White Paper

eCTD 4.0 Implementation Including Understanding of Regional Differences and Benefits

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Table of contents

eCTD 4.0 Implementation Including Understanding of Regional Differences and Benefits

The Electronic Common Technical Document (eCTD) is the standard format for submitting applications, amendments, supplements, and other regulatory reports to health authorities around the world. The specification of eCTD defines requirements for the creation and the packaging of regulatory submissions using extensible markup language (XML) files. The simplest way to view eCTD sequences is via a web browser, utilizing document type definitions (DTDs) and stylesheets (also defined with the standard), for properly displaying XML information about the sequences.

The creation of the electronic submission process enabled the phasing out of paper-based processes, allowing for more automated and efficient submissions to regulatory bodies. The first version of eCTD 3.0 was finalized in 2003, and eCTD v3.2 has been the default version for more than 10 years since its release in 2008. The initial draft implementation guidelines for eCTD 4.0 were developed between 2015–2016 and intend to improve robustness, flexibility, long-term stability, and a more advanced lifecycle management process. After many years of collaboration with regulatory bodies and industry sponsors, eCTD version 4.0 is finally ready for implementation.

Limitations of eCTD 3.x standard

In order to see the benefits of the new standard, it is key to look at the ways that v3.2 is lacking:

The structure caters only to human pharmaceutical submissions.

The structure varies by region and authority.

The metadata and table of contents are defined explicitly by structure changes to metadata, or the table of contents requires an updated structure.

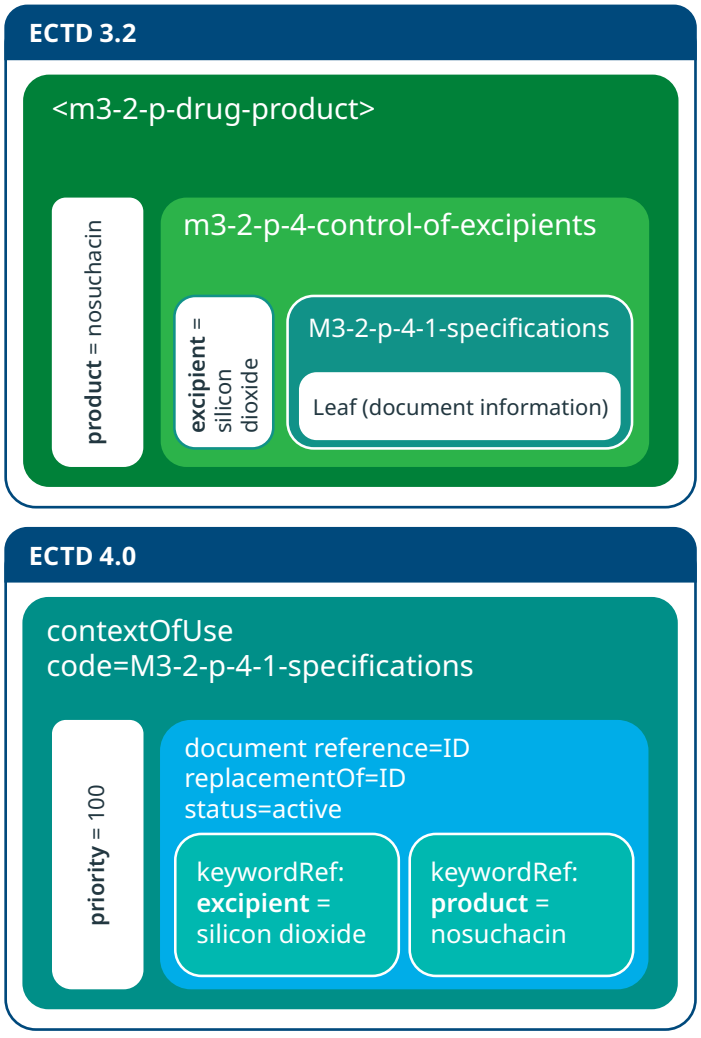
Benefits to eCTD 4.0 standard

With those limits to the current version in mind, eCTD 4.0 will prove to be beneficial:

