IMDRF International Medical Device Regulators Forum

PROPOSED DOCUMENT

International Medical Device Regulators Forum

Title: Assembly and Technical Guide for IMDRF Table of Contents (ToC) Submissions (ToC-based submissions)

Authoring Group: Regulated Product Submissions Table of Contents WG

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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. The document has been subject to consultation throughout its development.

1.0 Introduction

The International Medical Device Regulators Forum (IMDRF) was conceived in February 2011 as a forum to discuss future directions in medical device regulatory harmonization. It is a voluntary group of medical device regulators from around the world who have come together to build on the strong foundational work of the Global Harmonization Task Force (GHTF). The Forum will accelerate international medical device regulatory harmonization and convergence. The Regulated Product Submission (RPS) proposal was endorsed as a New Work Item (NWI) by IMDRF at its inaugural meeting in Singapore (March 2012). The working group to this point has accomplished the following:

1. Established that the Health Level Seven (HL7) RPS Standard is "fit for purpose" for the electronic exchange of information related to premarket medical device applications.
2. **Established a comprehensive Table of Contents (ToC) for the following premarket applications**
    a. **Non-IVD (nIVD) Market Authorization**
    b. **IVD Market Authorization**

The ToC Working Group[1] has previously conducted pilots for both the nIVD and IVD Market Authorization ToC structures, using historical submissions. These pilots provided valuable feedback regarding the ToC structure and completeness, however there were obvious limitations to using historical submissions and there were limited samples involving more than one region. Furthermore, there were no specific guidelines regarding the means of building a submission in a pre-RPS implementation.

This document is intended to supplement the IMDRF ToC Pilot Plan and describe additional harmonized guidelines for the acceptable folder structure and file format(s) for ToC-based submissions.

2.0 Scope

This guide is intended for use in the assembly of IMDRF Table of Contents (ToC) based medical device regulatory submissions currently within the scope of submission types accepted by each IMDRF region.

[1] The IMDRF Table of Content Working Group is composed of the regulatory authorities from the agencies represented by the IMDRF Management Committee.

3.0 GUIDE TO BUILDING A TOC-BASED SUBMISSION

There are a number of reference documents and guides that need to be consulted when creating a ToC-based medical device submission. This section provides information about these reference documents as well as information about how to use these documents to generate a ToC-based submission.

3.1 Pilot Documents

The table below lists the documents required to assemble an IMDRF ToC-based regulatory submission during the IMDRF TOC Pilot.

Table 1 - List of pilot documents

Document	Description	Location
IMDRF In Vitro Diagnostic Medical Device Market Authorization Table of Contents (IVD MA ToC) **or** IMDRF Non-In Vitro Diagnostic Medical Device Market Authorization Table of Contents (nIVD MA ToC)	These documents define the heading names and hierarchy of the ToC structure. They also include detailed information about the content that belongs under each heading.	www.imdrf.org
IMDRF Assembly and Technical Guide for IMDRF Table of Content (ToC) Submissions **[THIS DOCUMENT]**	This document provides information about the reference documents available relating to the IMDRF ToC and harmonized technical specifications for ToC-based submissions.	www.imdrf.org (when finalized)
IMDRF Frequently asked Questions Document	Additional reference document that provides responses to commonly asked questions.	www.imdrf.org (when available)
IMDRF Standard ToC Folder Structure (presented as a zip file)	This is a folder structure provided by IMDRF to replicate the hierarchy and headings of the ToC. Note: some headings have been modified from the full names defined in the nIVD and IVD MA ToC documents to reduce path lengths.	www.imdrf.org

Document	Description	Location
REGIONAL Classification Matrix	As the IMDRF ToC documents are comprehensive in nature, not all headings are required for all submission types and/or regions. The classification matrix defines whether for the given submissions type a heading is required, not required, optional, conditionally required, etc.	Various - contact region* of interest for details
REGIONAL Assembly and Technical Guide for IMDRF Table of Content (ToC) Submissions	Similar to this document, regions may have additional requirements or regional specific guidance relating to the building and submission of a ToC-based submission that will be included in a regional Assembly and Technical Guide (e.g. transmission methods or special instructions for file transfer media).	Various - contact region* of interest for details
REGIONAL Frequently asked Questions Document	Additional reference document that provides responses to commonly asked questions.	Various - contact region* of interest for details

*The regions involved in the pilot are ANVISA, EU, Health Canada, TGA, USFDA and CFDA.

