CTD Implementation
Update on Comparative Bioavailability

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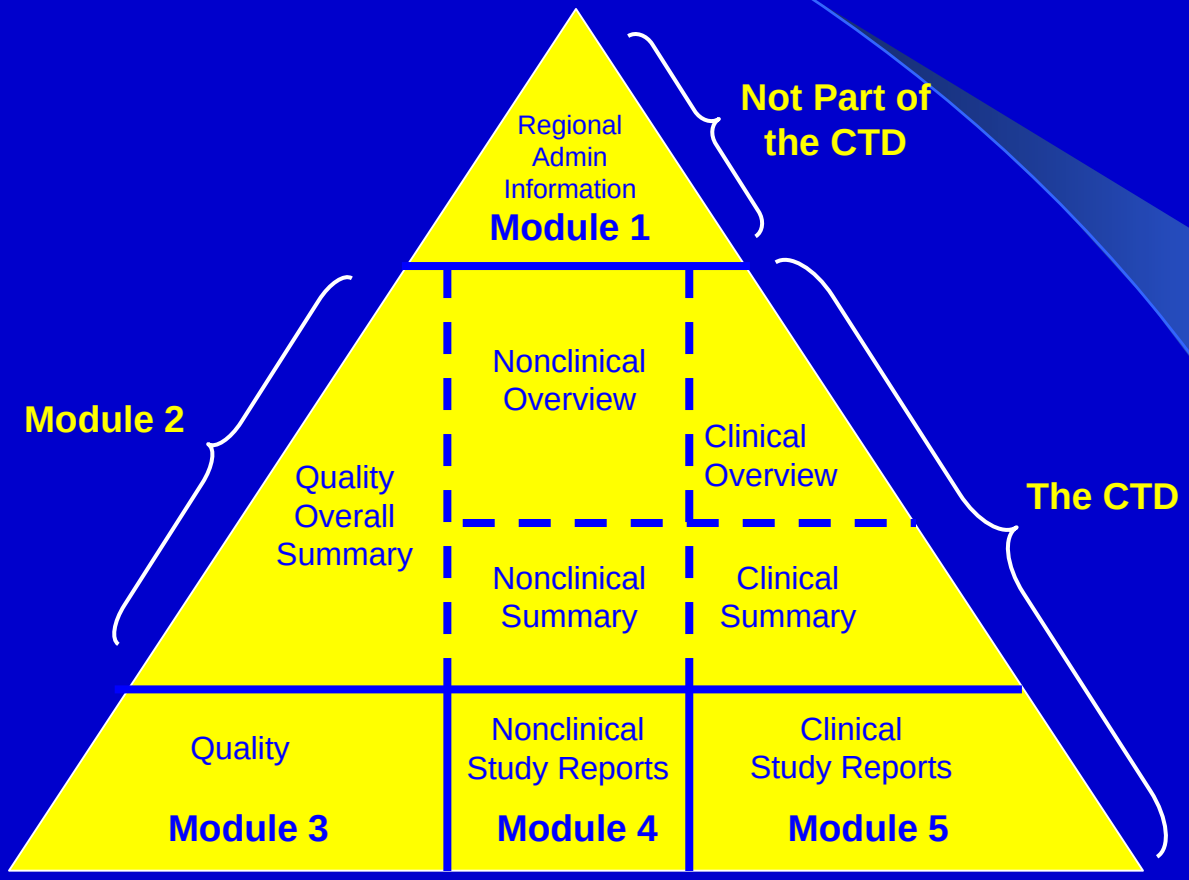
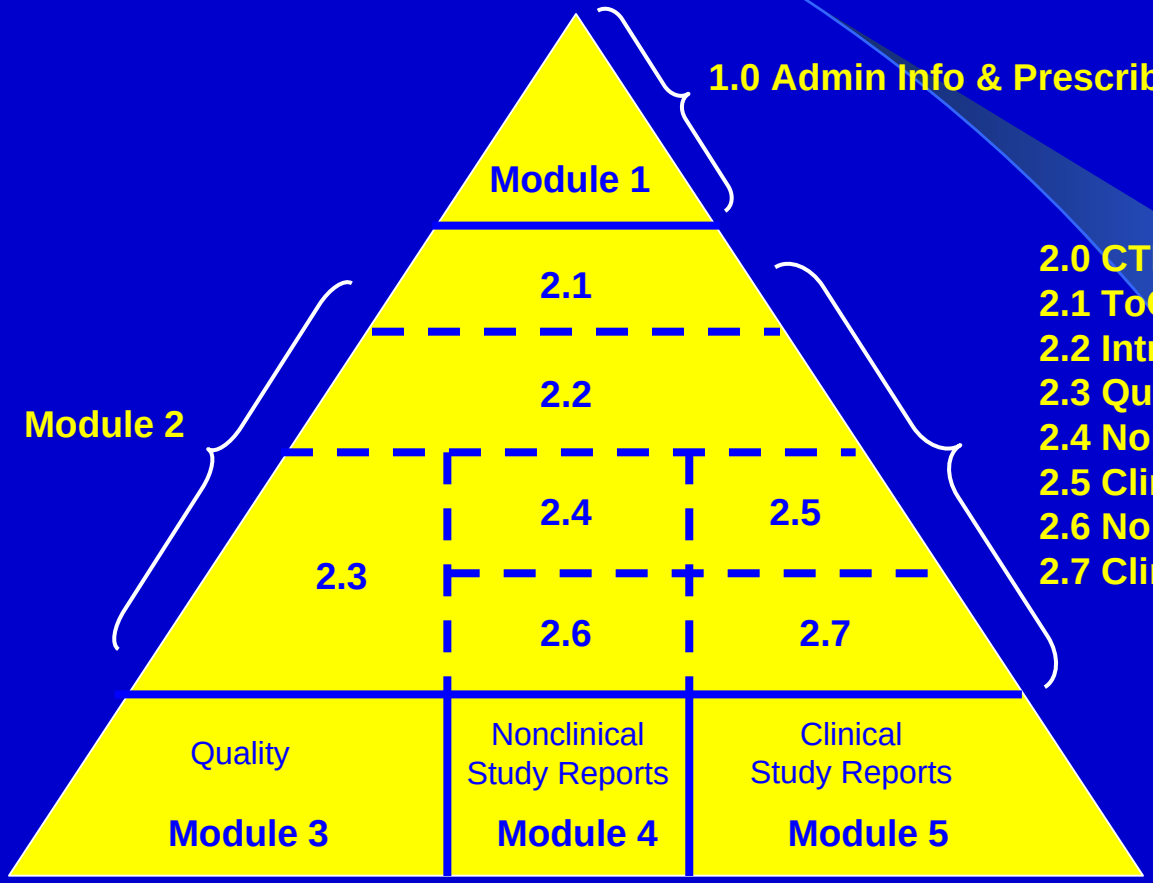
Presentation Outline

