Lorenz
LIFE SCIENCES GROUP

Dynamic Submission Management: The Future of Health Regulation

February 2022

White Paper

Executive Summary

PHARMACEUTICAL FILINGS HAVE EVOLVED CONSIDERABLY over the past half century in terms of content, process, and underlying supporting technologies. The industry as a whole has moved globally from primarily paper to mostly electronic submissions, and from almost entirely free-form text to an increasing amount of structured data for advanced internal analysis. Meanwhile, the size and overall complexity of these submissions continues to increase.

This paper discusses the background along with current events and trends impacting the industry today. These include changes to processes, such as the various expedited review processes used recently to address the COVID pandemic vaccine approvals, the increasing interest of agencies in shared reviews, and the broad desire to reduce the time and costs of the submission review process. It also includes changes in content, such as the structured content which is becoming increasingly common. All of this is supported by changes in technology, whether via data format standards such as CDISC or IDMP, or cloud-based deployments which can challenge old cost and security paradigms.

Back in the 90's, LORENZ introduced the term Electronic Submission to the industry. Now, based on the trends described below, we see industry is moving towards what we describe as Dynamic Submission Management (DSM). This is not a specific software or technology product. Rather, DSM represents the next stage in the evolution of pharmaceutical regulation, providing flexibility to the world of filed submissions to meet the challenges of the future.

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DSM provides many opportunities in terms of efficiency, risk-reduction and accessibility. The efficiency is provided by increased shared content, common automated processes, and faster reviews as discussed above. This in turn leads to the possibility of faster overall time-to-market and potentially lower regulatory costs.

The risk-reduction opportunity comes from broader content usage, data transparency, joint reviews and the use of advanced data management tools (e.g., AI and rules-based analysis). It is anticipated this will improve public confidence in the regulatory process as drugs move from relatively simple chemistry to advanced genome-based therapies aimed at small population subsets.

The accessibility aspect is exemplified by the use of cloud-based technologies and shared review procedures. While some agencies already work together to share resources, these changes will reduce the barriers further and increase this trend.

This evolution will take some time to be realized globally, and there will be inevitable challenges including the burdens on agencies to adapt their processes to a more dynamic approach. However, we are confident that DSM aspects will develop over time and lead to a better overall regulatory environment for everyone.

Wolfgang Witzel
President, LORENZ Life Sciences Group

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1. Introduction

1.1 Objectives

This document gives an overview of historical submission practices in the regulated life sciences industry and combines this with a review of current trends to project a future vision of submissions.

1.2 Intended Audience

This document is intended for thought leaders in the regulated life sciences agencies and industry as well as the many organizations supporting them. While some technical knowledge may be useful, it is not required and key concepts are explained to the degree required to support the discussion. We have provided links to additional information about many of the topics discussed in the paper in section 6.3.

The history of LORENZ is closely interwoven with the creation and development of the eCTD and the digitization of regulatory affairs.

1.3 LORENZ Corporate Background

LORENZ has been a key player in the Life Sciences market for over 30 years. The history of LORENZ is closely interwoven with the creation and development of the eCTD and the digitalization of regulatory affairs.

By the late 1980s, most pharma and life sciences companies were already working with PCs internally. However, authorities still required drug approval submissions on paper. So "compiling" a submission meant exactly that: assembling hundreds or thousands of word files, spreadsheets, and scanned-in documents, and then printing everything out in multiple copies, and collating it all in the right order. The final product, the actual submission, was quite literally a pallet (or two) of documents.