- The structure caters to all types of products, i.e., veterinary, tobacco, cosmetics, drugs, medical devices, food additives and more.
- A singular format is used for all agencies/ regions/centers.
- It allows for reduced structural changes and software release cycles.
- Harmonised submission unit: All content from Module 1 through Module 5 is contained in one exchange message — i.e., an XML file covers ICH, regional and study information.
- The metadata/keyword definition, display name (e.g., drug substance/product names, manufacturers, group title, etc.) and structure can be corrected easily without resubmitting the physical files.
- Set the order/priority of documents within a section over time.
- It allows for more advanced lifecycle management (i.e., one document can be replaced by many or vice versa).
- Change document granularity while maintaining lifecycle relationships.
- Previously submitted documents can be reused by referencing its unique identifier (ID) from the same or different submission, across regulatory activities and across different applications.
- Use of controlled vocabularies (CVs) allows easier update to the allowed values without the need for system or tool updates.
- Group documents within sections in a consistent way across ICH regions using group title.

- Lifecycle and reuse of v3.2.2 content.
- Additional document metadata can be added as required by region for additional processing.
- Two-way communication as a future option to exchange information between applicants and agency/regulators.

The new eCTD 4.0 standard resolves the limitation of eCTD 3.x to propel and transform the regulatory submission process. While v4.0 is very beneficial, it is key to prepare and implement the process correctly to ensure a smooth transition.



How eCTD 4.0 helps regulators and sponsors

- Automation of administrative processing is made easier through the data-driven structure and use of standard control vocabularies.
- Implementation of new regulatory and/or legal requirements and modification of the dossier structure to adapt to new business requirements are made easier due to the extensive use of controlled vocabularies.
- Referencing across applications helps reduce workload substantially.
- Document reuse reduces storage overhead.
- It is possible to indicate that submitted content has received agency assessment and what the outcome was, saving further review and assessment work.
- A common tool or one technical solution can be used for all product types.
- Much less maintenance effort is needed for submission management and reviewing tools, as few system updates are expected.

Differences across regions

As previously seen, when a standard is implemented across regions, there can be differences in implementation and acceptance. This is also true for eCTD 4.0. Variations in eCTD 4.0 implementation across regions may include differences in M1 submission structure, regional metadata and CVs, additional context of use in M2–M5, language and character support, study standards and group titles, group or worksharing submissions, and forward compatibility. Each of these changes is detailed further below.

M1 submission structure

The M1 structure for each region is unique and takes into account their specific requirements for submission in either eCTD 3.2 or 4.0. While there may be similarities among regions, such as the cover letter and application form, it is important to be aware of the differences between eCTD 3.2 and 4.0 for the same region. For example, the structure may be different or additional metadata may be required.

- **U.S. submission structure**

  In the U.S., the attributes/keywords and M1 structure for eCTD 4.0 are similar to the U.S. eCTD M1 Specification v2.5 (DTD v3.3). The section titles remain the same, but the eCTD 4.0 codes are different from the DTD element names. When submitting the eCTD 4.0 submission unit to the U.S., the Regionally Specified Folder (i.e., us) is not required in the M1 folder.

- **Japan submission structureFor Japan, the eCTD 4.0**

  M1 structure includes additional sections and attributes. The full details can be found in the table below.

SECTION	DESCRIPTION	
For all sections, codes are changed but section titles are maintained.		
jp_other	対応可能な手段が他に無くやむを得ない理由がある場合に限り使用する。使用にあたっては事前に審査当局に相談すること。	New section in JP eCTD 4.0
jp_m1.13.4.1	機構への提出資料	Section is changed from M1-13-04-01 機構への提出資料(写)
jp_m1.13.4.1.1	承認申請書上の製造方法欄における目標値/設定値等に関する一覧表	New section in JP eCTD 4.0
jp_m1.13.4.1.2	新添加剤に関する提出資料	New section in JP eCTD 4.0
jp_m1.13.4.1.3	その他	New section in JP eCTD 4.0
jp_m1.13.4.2	厚生労働省への提出資料（写）	Section is changed from m1-13-04-02 承認申請資料の訂正について（平成21年4月1日付）
m1-13-05	eCTDの形式に関する留意事項等	Removed in JP eCTD 4.0