- The CTD Triangle
- The CTD Numbering System
- Filing Comparative Bioavailability Studies
- Guidance for Industry
- Filing an ANDS in the CTD Format
- Regional Information for BA/BE
- Comprehensive Summary – Bioequivalence (CS-BE) Template
- Comparative BA and BE Study Reports
- Questions & Answers
- Next Steps

The CTD Triangle



CTD Numbering System



2.0 CTD Summaries
2.1 ToC of the CTD (Mod 2-5)
2.2 Introduction
2.3 Quality Overall Summary
2.4 Nonclinical Overview
2.5 Clinical Overview
2.6 Nonclinical Summary
2.7 Clinical Summary

Filing Comparative Bioavailability Studies

Pivotal comparative bioavailability studies include but are not limited to:

- Introduction of new dosage forms or strengths of an approved product
- Reformulation or change in manufacturing procedures for an approved product
- Bridging between the to-be-marketed formulation and the formulation(s) used in clinical trials
- Introduction of a new subsequent-entry product on the basis of “equivalency” with a marketed reference product

Guidance for Industry
Preparation of Comparative Bioavailability Information for Drug Submissions in the CTD Format

- Draft guidance posted for comment to the TPD website on June 25, 2003
- Updated draft guidance posted to the TPD website on May 21, 2004
- Defines the CTD format for drug submissions which rely on comparative bioavailability (BA) studies to establish safety & efficacy
- References some of the technical requirements related to the conduct and analysis of comparative BA studies
- Provides an outline for a clinical study report for a comparative BA study in accordance with ICH E3: *Structure and Content of Clinical Study Reports*