3.2 Sample general process for building a ToC-based submission

This section describes one example of how the pilot documents could be used to manually compile an IMDRF ToC pilot submission. It is important to note that this is intended to provide further context to the pilot documents. Other approaches may be acceptable, including using commercially available submission publishing software to generate a submission meeting the requirements defined in the pilot documents.

Step 1: Download[2] the required IMDRF Standard ToC Folder Structure for the applicable ToC structure (e.g. IVD or nIVD)

Step 2:

- **Step 2a**: Begin building the submission consulting the relevant IMDRF Market Authorization Table of Contents (IVD MA ToC or nIVD MA ToC) for content related guidance. Consult the regional classification matrix to establish the headings that require content based on the submission type. **See Implementation Considerations below for important considerations in this process.**

[2] See IMDRF Standard ToC Folder Structure file

- **Step 2b**: Consult this document as well as the IMDRF FAQ documents and regional equivalents for the region of interest for technical requirements relating to the files/folders that must be populated.

Step 3: Consult the regional classification matrix of interest to establish which folders can be deleted from the comprehensive structure based on the submission type – **see Section 4.1 below for further guidance.**

Implementation Considerations:

1. Implementers should consider the potential for maintaining content that will be submitted to multiple regions. Although certain regions may have additional content requirements for certain headings[3], it may be prudent to build a non region-specific version of the submission using the complete IMDRF Standard ToC Folder Structure[4]. Make copies of this complete version for each region that you are intending to submit before deleting any folders not required for the intended region. Future regional adaptations can then be more easily produced from this baseline submission structure and content. This reduces the risk of:
    - Inclusion of regional content that is not required for the submission.
    - Missing required elements due to folders that were deleted but are required for other regions.
2. Conversely, if the approach described above is not possible and a submission is being built from a folder structure previously submitted to another region, take care to:
    - Consider those heading that are regional or require regional focus and to ensure that regional content that is not relevant to the subject regulator is removed.
    - Ensure that any folders that may have been deleted for the original submission are reconsidered for inclusion in the new submission.
    - Ensure that content is current (e.g. market history is up to date).

[3] For a complete description of common and regional content requirements for each heading refer to: IMDRF In Vitro Diagnostic Medical Device Market Authorization Table of Contents (IVD MA ToC) or IMDRF Non-In Vitro Diagnostic Device Market Authorization Table of Contents (nIVD MA ToC)

[4] Note that the use of PDFs and folders is an interim format designed to test a standardised Table of Contents and future implementations may be more user friendly. It is time consuming for multiple reviewers to open chains of folders every time to find that they are empty and to ensure there is no evaluable content. It is not normal practice for regulators to alter submissions, e.g. by deleting unneeded documents or folders, as the regulators need to maintain the integrity of the original submission. The IMDRF ToC Working Group appreciates your efforts to delete empty folders and provide content as per the regional guidance documents before submission.

4.0 TECHNICAL GUIDELINES

The IMDRF ToC Pilot will rely on technical guidelines to provide consistency across the regions. The following sections include basic guidelines for submitting a ToC based submission.

4.1 Folder Structure

The IMDRF documents, In Vitro Diagnostic Medical Device Market Authorization Table of Contents (IVD MA ToC) and Non-In Vitro Diagnostic Device Market Authorization Table of Contents (nIVD MA ToC) define the content for each folder. The folder structure is to be built as prescribed by IMDRF. Refer to the IMDRF Standard ToC Folder Structure file, which is a physical folder structure template provided by IMDRF to help facilitate the preparation of applications in the required ToC format.

Regional Classification Matrices describe which elements of the ToC are required for each regulatory submission within scope. There are factors influencing the inclusion/exclusion of submission contents, these considerations are detailed below.

Each folder within the submission has been established as either **Required** or **Not Required** for the particular submission. This is explicitly defined by the classification matrix (e.g. *Required* or *Not Required* classification) or through interpretation of the classification (e.g. through assessment of conditions[5] for those that are classified as *Conditionally Required* or a decision by the applicant for those that are classified as *Optional*). With this in mind, Figure 1 below depicts many of the classifications that can result in a folder being **Required** or **Not Required** within the submission.

Any folder that is established as **Required** should **not** be deleted. Content must be submitted in this folder.

Any folder that is established as **Not Required** should be deleted to ensure the submission content package does not contain empty folders. If any parent folder contains no content, then that parent folder should also be deleted.

Any folder that is established as **Conditionally Required** requires a determination against the conditions by the applicant. A folder should be retained if content is required or should be deleted if content is not required.

Any folder that is established as **Optional** requires a decision by the applicant then should be deleted if not populated.