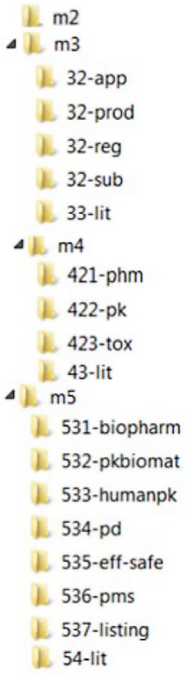
When submitting the eCTD 4.0 submission unit to the JP, the Regionally Specified Folder (i.e., jp) is required in M1 and additional subfolders can be used if needed.

ICH submission structure

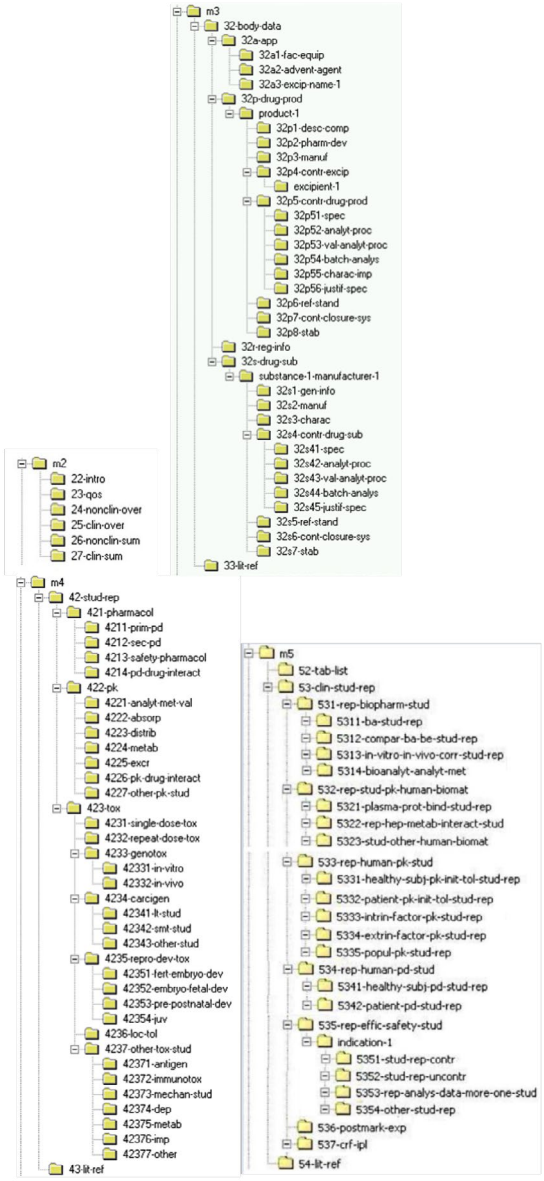
For content in M2 to M5, the ICH structure should be followed for all regions. There are some notable differences in folder structure for ICH when comparing eCTD 3.2 and 4.0, which are outlined below:

- M2 — no additional folders are necessary.
- M3 — the subfolder in M3 should be named as presented in the screenshot but can be changed.
- M4 — additional folders can be added, and the subfolder in M4 should be named as presented in the screenshot but can be changed.
- M5 — additional folders can be added, and the subfolder in M4 should be named as presented in the screenshot but can be changed.
  - » CTD organization provides locations for forms for case reports as well as individual patient data listings in folder 5.3.7.
  - » In eCTD 4.0, literature references and files for publications should be put in folder 5.4.

eCTD 4.0 folder structure



eCTD 3.2 folder structure



Regional metadata control vocabulary

There are variances in regional metadata and CVs for eCTD 4.0 among regions, for instance:

- CVs for application type, submission type, and submission unit types are applicable for the U.S., EU, and JP.
- CVs for product category and substances are applicable for the EU and JP, but not for the U.S.
- CV for submission type for Category Event is applicable for JP, but not for the U.S. and EU.
- CVs for submission mode, language, and territorial authority are applicable for the EU, but not for the U.S. and JP.

