Implementation of the ICH CTD Structure for Module 3 for Biotech: Health Canada’s Experience

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Background

- Since 2015, Health Canada is an official member to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).
- Health Canada is committed to the adoption and implementation of ICH guidance documents and standards.
- ICH M4Q reached Step 4 in September 2002
- Adopted by Health Canada in 2003
Reviewer’s experience

Prior to CTD submissions
- Inconsistency between submissions from different sponsors
- Missing information was frequently requested during screening via Screening Deficiency Notice (45 days to provide the information)
- Spent lot of time to locating information (paper copy)
- Causing delays in the review and in the approval of the dossier
- Delay access to patient

Submissions in CTD format
- Use of harmonized format
- Submissions much better organized
- Decrease number of missing information
- Decrease number of Screening Deficiency Notice
- Increase in the number of submissions meeting the review timelines
- Quicker access to patients
Health Canada CTD Guidelines

- General guidelines (2003, 2012):
  - Preparation of Drug Regulatory Activities in the Common Technical Format (CTD) Format (Module 1 regional specific regional requirements)

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

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

Scope:

- Biotechnological/ Biological proteins and polypeptides produced from recombinant or non-recombinant cell-culture expression systems
- Isolated from tissue and body fluids
- Can be highly purified and characterized.

*Currently under review*

Scope:

- Conventional biotherapeutic drugs isolated from biological sources such as tissues, organs and body fluids for which the other CTD Quality guidance document are not readily applicable.
  - Snake venom
  - Allergenic substances
  - Lung surfactant

*Currently under review*
Purpose of HC Guidelines

- Provide additional guidance to industry, for the preparation of the quality information for Drug Submissions, structured using the CTD format (including for clinical trial product).
- Supplements ICH M4Q
- Additional details on Module 1 and Module 3.2.R
- **References other available domestic Quality guidance documents** that can be useful in preparing the technical or scientific information required for certain sections of the submission.
  - Because the CTD guidance documents indicate *where* and *how* available information is to be presented. It does not indicate *what* is actually required.
Example of additional guidance

3.2.S.3.2 Impurities (name, manufacturer)
• Information on impurities should be provided (ICH).

<table>
<thead>
<tr>
<th>Impurity</th>
<th>Proposed Limit</th>
<th>Use of Batches and Lot Number</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Batches used in toxicological</td>
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<td>studies</td>
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<td>Batches used in clinical</td>
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<td></td>
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<td>studies</td>
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<tr>
<td>Product Related Impurities</td>
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<tr>
<td>TOTAL</td>
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<tr>
<td>Process Related Impurities</td>
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<tr>
<td>Residual Solvents</td>
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</table>

All potential impurities, including degradation products arising from manufacturing, storage or found in stability study batches, should be described regardless of whether they have been detected in any batches (Health Canada).
NDS Processing, Screening, and Authorization

- NDS Submission
  - Validation (OSIP)
    - Screening (BGTD/ORA)
      - Screening Clarifax
      - Screening Deficiency Notice
        - Rejected
        - Accepted for Review
          - Quality
          - Lab Testing
            - Clinical Review
            - Label Review
              - Review Clarifax
              - Notice of Deficiency (NOD)
                - Approval (NOC, DIN issued)
                  - Rejected (NON)
                  - Market Notification
                    - Post-Approval Commitments
                    - YBPR
                    - Lot Release
                      - Completed

Module 3 Biotech
Best practices
Module 3 Biotech – Best practices

- Validation Reports (and protocols)
  - Manufacturing process(es) (3.2.S.2.5 / 3.2.P.3.5)
  - Analytical method(s) (3.2.S.4.3 / 3.2.P.4.3)
  - Method transfer(s) (3.2.S.4.3 / 3.2.P.4.3)
  - Cleaning (3.2.A.1)
    - Including change-over procedures at the manufacturing site(s)
  - Shipping/Transportation (3.2.S.2.5 / 3.2.P.3.5)
    - For both Drug Substance and Drug Product

[Full validation reports best]

- Batch Analyses (3.2.S.4.4 / 3.2.P.5.4)
  - At least three (3) consecutive commercial scale batches
  - If do not have three (3) batches at commercial scale and manufactured consecutively, explain how the batches available and presented in the submission are supportive
Module 3 Biotech – Best practices (cont’d)

- Batch Analyses
  - In section 3.2.P.5.4, it is extremely helpful to include overall summary tables clearly identifying and linking all drug product batches to their use in clinical, preclinical, comparative in-vitro and stability studies.
    - Include identification of API drug substance batch number and manufacturing site, batch size and manufacturing date for the drug product, and specific use of the product, including study number, where relevant.
    - Where different batch numbers are assigned to drug product intermediates or where a manufacturing batch is assigned a different number when used in a clinical study, the tabulated summary should include and link together these data.
Module 3 Biotech – Best practices (cont’d)

- Container Closure System
  - Information on packaging materials should be included in section 3.2.P.7, if it pertains to composition and specifications and in section 3.2.P.2.4 if it pertains to qualification of packaging materials.