It should be noted that some regions may require a statement describing why a section is not provided. Refer to regional pilot instructions for additional details.

[5] Conditions for *Conditionally Required* headings are outlined in the Classification Matrices

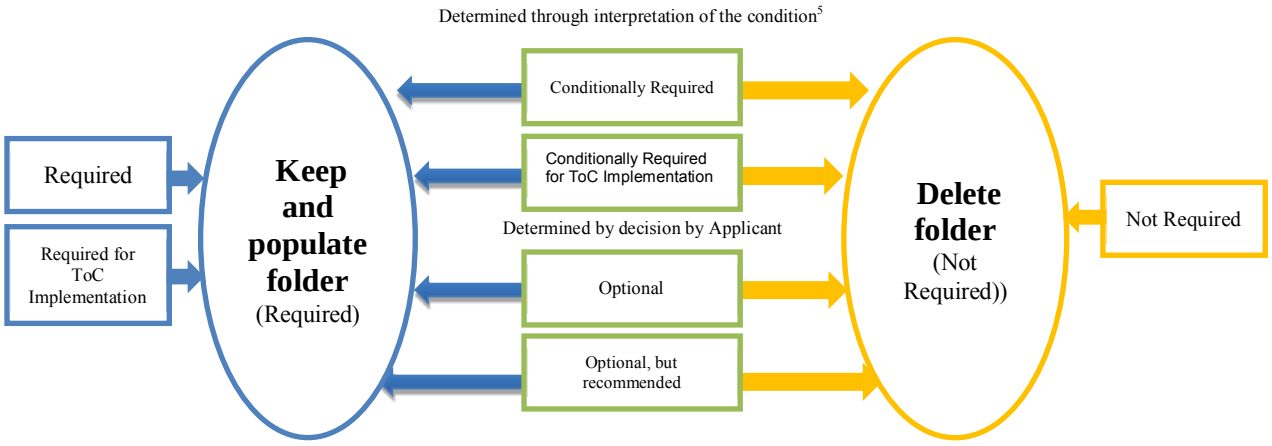

Figure 1 - Those classifications defined in the classification matrix (rectangles) that can lead to content being Required or Not Required in for a particular submission (ovals).

4.2 Folder Naming Convention

The folders in the provided templates will be numbered and named per the ToC requirements, with the exception of the custom headings which are to be numbered and named as defined in the IMDRF ToC (e.g. [Study description, study identifier, date of initiation] indicating the information the sender should include as the folder name of the custom folder. In the IMDRF Standard Folder Structure file – these folders appear with "[Custom]" in the folder name). The final digit of the heading number should be revised as appropriate to ensure appropriate sequential presentation of the custom folders when more than one study is being included. For example, for the Physical and Mechanical Characterization heading, the first custom study folder should be named *"3.5.01.1[Study description, study identifier, date of initiation]"* and the second custom study folder should be named *"3.5.01.2[Study description, study identifier, date of initiation]"*. If there are more than 10 studies, the sequence numbering should use 2 digits (e.g. 3.5.01.01… 3.5.01.10 for the example above).

The character count for the [Custom] or [Trial Details] folder names should be no more than 50 characters (including the section number). Abbreviations in their names are expected and acceptable

NOTE: Restrictions in file and folder names exist to ensure maximum allowable system file path lengths are not exceeded.

"Overview" folders have been created in the folder template where the IMDRF guidance indicates a requirement for content at a parent folder. This folder structure was created to ensure the sequence of information presented is maintained in a Windows environment. For example, in

the nIVD structure, Section 3.5.06 Biocompatibility & Toxicology Evaluation, there is a sub-folder named "3.5.06.0-Overview" in the template. The content prescribed by the IMDRF guidance for Section 3.5.06 should be placed in this folder.

4.3 File Format and Naming

Portable document format (PDF) files are the preferred file format although other formats such as Microsoft Office (.doc, .ppt, .xls) are also acceptable in some regions. Refer to regional pilot instructions for specific file format and versions.

The applicant should create all PDF files directly from the source documents whenever feasible rather than creating them by scanning. **PDF documents produced by scanning paper documents are far inferior to those produced directly from the source document, such as Word document, and, thus, should be avoided if at all possible**. Scanned documents, particularly tables and graphs, are more difficult to read and do not allow the reviewers to copy and paste text.

For any scanned document, you should perform optical character recognition (OCR) so that the text is searchable. Check to see that the content has been correctly converted by: (1) highlighting an area of text and (2) searching for a word or phrase. If the word or phrase is not returned in the search, then the OCR did not recognize the text. We recognize that OCR may not be feasible in some cases for documents with figures and images.

