

IMDRF ToC

Health Canada's new submission format

What is it and how does it work?

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Objective

Gain an understanding of:

- The IMDRF ToC (International Medical Device Regulators Forum Table of Contents) and its overall layout
- What types of Medical Device Regulatory activities are in scope
- The Health Canada Guidance developed in support of the IMDRF ToC Implementation
- The tools available to support creation of ToC formatted submissions
- Definition of summary and what makes a good summary

What is IMDRF?

The International Medical Device Regulators Forum (IMDRF) 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 on Medical Devices (GHTF), and to accelerate international medical device regulatory harmonization and convergence limitations of a paper format

www.imdrf.org

The IMDRF has identified the need to harmonize the documentation of evidence to support medical device market authorization requests.

What is the IMDRF Table of Contents (ToC)?

IMDRF has developed the Table of Contents (ToC) formats for submissions.

The ToC is a harmonized structure for use in an electronic environment and intend to replace the GHTF's Standard Technical Document (STED) submission format that had been designed with limitations of a paper format.

The IMDRF ToC defines the heading structure and hierarchy as well as the general content of regulatory submissions.

The current ToC implementation uses a standardized folder structure.

Expected Benefits

- Single format for all device submissions and phase out of STED
- Improved consistency for reviewers and regulatory reps in what they see and how they navigate submissions while building and reviewing
- The granulated structure should reduce the probability of missing information
- Eliminate the need for embedded Tables of Contents
- Reduce the number of formats requiring support with any submission validation software/tools
- Harmonization - with adoption by other jurisdictions, use will improve reuse of documentation and submissions for multiple regulatory authorities

Limitations/Challenges

- Granularity of the structure is different requiring some adjustment by regulatory representatives - feedback from users to date has been positive.
- File path lengths can be challenging, however
 - HC has received nearly 100 medical device licence applications created using this structure without issue.
 - Since the pilot, we have further reduced our file path lengths where possible, and are well below the 260 (259 effective) file path limit of Microsoft Windows.
 - We encourage users to investigate the how Microsoft Windows 10 can support file path lengths beyond the 260 character limit – as noted [here](#)*: *“Starting in Windows 10, version 1607, MAX_PATH limitations have been removed from common Win32 file and directory functions. However, you must opt-in to the new behavior.”* *<https://docs.microsoft.com/en-us/windows/desktop/fileio/naming-a-file>

Formats of IMDRF ToC

Two ToC formats were developed and published in August 2014:

- In Vitro Diagnostic Medical Device Market Authorization Table of Contents (IVD ToC)
- Non-In Vitro Diagnostic Device Market Authorization Table of Contents (nIVD ToC)



What do they look like?

- nIVD ToC is composed of 7 chapters
 - CHAPTER 1 – REGIONAL ADMINISTRATIVE
 - CHAPTER 2 – SUBMISSION CONTEXT
 - CHAPTER 3 – NON-CLINICAL EVIDENCE
 - CHAPTER 4 – CLINICAL EVIDENCE
 - CHAPTER 5 – LABELLING AND PROMOTIONAL MATERIAL
 - CHAPTER 6A – QUALITY MANAGEMENT SYSTEM PROCEDURES
 - CHAPTER 6B – QUALITY MANAGEMENT SYSTEM DEVICE SPECIFIC INFORMATION
- IVD ToC is composed of 7 chapters, with one difference:
 - CHAPTER 3 – ANALYTICAL PERFORMANCE AND OTHER EVIDENCE

Scope

Pre-Market Submissions

- New and Amendment Class 2, Class 3 and Class 4 medical device licence applications
- All medical device Private Label licence applications
- All Fax-back (Minor Change) applications
- All Screening Deficiency, Clarification, and Additional Information Responses associated with those activities listed above
- **NOT** applicable:
 - Investigational Testing Authorization (ITA) Applications
 - Special Access Program (SAP) Requests

Scope (cont'd)

Post-Market

- Responses to Class 2, Class 3 and Class 4 post-market requests issued under the *Medical Devices Regulations* (e.g. Responses to Section 39 or Section 36 of the *Medical Devices Regulations*)
- Responses to all Classes (1 to 4) for IVD and nIVD Post-Market Requests from the Marketed Health Products Directorate
- All Clarification and Additional Information Responses associated with those activities listed above
- Refer to the Guidance Main Page for clarifications about where to send each Post-Market response type.