There are also changes in regional metadata between multiple versions of eCTD specification for the same region. For example:

- DUNS number is applicable for U.S. 3.3 but not for the U.S. 4.0.
- Contact person organization is applicable for U.S. 4.0 but not for the U.S. 3.3.
- Submission date is applicable for JP 1.0 but not for the JP 4.0.
- Product category and application cross-reference are applicable for JP 4.0 but not for JP 1.0.

Additional context of use in M2–M5

For JP 1.0, documents in folder 5.3.7 were organized into subfolders, but with the introduction of JP eCTD 4.0, additional contexts of use are added to M5 (details are provided in the table below). However, these additional contexts of use are not applicable to other regions.

CODE	DESCRIPTION (ENGLISH)	DESCRIPTION (JAPANESE)	KEYWORDS
jp_m5.3.7_other	Other documents under m5.3.7	M5.3.7に格納されるその他の資料	group title (O)
jp_m5.3.7.1	Patient listings	用量設定の根拠となった主要な試験及び主要な有効性の検証試験の症例一覧表	study id_study title (O), study group order (O), site-id (O), document type (O), group title (O)
jp_m5.3.7.2	List of adverse events	実施された全ての臨床試験において副作用が観察された症例の一覧表	study id_study title (O), study group order (O), site-id (O), document type (O), group title (O)
jp_m5.3.7.3	Serious adverse event list	実施された全ての臨床試験において重篤な有害事象が観察された症例の一覧表	study id_study title (O), study group order (O), site-id (O), document type (O), group title (O)
jp_m5.3.7.4	List of abnormal laboratory test values	実施された全ての臨床試験において臨床検査値異常変動が観察された症例の一覧表	study id_study title (O), study group order (O), site-id (O), document type (O), group title (O)
jp_m5.3.7.5	List of figures showing abnormal laboratory test values	実施された全ての臨床試験において観察された臨床検査値の変動を適切に示した図	study id_study title (O), study group order (O), site-id (O), document type (O), group title (O)

Language and character set support

It is understood that regional language support in the display names for the titles and keywords is a requirement for the JP region, but not for other regions. Furthermore, JP eCTD 4.0 specifications dictate that each attribute or field defines the type of values allowed. The following types can be used:

VALUE TYPE	VALUE ALLOWED
Text	UTF-8 characters (including Japanese characters) * can be used.
Fixed	Only the values given as examples can be used.
Alphabetic characters	Half-width/Single-byte alphabetic characters (a to z and A to Z) can only be used.
Single-byte numbers	Single-byte Arabic numerals (from 0 to 9) can only be used.
Single-byte alphanumeric characters	Only single-byte alphabets and single-byte numbers can be used.

Study standards and group title (JP)

For eCTD 4.0 in Japan, clinical studies are accepted in CDISC standard using ADaM and SDTM formats, similar to the U.S., though JP requires additional keywords for the studies.

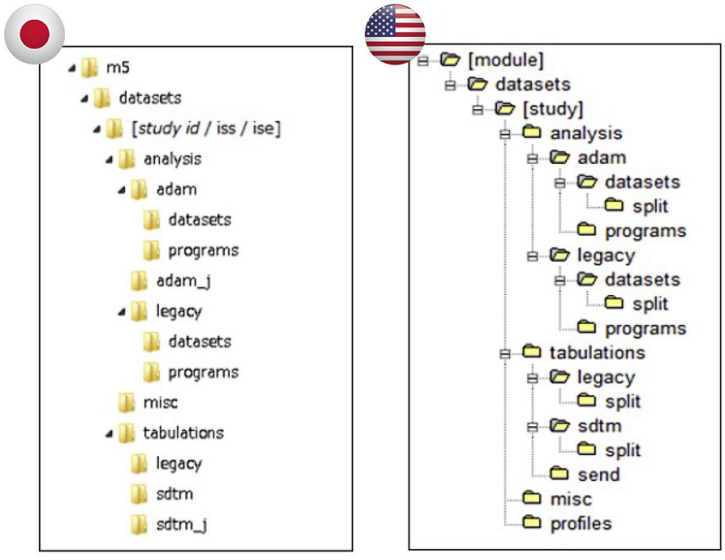
The Standard for Exchange of Nonclinical Data (SEND), one of the CDISC standards, is being considered for a potential requirement for electronic submissions in JP, but it is currently accepted for the U.S.

