Final Document

Title: Points to Consider in the use of the IMDRF Table of Content for Medical Device Submissions pre-RPS

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Table of Contents

Preface

The document herein was produced by the International Medical Device Regulators Forum (IMDRF), a voluntary group of medical device regulators from around the world.

1.0 Introduction

The IMDRF first final version of the In Vitro Diagnostic Medical Device Market Authorization Table of Contents (IVD MA ToC) and Non-In Vitro Diagnostic Medical Device Market Authorization Table of Contents (nIVD MA ToC) are now available on www.imdrf.org.

The release of the first version of the final ToC documents makes available harmonized formats for use in filing IVD and nIVD medical device submissions for market authorization.

These documents provide internationally harmonized, modular, format for use when filing medical device submissions to regulatory authorities for market authorization. The Table of Contents documents are comprehensive in scope in that they define the location of both common (IMDRF) and regional content for all submission types. As a consequence, not all headings are required for all submission types and/or IMDRF jurisdictions. As such, these documents are intended to work together with a separate document created for each participating jurisdiction – a classification matrix. The classification matrix defines whether for the given submissions type a heading is required, not required, optional, conditionally required, etc. The classification matrices are the published under the authority of participating authorities and are not products of IMDRF, please consult regional regulator websites for further information.

The ToC documents were designed for eventual use in an electronic submission environment, defining the location and format of submission content that would be assembled and displayed by software tools for each participating IMDRF jurisdiction based on the classification matrices.

It is anticipated that the Health Level Seven (HL7) Regulated Product Submission (RPS) electronic exchange standard, once final and recognized, will serve as the international standard for health product submissions, including medical devices and pharmaceutical for human use. This will permit the development of RPS compliant software tools. In the interim, the IMDRF RPS working group intends to provide recommendations on the filing of electronic copies of medical device submissions in the IMDRF ToC formats.

IMDRF recognizes that continued piloting, adequate training and additional guidance will be important to the successful adoption and use of the new ToC formats. To this end, IMDRF has produced this Points to Consider document, which will be updated, as necessary, based on experience and feedback from stakeholders. Further documentation, including educational material, will also be considered by IMDRF and its members to support the implementation of the ToC formats. Please consult www.imdrf.org and regional regulator websites for the most up-to-date information on implementation plans and requirements.

This Points to Consider document has been developed based on experience gained in piloting the draft In Vitro Diagnostic Medical Device Market Authorization Table of Contents (IVD MA ToC) and non-In Vitro Diagnostic Medical Device Market Authorization Table of Contents (nIVD MA ToC). It is intended to provide clarification and guidance regarding the use of the ToC format in a pre-Regulated Product Submission (RPS) compliant electronic environment. Further harmonized guidance is to be developed in the near future and will elaborate on these

concepts and provide the foundation required for participating jurisdictions to move to effective adoption of these structures.

2.0 Scope

This document has been developed for medical device industry to assist in the development of submissions based on the IVD MA ToC and nIVD MA ToC in a pre-RPS electronic environment. The determination of accepted submission types using the IVD MA ToC and nIVD MA ToC will be established by each jurisdiction, refer to regional websites for details.

3.0 References

Not Applicable

4.0 Definitions

Not Applicable

5.0 General Background – Points of Clarification

5.1 The Classification Matrices & Heading Class

As the ToC documents are comprehensive in nature, not all headings are required for all submission types and/or jurisdictions. The ToC documents are therefore intended to work together with a separate document created for each participating jurisdiction – a classification matrix.

5.1.1 What are the classification matrices?

The classification matrices are tables that define the class of each heading in the ToC (e.g. Required (R), Not Required (NR), Conditionally Required (CR), Optional (O), Optional but Recommended (OR)). Each jurisdiction has its own classification matrix. Supported submission types are listed separately within the matrix.

For example, Figure 1 shows the first four headings of Chapter 1 for a Health Canada Class III New submission. It should be noted that if the heading is CR the condition will be described in the condition column.

		HC CIII NEW	
Code	**Display Name**	**Classification**	**Condition**
CHAPTER 1 – REGIONAL ADMINISTRATIVE			
CH1.01	Cover Letter	R	
CH1.02	Submission Table of Contents	R	
CH1.03	List of Terms/ Acronyms	OR	
CH1.04	Application Form/ Administrative Information	R	

Figure 1 - Example Classification Matrix

5.1.2 Where can the classification matrices be found?

The classification matrices are to be made available on regional regulator websites.