ToC Guidance Documents

HC provides guidance documents for both the ***assembly*** of the submission and the ***content*** of the submission.

Assembly Guidance focusing primarily on file format, file name, path length, folder structure, and submission media file system concerns.

Content Guidance provides guidance regarding the content of an application.

- IMDRF guidance
- HC (regional) guidance
- Arranged by type of device application

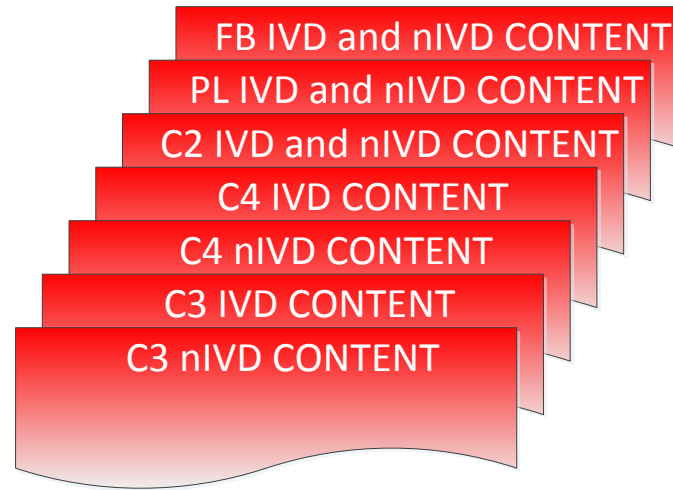
Draft Health Canada IMDRF table of contents for medical device applications guidance

1. Introduction and background
 - 1.1 Purpose
 - 1.2 Scope and application
 - 1.2.1 Structure guidance
 - 1.2.2 Content guidance
 - 1.2.3 Assembly and system requirements guidance
 - 1.3 Policy objectives
 - 1.4 Policy statements
 - 1.5 Abbreviations and acronyms
 - 1.6 Definitions
2. Guidance for implementation
 - 2.1 IMDRF ToC folder structure
 - 2.2 Heading classifications and content guidance
 - 2.2.1 Class 3 & 4
 - 2.2.2 Class 2/private label/fax-backs (minor changes)
 - 2.2.3 Responses to additional information or screening deficiency letters
 - 2.2.4 Combination products
 - 2.2.5 Market health products directorate (MHPD) post-market responses
 - 2.3 How-to and system requirements
3. Filing process
 - 3.1 Transmission options
 - 3.1.1 Physical media
 - 3.1.2 Email
 - 3.2 Where to submit
 - 3.2.1 Licence application and section 36 and 39 responses
 - 3.2.2 Responses to requests from MHPD
4. Resources, tools and classification matrices
 - 4.1 Resources
 - 4.2 Tools
 - 4.3 Classification matrices
5. Access to information
6. Contact information

zip template

zip samples

CONTENT GUIDANCE PAGES



Marketed health products directorate post-market submission guidance

zip template

Health Canada adapted assembly and technical guide for IMDRF table of contents submissions

Content Guidance Types

- IMDRF Common Content
 - Common across all participating countries
- IMDRF Health Canada Content (regional guidance)
 - Identified in the IMDRF publication specific to Canada
- Health Canada Specific Guidance
 - Can go beyond content and provide more specifics about the type of evidence that should be provided and when
 - Baseline content is derived from previously existing HC Guidance

Content Guidance Types (Example)

