be obtained from the Health Canada website at:

http://www.HealthCanada-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index-eng.php
http://www.HealthCanada-sc.gc.ca/hpfb-dgpsa/bgtd-dpbtg/index-eng.php

- Guidance for Industry: Management of Drug Submissions
- Guidance for Industry: Preparation of a Drug Submission in Electronic Common Technical Document (eCTD) Format
- Guidance for Industry: Reconsideration of Final Decisions Issued for Human Drug Submissions
- Guidance Document on Cost Recovery Submission Evaluation Fees
- Draft Guidance Document: Drug Master Files (DMF)
- Drug Good Manufacturing Practices (GMP), and the Establishment Licensing Enforcement Directive (POL-0004).
- Good Manufacturing Practices (GMP) Guidelines
- Notice: Submission Filing Requirements - Good Manufacturing Practices (GMP) / Establishment Licences (EL)
- Guidance document Non-Clinical Laboratory Study Data Supporting Drug Product Applications and Submissions: Adherence to Good Laboratory Practice
- Guidance for Industry Product Monograph
- Guidance for Industry: Drug Name Review: Look-alike Sound-alike (LA/SA) Health Product Names
- Guidance for Industry: Priority Review of Drug Submissions
- Guidance for Industry: Notice of Compliance with Conditions
- Quality Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) for Chemical Entities (products containing drugs of synthetic or semi-synthetic origin, excluding Schedule C and D drugs)
- Notice: Revised Quality Guidances on the Implementation of the Common Technical Document for Biological Products
- Preparation of the Quality Information for Drug Submissions in the CTD Format: Biotechnological/ Biological (Biotech) Products
- Preparation of the Quality Information for Drug Submissions in the CTD Format: Blood Products
- Preparation of the Quality Information for Drug Submissions in the CTD Format: Conventional Biotherapeutic Products
- Preparation of the Quality Information for Drug Submissions in the CTD Format: Vaccines
- Guidance for Industry: Preparation of Comparative Bioavailability Information for Drug Submissions in the CTD Format
- Notice Regarding Implementation of Risk Management Planning including the adoption of International Conference on Harmonisation (ICH) Guidance Pharmacovigilance Planning - ICH Topic E2E
- Guidance for Clinical Trial Sponsors - Clinical Trial Applications
- Post-Notice of Compliance (NOC) Changes Guidance Documents
- Guidance for Sponsors: Lot Release Program for Schedule D (Biologic) Drugs

- Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs)
- Notice: Common Technical Document - ICH Topic M4

The ICH M4 guidelines adopted by Health Canada can be obtained from the ICH website at www.ich.org

M4	Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use
M4E (R1)	The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Efficacy • Clinical Overview and Clinical Summary of Module 2 • Module 5: Clinical Study Reports
M4E (R4)	Implementation Working Group Questions and Answers
M4Q (R1)	The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality • Quality Overall Summary of Module 2 • Module 3: Quality
M4Q (R1)	Implementation Working Group Questions and Answers
M4S (R2)	The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Safety • Non-Clinical Overview and Non-Clinical Summaries of Module 2 • Organization of Module 4
M4S (R4)	Implementation Working Group Question and Answers

6.2 Other References

Uniform Requirements for Manuscripts Submitted to Biomedical Journals, International Committee of Medical Journals Editors (ICMJE).
http://www.icmje.org/

Summary Technical Document (STED), developed by the Global Harmonization Task Force (GHTF).

(OECD) *Principles of Good Laboratory Practice (GLP)*