- Medical Device – Autoinjector
  - Information on the primary container closure system (e.g. semi-finished syringe) should be filed under 3.2.P.7.
  - Information on the autoinjector should be filed under 3.2.R.2 (in Canada)
Module 3 Biotech – Best practices (cont’d)

- **Stability Data**
  - If do not have full stability data as per guidance requirement, provide scientific rationale for how the information presented in submission is supportive. Explain bracketing/matrixing approach if used.
  - Explain why stability batches tested/manufactured are “worst case scenario” or how data demonstrates the product was stressed.
  - Present stability data for individual batches.

- **Trends (e.g. impurity) may be better presented in grouping and summarizing of stability data**
  - For example, if all batches show similar impurity tends, group together and list trends and maximum impurity levels
  - Minimum and maximum assay values across the whole range of batches are illustrative if there are no trends.
  - Highlight different trends across strengths or packaging materials.
Module 3 Biotech – Best practices (cont’d)

- Excipients
  - Provide information regarding *animal and/or human sourced* excipients (Section 3.2.P.4.5)
  - A tabulated summary of excipients of *human or animal origin* that are used, including the source, country of origin, manufacturer, and a brief description on the suitability for use based upon the controls evaluated (e.g. history, testing, screening), should also be provided.

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Biological Source</th>
<th>Country of Origin</th>
<th>Manufacturer</th>
<th>Suitability for Use</th>
</tr>
</thead>
<tbody>
<tr>
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</table>
Module 3 Biotech – Best practices (cont’d)

- Novel excipient:
  - Background information regarding the novel excipient should be provided under 3.2.4.6
  - The detailed quality information necessary to support its quality, safety, suitability for use, and “approvability”, should be submitted under 3.2.A.3 according to the drug substance format.
Pre-Submission Meetings

• Early communication and interaction between Industry and Health Canada

• Discussion of any potential and/or foreseeable issues and questions related to CTD format (e.g. for gene therapy products)

• Share discussions/decisions/communications with other regulatory authorities
Filing of Post-approval changes in CTD

- Filed according to the Canadian Post-NOC changes quality guidance document
- Appendix 3 - Biologics
- Expected location of the supporting data provided
Change in the control strategy

<table>
<thead>
<tr>
<th>Description of Change</th>
<th>Conditions to be Fulfilled</th>
<th>Supporting Data</th>
<th>Reporting Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Changes in the control strategy of the drug product, involving:</td>
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</tr>
<tr>
<td>a. Change from end-product testing to upstream controls for some test(s) (e.g., Real-Time Release Testing, Process Analytical Technology)</td>
<td>None</td>
<td>1-5</td>
<td>Supplement</td>
</tr>
<tr>
<td>b. Addition of a new Critical Quality Attribute (CQA) in the control strategy</td>
<td>None</td>
<td>1-5</td>
<td>Notifiable Change</td>
</tr>
<tr>
<td>c. Deletion of a Critical Quality Attribute (CQA) from the control strategy</td>
<td>None</td>
<td>1,5</td>
<td>Notifiable Change</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Supporting Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed product.</td>
</tr>
<tr>
<td>2. Updated, QC approved copy of the proposed drug product specifications (or where applicable, the final version of the specifications to be signed by QC after HC approval), if changed.</td>
</tr>
<tr>
<td>3. Copies or summaries of analytical procedures, if new analytical procedures are used.</td>
</tr>
<tr>
<td>4. Copies or summaries of validation reports, if new analytical procedures are used.</td>
</tr>
<tr>
<td>5. Justification and supporting data for each proposed change to the control strategy.</td>
</tr>
</tbody>
</table>
Foreign Review (Reliance)

Health Canada has, on occasion, used review assessment information from foreign regulatory agencies (i.e. FDA, EMEA) to support the review of an NDS filed in Canada.

Purpose:
- enhance the quality of Health Canada regulatory assessments
- assist Health Canada in meeting performance targets
- Canadians' timely access to safe, efficacious, and high quality drugs.

The sponsor should confirm in writing that the documentation filed in the NDS is identical to that on which the foreign review report(s) and authorization decision was based. If it is not identical, all differences should be clearly indicated.
Foreign Review (con’d)

Different methods are available for using a foreign review:

- **Method 1** - The Canadian regulatory decision is based on a critical assessment of the foreign review only.
- **Method 2** - The Canadian review is based on a critical assessment of the foreign review, referring to the data filed in Canada as necessary.
- **Method 3** - The Canadian review is based on a critical assessment of the Canadian NDS package, with the foreign review as an added reference.
- **Method 4** - The Canadian review is based on a critical assessment of the Canadian NDS package. The foreign review is not referenced, because it does not address Canadian regulatory requirements or is otherwise not relevant.

Some factors which may inform the choice of method include:

- degree of similarity between the foreign and Canadian regulatory frameworks
- **degree of similarity between the product reviewed and the product proposed for the Canadian market**
- level of detail of the foreign review report
Conclusion

• Very positive experience!
• Use of CTD format improve the consistency and quality of the drug applications.
• Increases efficiency in the review process (spend less time trying to locate information).
• Help confirm that similar (identical) package have been filed in different countries.
• May allow the use of foreign review to decrease the review time and thus promote population’ timely access to safe, efficacious, and high quality drugs.
THANK YOU!!!