1.01 - Cover Letter

IMDRF COMMON CONTENT

- a) The cover letter should state applicant or sponsor name and/or their authorized representative, the type of submission, the common name of the device (if applicable), device trade name or proprietary name (both of the base device and a new name if one is given to the new version/model of the device) and include the purpose of the application, including any changes being made to existing approvals.
- b) If applicable and accepted by the regulator, it should include information pertaining to any Master Files referenced by the submission.
- c) If applicable, acknowledgement that a device sample has been submitted or offered alternatives to allow the regulator to view or access the device (when the regulator requests a sample).
- d) If the submission is requesting approval of a change that is the result of CAPA due to a recall, this should be stated.
- e) If the submission is in response to a request for information from the regulator this should be stated and the date of that letter should be included as well as any reference number(s).
- f) If the submission is unsolicited information (where accepted), this should be stated and any related reference number(s) provided.

NOTE: The cover letter should not contain any detailed scientific information.

HEALTH CANADA SPECIFIC GUIDANCE

Any information submitted to Health Canada should be accompanied by a cover letter. The cover letter should include the purpose of the application and a brief description of the package being submitted. It may also include information pertaining to Proprietary Information Submission.

HC CLASSIFICATION

Class 3 New and Amendment: Required

Examples (cont'd)

3.05.08.00-Overview:Safety of Materials of Biological Origin (human/animal)

IMDRF COMMON CONTENT

Evaluations performed to demonstrate the safety of materials of biological origin (e.g. animal sourced, human sourced material) are to be included in this section. This should include:

- a) A description of biological material or derivate
- b) State the harvesting, processing, preservation, testing and handling of tissues, cells and substances
- c) If applicable, discussion of infectious agents/transmissible agents known to infect the source animal
- d) Clarify the origin (including details of donor screening and source country), and describe the tests on validation of removal or inactivation methods of viruses and other pathogens in the manufacturing process.

HEALTH CANADA SPECIFIC GUIDANCE

This section is applicable to all medical devices which are manufactured from or incorporate biological material from human, animal or microbial origin. If the only biological materials are heparin or tallow derivatives (e.g., glycerol) this in itself does not change the classification of the device to class IV. Additional classification guidance can be sought through the Medical Devices Bureau.

The detailed information expected for each material depends on the type of biological material and the particular risks inherent in that particular material. Some guidance can be found below.

Published Guidance - Walkthrough

Main ToC guidance webpage:

- <https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/application-information/guidance-documents/international-medical-device-regulators-forum.html>
 - Chapter 2.1 – link to Assembly & Tech guide
 - Chapter 2.2.1 – links to Class 3 & 4
 - Chapter 2.2.2 – Class 2, private label, fax-backs



Samples and Templates – Walkthrough

Samples

- Folders with Word documents within the specific structure of interest.
- Same guidance as webpages

Templates

- These are empty folder structures with the defined heading names.
- Custom folders will need to be adjusted, but others are to be left unchanged.

Where to find: <https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/application-information/guidance-documents/international-medical-device-regulators-forum.html>

- Chapter 4.2 Tools

Folder Naming Convention

Most folders in the provided templates:

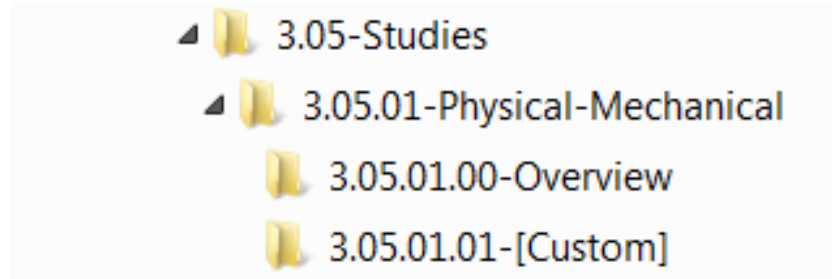
- Numbered and named per the ToC requirements
- Should **NOT** be changed

Exception in templates: “[**Custom**]”

- Should be adapted to describe identifying study details
- Example: “[**Study description, study identifier, date of initiation**]”
- **NOTE:** The character count for the [Custom] or [Trial Details] folder names should be **no more than 50 characters (including the section number)**. Abbreviations in folder names are expected and acceptable.