Additionally, for JP eCTD 4.0, clinical pharmacology documents require the addition of a File Description attribute, and dataset files (.xpt) require a character code for encoding, which is not required for U.S. eCTD.

The table below illustrates the relationship between electronic study data and the selectable CVs to be used for Japan eCTD 4.0.

	STUDY DATA CATEGORY	JP ANALYSIS TYPE	JP TERMINOLOGY (TABULATION)	JP TERMINOLOGY (ANALYSIS)
SDTM DATASET (FILES SUBORDINATE TO "SDTM" OR "SDTM_J" FOLDER)	jp_cdisc_single jp_cdisc_integrated	All	All	–
ADAM DATASET (FILES SUBORDINATE TO "SDTM" OR "SDTM_J" FOLDER)			–	All
ELECTRONIC STUDY DATA FILES OTHER THAN THOSE LISTED ABOVE	All		–	–

The folder structure for study datasets is slightly different when comparing U.S. and JP submissions; this is common for both eCTD 3.2 and 4.0.



Group or worksharing submissions

Group submissions are supported across applications and regulatory activities in the U.S., but not in Japan. In the EU, grouped variations or workshare procedures are supported.

Transition and forward compatibility

Though a unified format is employed by all agencies, the transition from eCTD v3.x to v4.0 is not universally accepted. For the U.S., submissions can be transitioned from eCTD 3.2.2 to eCTD 4.0 without requiring a transition sequence, a process similar to the EU, which allows regional submissions to be transitioned from eCTD 3.2.2 to eCTD 4.0. Unfortunately, Japan does not provide support for transitioning from JP 1.0 to JP 4.0, and the eCTD version number is maintained throughout the submission's lifecycle from initial submission to final approval.

Other differences

When it comes to additional differences, U.S. submissions require a cover letter in the m1.1 form (us_1.1) section, while Japan does not require one when submitting via gateway but does require it when submitting via other methods in the application/sequence/m1/jp folder and should not be referenced in the submission unit XML file.

Category Event is not allowed in the U.S. and EU, but it can be submitted for Japan; Contact Party is required for U.S. and EU submissions but excluded for Japan.

Implementation

The timeline for implementation varies by region, with the mandatory date for implementation ranging from 2023 to 2028 for different health authorities. See the table below for more information regarding deadlines by region.

REGION	TECHNICAL PILOT	IMPLEMENTATION DATES	IMPLEMENTATION DOCUMENTS	IMPLEMENTATION GUIDE VERSION
ANVISA, Brazil	2Q 2023 (Planned)	3Q 2023 (Production Pilot) 2023 (Voluntary)	TBD	-
EC, Europe	2024 CAPs (Planned)	2024 (Voluntary for CAPs) 2025 (Voluntary for MRP/DCP) 2026 (Voluntary for NAPs) 2026 (Mandatory for CAPs) TBC (Mandatory for MRP/DCP)	EC, Europe regional implementation page	1.0
FDA, United States	2022 – IQ 2023 (In progress)	2023 (Voluntary) 2028 (Mandatory)	FDA, United States regional implementation page	1.5
Health Canada, Canada	2023 (Planned)	2024 (Voluntary) 2027 (Mandatory)	Health Canada, Canada regional implementation page	Draft
MHLW/ PMDA, Japan	2Q 2021 (Completed)	2022 (Voluntary) 2026 (Mandatory)	MHLW/PMDA, Japan regional implementation page	1.4
Swissmedic, Switzerland	2024 (Planned)	2024 (Voluntary) 2028 (Mandatory)	Swissmedic, Switzerland regional implementation page	Draft
TGA, Australia	TBD	2023 (Voluntary)	2023 (Planned)	

Source: ICH https://ich.org/page/ich-electronic-common-technical-document-ectd-v40

How to prepare

The new standard aims to meet the needs of the industry, but as we adapt any system/requirement, it is essential to understand and consider the practical nuances, thus a careful implementation and preparation is necessary to ensure that all processes are transitioned correctly for the applications at different stages with the health authorities.