5.1.3 How do I use the classification matrix with the ToC?

The following describes the general steps in using the classification matrices

a. Obtain the classification matrix for the jurisdiction of interest.
b. Establish the submission type and verify that the submission type is within the scope of the current classification matrix for that jurisdiction.
c. Build your submission structure based on the guidance provided for that submission type. Any headings that are marked Not Required (NR) should not be included in the submission. Any headings that are Conditionally Required (CR) need to be considered within the context of the device type and or any conditions stipulated in the classification matrix. The applicant must address **ALL** Required (R) headings in the submission**.**

For example, many submission types require only a few elements of Chapter 6B. A specific example is a New Class IV Health Canada submission. In this case the classification matrix is shown in
Figure 2 below.

In this case, Chapter 6B would only contain three or four headings (highlighted in green), depending on whether or not the condition for the CR classified heading establishes the heading is relevant to the submission.

		CIV New	
		Classification	Condition
CHAPTER 6B – QUALITY MANAGEMENT SYSTEM DEVICE SPECIFIC INFORMATION			
CH6B.1	Chapter ToC	R	
CH6B.2	Quality management system information	NR	
CH6B.3	Management responsibilities information	NR	
CH6B.4	Resource management information	NR	
CH6B.5	Device Specific Quality Plan	R	
CH6B.6	Product realization information	NR	
CH6B.6.1	Design and development information	NR	
CH6B.6.2	Purchasing information	NR	
CH6B.6.3	Production and service controls information	R	
CH6B.6.4	Control of monitoring and measuring devices information	NR	
CH6B.7	QMS measurement, analysis and improvement information	NR	
CH6B.8	Other Device Specific Quality Management System Information	CR	When information is requested by the regulator (through guidance documents or other communication) but does not belong in any of the other headings of this Chapter

Figure 2 - Health Canada New Non-IVD Class IV Submission Classification Matrix Excerpt

Important Note

Each *classification matrix* is being developed based on a variety of sources including the individual regulator's laws, directives, regulations, guidance documents, etc. When any requirements are conflicting between the classification matrix and these sources, the source requirement will take precedence.

5.1.4 How will the Classification Matrices be used in the future?

It should be noted that both the ToC and the matrices were developed for interpretation by an electronic submission system such as a Regulated Product Submission standard compliant system.

The long term vision is that these matrices will be used as a means of validating content of electronic submissions and guiding submission building and publishing.

5.1.5 What about the heading classes defined in the ToC documents?

Headings are also classified in the ToC documents as either **IMDRF; IMDRF, RF; or Regional.** Definitions of these terms are provided in the ToC documents.

Heading classification is provided in the ToC documents to provide an indication of the relevance of any given heading to a particular jurisdiction and **more importantly, provide an indication of when the applicant needs to consider the common content within the context of the specific jurisdiction.** The classification matrices provide more specific requirement classification by jurisdiction and submission type and should be used as the final reference for information of this type.

5.2 The Parent/Child Hierarchy – Chapters 3 & 4

The ToC has been developed with flexibility to allow for use of the same structure across a variety of risk classes. One particular sub-structure is repeated throughout the document. This structure includes a parent heading, a custom child heading for each specific study/piece of evidence, and a summary and full report grandchild heading. For example, "Physical and Mechanical Characterization" is structured as shown below.

Physical and Mechanical Characterization	This parent heading provides a summary of all studies that fall under this category (i.e. Physical and Mechanical Testing). **Each of these parent headings has slight variations so refer to the ToC document for content under these headings.**
[Study description, study identifier, date of initiation]	This is a custom heading based on the particular study described below – NO CONTENT AT THIS LEVEL
Summary	A summary of the specific study described in the custom heading above.
Full Report	The test report for the test described in the custom heading above.

Figure 3 – Example Parent/Child Hierarchy – Physical and Mechanical Testing

In the case where there are many studies under a particular heading the studies should be presented sequentially under the parent heading, for example:

Physical and Mechanical Characterization
Component A Fatigue Test, MT4203, 2010-10-10
Summary of MT4203
Full Report for MT4203
Assembly B Wear Test, MT4584, 2011-01-23
Summary of MT4584
Full Report for MT4584
…

Figure 4 - Specific example of Parent/Child Hierarchy

The content at the Parent Heading level is intended to provide context to all the studies included below. The summary should be a high level description, for example:

PHYSICAL AND MECHANICAL CHARACTERIZATION (hip liner example)
Based on the risks associated with hip liner the following evaluations were considered:

- *wear testing*
- *lever-out testing*
- *…*

However, because the locking mechanism and overall geometry remain identical to previous versions, it was not considered necessary to repeat lever-out testing for the new design. Wear testing was deemed necessary because of the change in manufacturing processes for the UHMWPE. A copy of the previously conducted test has been included for reference and was previously reviewed under submission XYZ.