Custom Heading Example

nIVD Class 3 and 4: Section 3.05.01 – Physical and Mechanical Characterization:



Example:

A custom folder named "3.5.01.01-Component A Fatigue Test, MT4203, 2012-03-20" containing:

- 1-MT4203Summ.pdf
- 2-MT4203Report.pdf

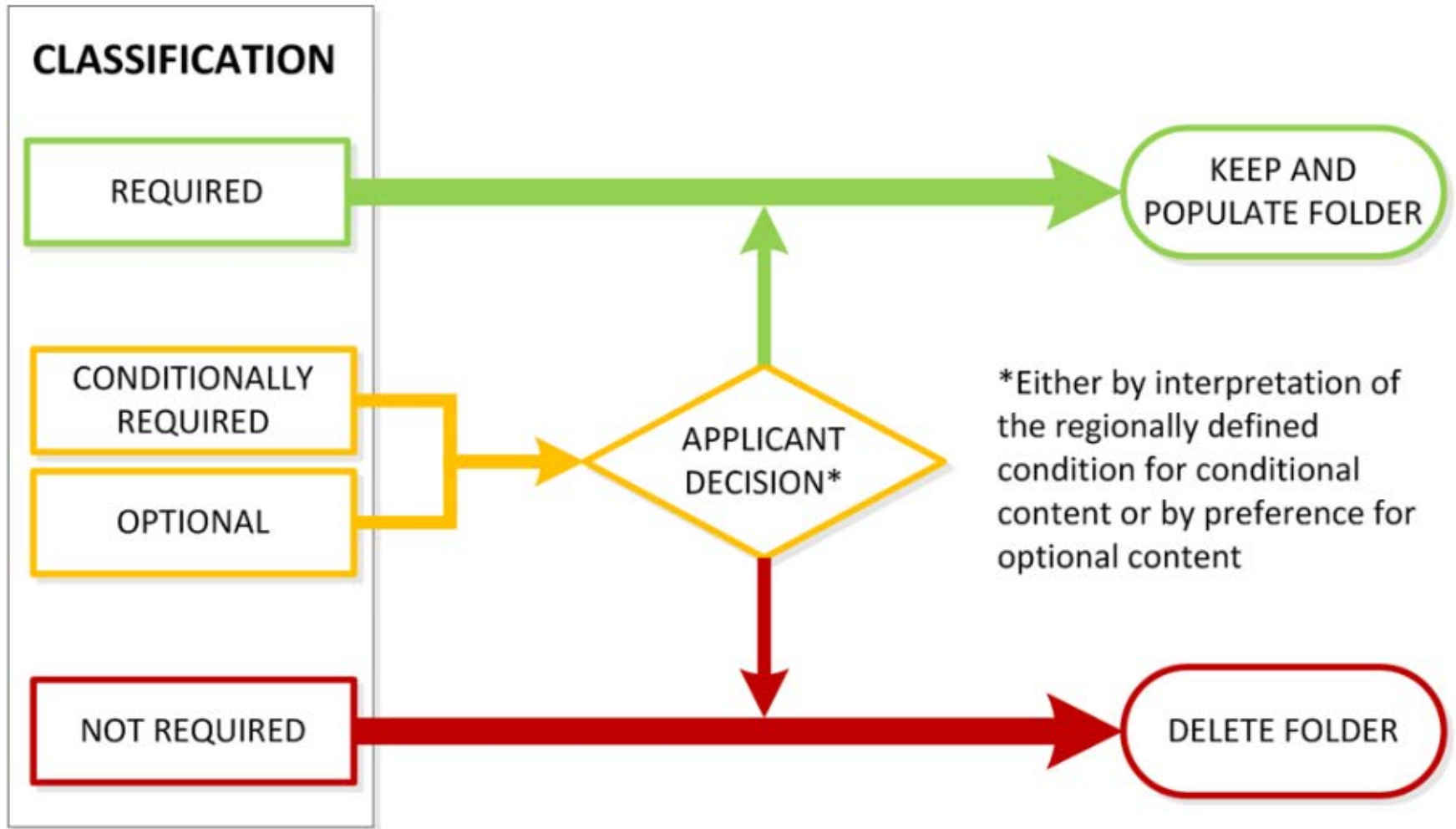
and a custom folder named "3.5.01.02-Assembly B Wear Testing, MT4584, 2012-04-12" containing:

- 1-MT4584Summ.pdf
- 2-MT4584Report.pdf

Heading Classification

- **R - Required.** Any folder that is established as Required must not be deleted. Content must be submitted in this folder.
- **NR - Not Required.** Any folder that is established as Not Required must be deleted.
- **CR - Conditionally Required.** Any folder that is established as Conditionally Required needs a determination against the conditions by the applicant. Specific conditions are defined by Health Canada for each CR heading and can be found in the detailed content guidance.
- **O - Optional.** Any folder that is established as Optional requires a decision by the applicant and then must be deleted if not populated.
- **OR - Optional but Recommended.** Any folder that is established as Optional but Recommended requires a decision by the applicant and then must be deleted if not populated.

Decision Chart for Folder Inclusion



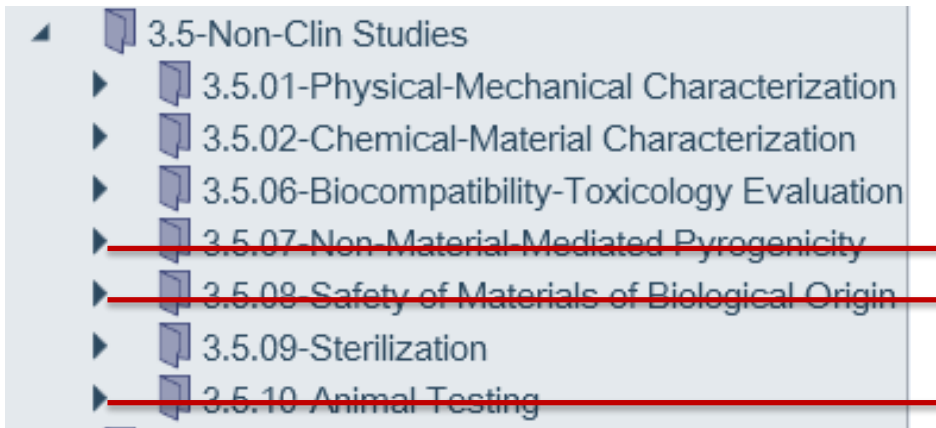
Conditionally Required - Example

Manufacturer sterilization – Section 3.05.09.02

- Conditionally required - Not required when this type of evidence/testing is clearly not applicable to the device or submission. If scientific judgement is required to justify why no information is required, then the heading is considered required and the justification should be provided.
- Sterilized by end-user or non-sterile -> Not required
- Fits within a sterilization product family/not worst case -> Required

Empty Folders

- Empty Folders should be DELETED.
 - Time consuming for reviewers
 - No internal ToCs required



Preclinical: Summary vs. Full Report

nIVD

IVD

-
- | nIVD | IVD |
|--|--|
| <ul style="list-style-type: none">• Class 3 nIVD<ul style="list-style-type: none">– Summaries: CR– Full reports: O | <ul style="list-style-type: none">• Class 3 IVD<ul style="list-style-type: none">– Summaries: CR– Full reports: O |
| <ul style="list-style-type: none">• Class 4 nIVD<ul style="list-style-type: none">– Summaries: CR– Full reports: CR | <ul style="list-style-type: none">• Class 4 IVD<ul style="list-style-type: none">– Summaries: O– Full report: CR |

Definition of “Summary”

From Section 1.6 of the Main Guidance:

A summary should include a brief synopsis of the (1) purpose, (2) methods, (3) **acceptance criteria**, (4) results and (5) discussion and conclusions. Outliers and deviations should be reported with the results. Results should be stated **quantitatively** with appropriate statistical context where applicable (e.g. value \pm SD, confidence intervals, etc.).