Filing an ANDS in the CTD Format

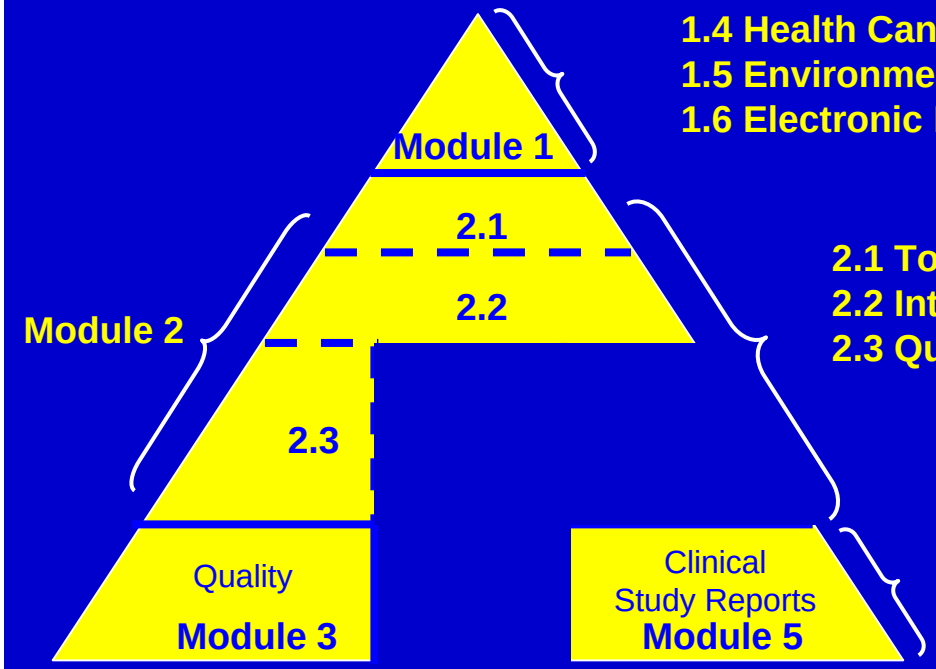
- From a clinical perspective, filing an ANDS in the CTD format will not change the Canadian (technical) data requirements for pivotal comparative bioavailability studies. It simply imposes specific formatting for the required information

Filing an ANDS in the CTD Format

It is likely that only the following relevant modules will be required:

- Module 1.1-1.6 (Administrative Information and Prescribing Information)
- Module 2.1 (Overall CTD Table of Contents)
- Module 2.2 (Introduction)
- Module 2.3 (Quality Overall Summary)
- Module 3 (Quality)
- Module 5.1 (Table of Contents for Module 5)
- Module 5.2 (Tabular Listing of all Clinical Studies)
- Module 5.3.1.2 (Comparative BA and BE Study Reports)
- Module 5.3.1.4 (Reports of Bioanalytical and Analytical Methods for Human Studies)
- Module 5.3.7 (Case Report Forms and Individual Patient Listings)
- Module 5.4 (Literature References)

Filing an ANDS in the CTD Format



1.1 ToC (Modules 1-5)
1.2 Application information
1.3 Product Labelling
1.4 Health Canada Summaries
1.5 Environmental Assessment Statement
1.6 Electronic Review Documents

2.1 ToC of the CTD (Modules 2-5)
2.2 Introduction
2.3 Quality Overall Summary

5.1 ToC (Module 5)
5.2 Tabular Listing of all Clinical Studies
5.3 Clinical Study Reports
5.3.1.2 Comparative BA & BE Study Reports
5.3.1.4 Reports of Bioanalytical & Analytical Methods for Human Studies
5.3.7 CRFs and Individual Patient Listings
5.4 Literature References

Regional Information for BA/BE

- Module 1.2.8 (Other Application Information)
  - Canadian Reference Product (CRP) confirmation
  - Waiver requests
  - Certificates of Analysis
- Module 1.3.1 (Product Monograph)
  - Current labelling and Product Monograph for the reference product
- Module 1.4 (Health Canada Summaries)
  - CS-BE template (paper copy)
- Module 1.6 (Electronic Review Documents)
  - BE data sets (*.inf and *.dat)
  - CS-BE template (electronic copy)

CS-BE Template

- Paper copy to be included in Module 1.4.2
- Electronic copy to be included in Module 1.6
- If completed for submissions that rely solely on pivotal comparative bioavailability (BA) studies to establish safety & efficacy, Modules 2.4-2.7 of the CTD do not need to be completed
- If the dossier includes pivotal comparative BA studies as well as other types of safety & efficacy studies, Modules 2.4-2.7 must be completed (as applicable) regardless of whether or not the CS-BE was completed for the pivotal comparative BA studies

CS-BE Template

- A regional template
- Not mandatory
- Completion will help to expedite the review process
- Draft CS-BE posted for comment to the TPD website on May 21, 2004

Comparative BA and BE Study Reports

- Structured in accordance with ICH E3: *Structure and Content of Clinical Study Reports*
- Some sections outlined in E3 will not be applicable
- Sections of E3 that are not applicable should appear in the T of C for the study report with the words “not applicable” but tabs for not applicable sections not needed in the body of the report
- NEW: Appendices 16.5 (Analytical Study Report) and 16.6 (Analytical Validation Report)

Questions & Answers (1)

Q. As a contract research organization (CRO), some information in Section 9.4.2 (Identity of Investigational Products) [of the clinical study report] is not always available or shared by the manufacturer. In particular, the proportion of excipients and drug of total core weight of the test product. How should this be handled?