Most file names are user defined, with a limitation of 50 characters (including the file extension and section number). File names should be meaningful and provide some indication of their content. When more than one file is presented in a folder, suffix number should be used to ensure the intended sequence of presentation is maintained.

File names are prescribed under the user defined [Custom] folders and must be:

- 1-Summary
- 2-Full Report
- 3-Statistical Data

File names are prescribed under the user defined [Trial details] folder and must be:

nIVD	IVD
1-Clinical Trial Synopsis	1-Clinical Study Synopsis
2-Clinical Trial Report	2-Clinical Study Report
3-Clinical Trial Data	3-Clinical Study Data

NOTE: Restrictions in file and folder naming exist to ensure maximum allowable system file path lengths are not exceeded. Applicants should be aware that computer operating systems have limitations and are requested to **keep filenames and pathnames in submissions as short as possible.**

The IMDRF folder templates and file naming specifications have been established in an effort to ensure submissions can be received and stored by regulators without reaching the operating system limits. It is recommended that applicants examine the length of the entire pathname (i.e. all nested folders and file name and file extension) prior to transmission to verify the path length is 200 characters or less.

4.4 File and Submission Size Limitations

No individual PDF file in the submission shall exceed 100 MB.

The entire submission should not exceed 4GB to ensure acceptance by all participating regions.

4.5 Document Security

Files should not have any security settings, specifically:

- Files must not have password protection preventing the file from opening.
- Files should be set to allow printing, selecting text and graphics, and adding or changing notes and form fields.

Applicants should use secure upload facilities or reputable couriers to protect the transmission to the regulators.

4.6 Bookmarking in PDF Files

It is also important that PDF files be properly structured, with a properly bookmarked internal table of contents. The following are recommended as good structuring practices:

- Documents of ten pages or more should have their own internal table of contents.
- When creating bookmarks, the magnification setting should be set to Inherit Zoom so that the destination page displays at the same magnification level that the reviewer is using for the rest of the document.
- Sections, subsections, tables, figures and appendices should all be bookmarked.
- Attachments to PDF files should be avoided.
- Too many levels of bookmarks are inefficient. In most instances, three levels of bookmarks should be sufficient:

  1 Heading

  1.1 Subheading

  1.1.1 Sub-subheading.

It is recognized that bookmarks are generated automatically from document headings; nevertheless, it is recommended that they be kept concise.

Set the Navigation Tab to open to "Bookmarks Panel and Page." This sets the initial document view when the file is opened. If there are no bookmarks, set the Navigation Tab to "Page Only." Page Layout and Magnification should be set to "Default."

4.7 Hyperlinking in PDF files

Hyperlinks are used to improve navigation through individual PDF documents and are encouraged. Hyperlinks can be designated by rectangles using thin lines or by blue text or you can use invisible rectangles for hypertext links in a table of contents to avoid obscuring text. Hyperlinks throughout the body of the document to supporting annotations, related sections, references, appendices, tables, or figures that are not located on the same page are helpful and improve navigation efficiency.

Hyperlinks between documents are acceptable but care must be taken in creating the links between different documents so that they will function once the application is received by the regulator (the use of relative linking is recommended). It is the applicant's responsibility to ensure that hyperlinks are functioning. Links must also include references to the specific section or page in the event the link is broken.

4.8 Granularity Rules

There are no limitations on the number of files per heading within the submission, however, the following guidelines should be considered.

1) Efforts should be made to draft documents that concisely communicate the content described in the IMDRF In Vitro Diagnostic Medical Device Market Authorization Table of Contents (IVD MA ToC) or Non-In Vitro Diagnostic Medical Device Market Authorization Table of Contents (nlVD MA ToC), rather than simply including existing documentation that contains superfluous information not required for the particular heading. For example:
   - Including a number of Material Safety Data Sheets within *"2.4.1 - Comprehensive Device Description and Principle of Operation"* is less helpful than summarizing the specific details of relevance to this heading.

2) When multiple files are considered necessary, file naming methods should ensure that the files are presented in their intended sequence, for example in folder named *"2.4.1-Comprehensive Device Description & Principle of Operation"* the files would appear as:
   2.4.1.0-Comprehensive Device Description and Principle of Operation.pdf
   2.4.1.1-Engineering drawings.pdf

4.9 Pagination

Pages of the submission should be numbered in such a manner that information can be easily referenced by page number. Pagination should be applied to each document (i.e., the physical file). This may be done by numbering the pages within a section or chapter (e.g., CH2.4.1-1, CH2.4.1-2).