Wear testing – this testing was conducted on the largest component listed in this submission: size 36, +4mm offset according to ASTM F1714 for 10 MC. Wear results assessed for volume and morphology and were found to be comparable to clinically proven devices tested under identical conditions.

Wear is one of the primary causes of clinical failure in hip implants. This characterization shows that the wear properties of this device are similar in volume and morphology to clinically successful devices.

5.3 Statements of Not Applicable

Many headings in the submission require a statement of why the category does not apply in the particular case. The level of support for such statements will vary and can be presented by the following categories:

Category	Description	Suggested Action
Category 1 - **No Relevance to the submission.**	In this case the information is obviously not applicable to the device. For example, evidence of biological material safety would not be required if no biological material is used in the device.	No explanation required, statement "Not relevant to this submission" is sufficient.
Category 2 **– Potential relevance to the submission but still clearly not applicable**	In this case the information may be relevant in some situations, but in the specific context it is still clearly not applicable. For example, a case where the manufacturer is changing the sterilization method but the device remains unchanged and therefore no biological safety information is provided.	Further explanation of the specific context is required, but can be limited to a few sentences in cases such as this. For example, "The change in sterilization methods have no impact on the safety of the source of the biological materials which have been reviewed previously"
Category 3 **– Relevant to the submission but not included**	In this case the information would be expected for the submission but has been omitted after careful consideration of the applicant. For example, disassembly testing for a new modular hip implant system would typically be expected for the device type.	Detailed scientific support for the decision not to conduct this testing should be presented and any relevant references provided in the submission to support the rationale.

Figure 5 – Descriptions and examples of Categories of Not Applicable statements

5.4 Quality Management System Chapters, 6A vs. 6B

There are two Quality Management System Chapters in the ToC. Both Chapter 6A & B of the ToC have been written in terms of the quality management system language employed in ISO 13485-2003. **Chapter 6A** is where the company places the standard operating procedures (SOPs) the company utilizes to implement its overall high level quality management

system. **Chapter 6B** is where the company places the documents and records the company utilizes to implement the quality management system SOPs described in Chapter 6A.

6.0 Pre-RPS Implementation Considerations

6.1 Numbering of Headings

Numbering should remain consistent regardless of whether the heading is required or not. For example, if Heading CH1.02 is not required for the submission type or jurisdiction, but Headings CH1.01 and CH1.03 are, then the numbering would remain CH1.01 followed by CH1.03.

In a pre-RPS implementation there is a need to provide a means of ensuring that custom headings are presented in the desired sequence. In order to do this, each custom heading folder should have a letter suffix added to the numbering of custom headings to indicate the sequence of presentation. For example, under stability of samples, CH3.5.01.1 is a custom heading and should be presented as shown below.

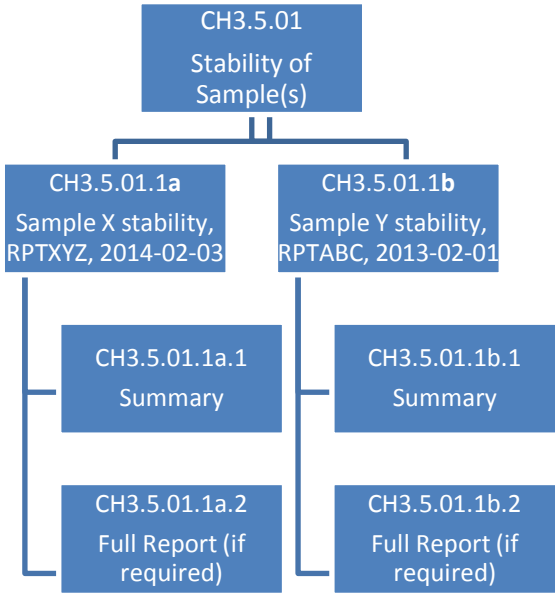

Figure 6 - Numbering of Custom Headings (example using CH3.5.01 of the IVD ToC)

6.2 Pagination

Pages of the submission should be numbered in such a manner that information can be referenced by page number. This may be done either by consecutively numbering the entire submission, or numbering the pages within a section or chapter (e.g., CH2.4.1-1, CH2.4.1-2).