When transitioning to eCTD 4.0, the people, processes, strategies, and technologies involved are all critical components to consider. Organizations should be aware of a few key factors in order to best prepare, such as the fact that:

- eCTD 4.0 XML is complex and cannot be easily adjusted manually.
- Lifecycle management (using forward compatibility) between eCTD v3.2.2 and v4.0 will be difficult without a proper and compliant toolset.
- There is no stylesheet available for eCTD 4.0 to easily view the submission TOC and content in the browser.
- To enable a seamless shift to eCTD 4.0, all PDFs need to be prepared for submission readiness with the latest compression standards.
- Metadata (user-defined vocabulary) should be streamlined for consistent use in both eCTD 3.2 and 4.0 submissions.
- Internal teams must be trained in relevant terminology and concepts and be aware of the most recent ICH and regional specifications and guidelines.
- It is also important to note that support for eCTD 3.x must continue concurrently until eCTD 4.0 is made universally mandatory, which is not until 2028 for some regions. Therefore, the two submissions will overlap in use, and organizations may fall behind in following relevant regulatory processes if the new standard is not properly established.

Conclusion

The benefits of eCTD 4.0 are numerous and include improved structure, a singular format that can be used for multiple agencies/regions/centers, reduced structural changes, better metadata/keyword definition, display name, and structure, advanced lifecycle management, document reuse, and two-way communication as an option for exchanging information between applicants and regulatory bodies.

eCTD 4.0 is an essential step to streamlining the regulatory submission process, and it is important to understand regional differences when implementing it to maximize its potential.

"Be prepared — eCTD 4.0 is here! Be ready to take advantage of its benefits and ensure you are properly equipped to make the transition."