Definition of “Summary” (cont.)

The summary should specifically address:

1. Why the characteristic being evaluated is of interest;
2. Why the particular methods are being used to evaluate the characteristic, if applicable including why a regional or harmonized/recognized standard/guidance has or has not been complied with;
3. How the stated **acceptance** and sample size are scientifically supported;

Definition of “Summary” (cont.)

4. What device was tested and how it relates to the devices that will be marketed;
5. Why the **tested components are representative** of the range of devices that will be marketed;
6. Whether the summary has been previously submitted and reviewed by the regulator, including identification of the device and the reference number for the submission; and
7. Whether the testing has been conducted in-house or by a 3rd party.

Summary – Examples

- Good example



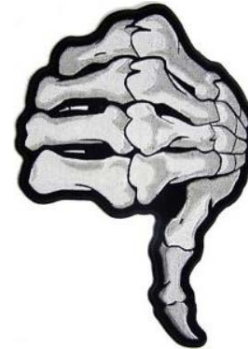
Microsoft Word
Document



- Not so good examples



Microsoft Word
Document



Duplicate files

No Duplicates:

- Match the granularity of the ToC structure and ensure content is specific to the content guidance for that section
- Possible inclusion under multiple headings?
 - Provide once under one appropriate heading
 - Reference/link in subsequent relevant sections
 - Be specific: references to specific sections or pages should be provided when possible
- Examples:
 - Biocompatibility and Animal testing
 - Pyrogenicity and Sterilization



SD or AI Letter Responses

Screening Deficiency (SD) letters, Clarification Requests, Additional Information (AI):

- Identify the Application Number
- Section 1.01 – Cover Letter
 - Q & A format
 - Copy of the original HC letter
 - Supporting information structured using same format as initial application

Note: Your Additional Information response should **not** contain information that was previously submitted within the same application. Only submit any documents that have been modified and place them in the appropriate folders with a clear reference to the changes outlined in the cover letter.

Feedback Form

- Full listing of different pages and tools is included in the feedback form
- Section/location is used to identify area relating to comment

	A	B	C	D	E	F	G	H
1	Reporter's Details							Français
2	Name							
3	Company							
4	Email Address							
5	Application Number(s)*							
6	*list all application numbers for ToC formatted submissions <u>created using the latest ToC guidance.</u>							
7								
8	Specific Comments							
9	Name	Company	Email Address	Document/Tool	Section or Location	Comment Type	Comment	Proposed Resolution
10								
11				Draft Health Canada IMDRF table of cont				
12				Health Canada adapted assembly and te				
13				Class 3 nIVD Applications Content and C				
14				Class 4 nIVD Applications Content and C				
15				Class 3 IVD Applications Content and CI				
16				Class 4 IVD Applications Content and CI				
				Class 2 Licence Application Content and				
				Private Label Application Content and CI				

Feedback Form

- HC has presented identical content in many different places and formats and we are using section/location rather than line numbers. For example:
 - 2.04.01 - Comprehensive Device Description and Principle of Operation
 - Content is common across all content sub-pages, identifying the section will allow us to review comments by section rather than by line number (which will vary across the different documents for the same content)
 - **You only need to provide the comment once** - we have a common dataset that generates all documentation.

Key Takeaways

- Samples and templates
- No new headings unless “Custom”
- Heading classifications
 - Conditionally required
 - Delete empty folders
- Summaries
- No duplicated files



Future and Conclusions

- As of April 1, 2019:
 - ToC and HC format only
 - STED no longer accepted
 - Feedback until March 31, 2020



- IMDRF and HC are looking at alternative ways of packaging ToC submissions (i.e. non-folder based)
- Consistent reuse of the same format over product lifecycle increases review efficiency

Thank You!



Questions later?

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