R. If the CRO is preparing the clinical study report, and is not privy to this type of proprietary drug product information, it is suggested that the proportion of excipients as a % of total core weight of the test product be cross-referenced to the CS-BE template or the appropriate chemistry and manufacturing module.

Questions & Answers (2)

Q. Please clarify the information required in Appendix 16.1.10 (Documentation of inter-laboratory standardisation methods and quality assurance procedures used) for bioequivalence (BE) studies.

R. If the bioequivalence study is conducted at more than one clinical site or if the study protocol allowed for an “add-on”, the standardisation methods used and quality assurance procedures in place should be provided in Appendix 16.1.10. Similarly, if more than one clinical laboratory site was used for analysing samples from the pre-dose (screening) and post-dose laboratory procedures (e.g., haematology, biochemistry, urinalysis, and drug screening), documentation to support inter-laboratory standardisation should be provided in Appendix 16.1.10.

Questions & Answers (3)

Q. Please clarify the information required in Appendix 16.1.11 (Publications based on the study) for bioequivalence (BE) studies.

R. It is unlikely that data from a BE study will be published in the literature; however, in the rare event that a publication is made based on this type of study, Appendix 16.1.11 provides a placeholder for this publication.

Questions & Answers (4)

Q. Is the provision of case report forms (CRFs) required for bioequivalence (BE) studies?

R. Submission sponsors are required to file CRFs for all comparative bioavailability studies, including BE studies. Specifically, the CRFs for deaths and other serious adverse events (AEs) and withdrawals for AEs (as described in Appendix 16.3.1 of E3) are required and should be placed in Module 5.3.7.

See the general filing guidance, *Guidance for Industry - Preparation of New Drug Submissions in the CTD Format.*

Questions & Answers (5)

Q. Please clarify if the paper copy of the case report forms (CRFs) should be included in Appendix 16.3 of the clinical study report or Module 5.3.7.

R. CRFs that are described in Appendix 16.3.1 of E3 should be placed in Module 5.3.7, in the same order as the clinical study reports and indexed by study.

Appendices 16.3.2 (Other CRFs) and 16.4 (Individual Patient Data Listings) are to be sent only upon request.

When all CRFs (including 16.3.2) are available in PDF file format on CD ROM, applicants are encouraged to provide one copy at the time of filing in Module 1.6. In such instances, applicants are not required to provide the paper copy of the CRFs.

Appendix 16.3 of E3 is a placeholder for a listing of CRFs, and Module 5.3.7 is a placeholder for an actual copy of the CRFs listed under Appendix 16.3.

Questions & Answers (6)

Q. Why were Appendices 16.5 (Analytical Study Report) and 16.6 (Analytical Validation Report) created for BA/BE studies when Module 5.3.1.4 was created for these reports?

R. Refer to ICH M4 – Module 5, Clinical Study Reports, C. Clinical Study Reports, Section 1.4 (Reports of Bioanalytical and Analytical Methods for Human Studies).

Bioanalytical and/or analytical methods for BA/BE or in vitro dissolution studies should ordinarily be provided in individual study reports. Where a method is used in multiple studies, the method and its validation should be included once in Section 1.4 and referenced in the appropriate individual study reports.

….continued

Questions & Answers (6)

Q. *continued…*

R. This statement is interpreted to mean that analytical methods and their validation is to be provided as part of the clinical study report unless it applies to more than one study, in which case these documents should be provided (only once) in Module 5.3.1.4.

However, ICH E3 does not provide a placeholder for this documentation. As a result, Appendices 16.5 and 16.6 were created as a placeholder for these documents.

Questions & Answers (7)

Q. Clarify the information required in Appendices 16.2.1 (Discontinued patients) and 16.2.3 (Patients excluded from the efficacy analysis) for BA studies.

R. Appendix 16.2.1 and 16.2.3 as described in ICH E3 do apply to comparative BA studies. However, because of the relatively small number of subjects included in these types of studies, the number of discontinued and/or patients excluded from the efficacy analysis is usually very small. Therefore, an applicant may choose to provide a discussion of this subject matter within the core study report without having to supplement the narrative with appendices. Nevertheless, these placeholders are available should the applicant wish to use them. If these appendices are not used, the information that would normally appear in them should be addressed fully in the core report.

Next Steps

- Finalize, *Draft Guidance for Industry – Preparation of Comparative Bioavailability Information for Drug Submissions in the CTD Format*
- Finalize CS-BE template