About the authors

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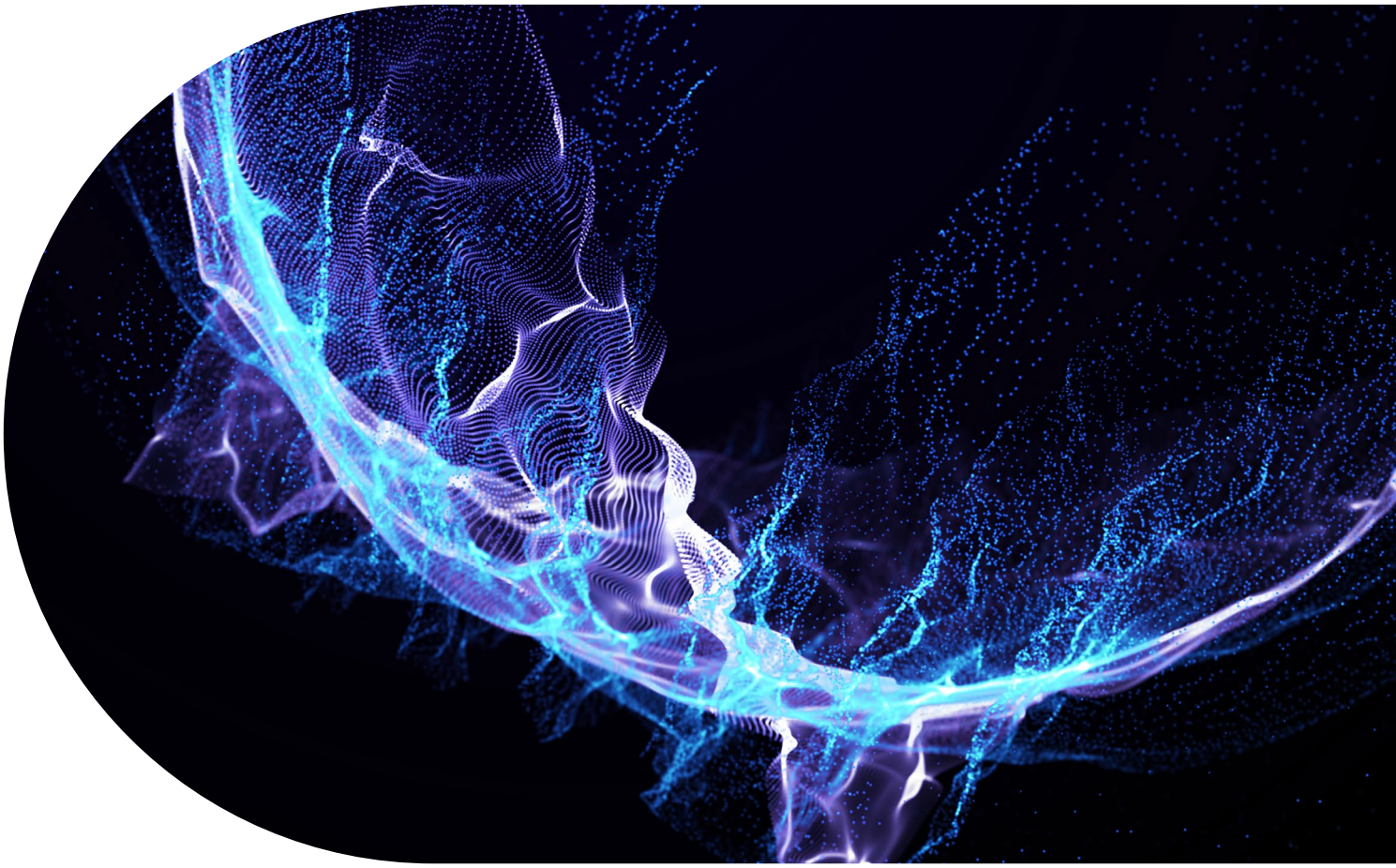
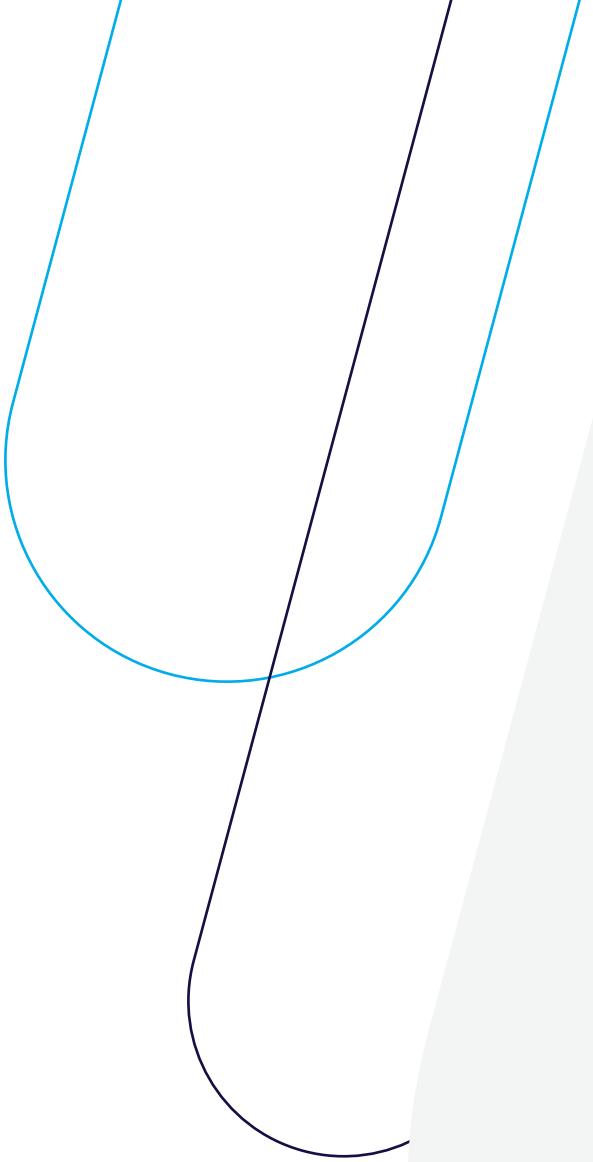
Sadia leads the team responsible for RIM Smart Submission Management at IQVIA. She has over 20 years of experience in IT and Life Sciences Industry. Sadia has extensive global knowledge of regulations and guidances for electronic submissions publishing.





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