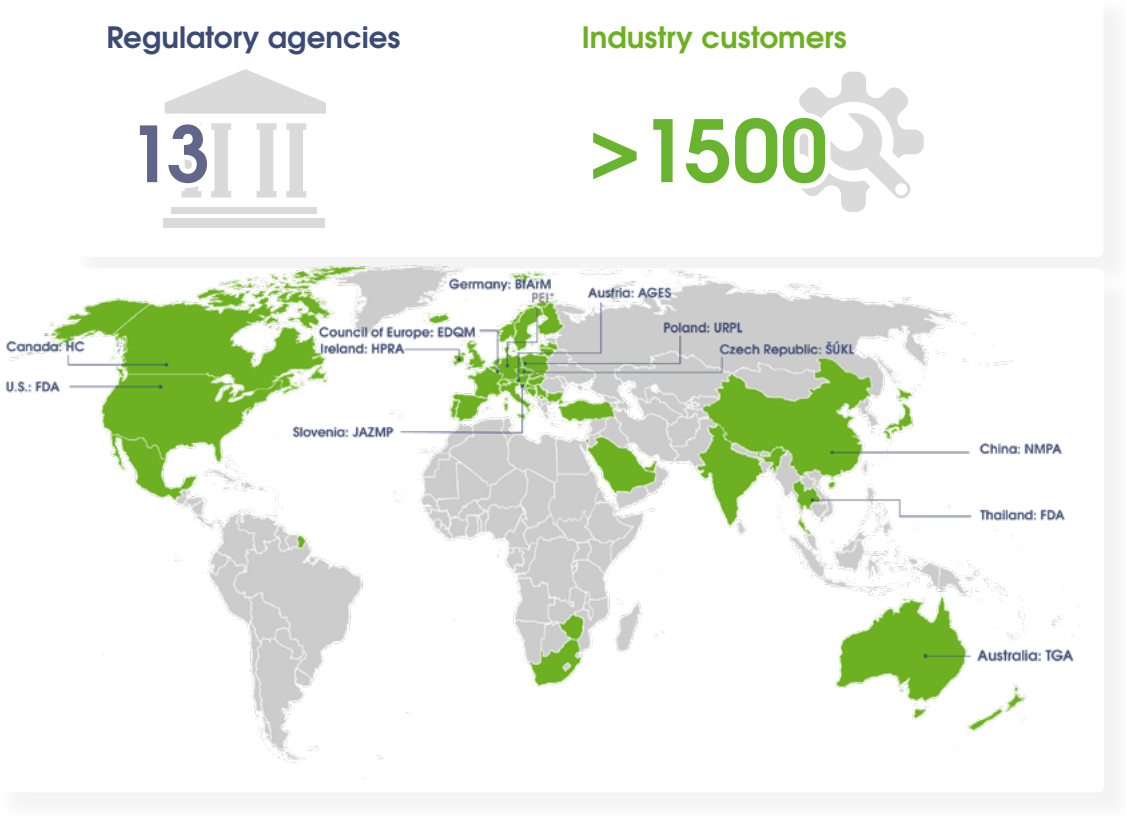
The emergence of the first electronic submission in Europe in 1995 happened differently than the earliest electronic submissions in the US in the late 1980s. In Europe, our PharmBridge software built an inner document structure designed to help the compilation of the submission, but also to facilitate its review and approval on the authority side. Lifecycle Management was built into the software! From the start, it was used by both submitters and reviewers.

Since these early beginnings, LORENZ has kept its finger on the pulse of the sector and played a critical role in the definition of the first electronic standard for the Common Technical Document – commonly known as the eCTD. In 2000 a new product docuBridge signaled the start of a whole new era in high-volume,

high-performance submission creation and management and the term “submission management system” was introduced. The number of submissions to individual authorities soon skyrocketed into the thousands.

Today, LORENZ products are utilized by 13 global regulatory agencies and over 1500 sponsors around the world.

Continuous technical advances in the digital world bring new challenges and



new opportunities. Efficient data and process management and the integration of process steps are becoming ever more complex for both sponsors and agencies. Regulatory Submission Management is taking on a new meaning and we are at the start of a new digital transformation journey in this space.

2. Evolution of Regulatory Submissions

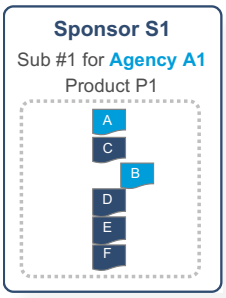
In this section we will discuss the background of regulatory filing in order to establish a baseline pattern against which to examine current trends and future directions. We will focus here on those submissions supporting product registration, i.e., achieving and maintaining market authorization (MA) for a pharmaceutical product in a given region. While there are many other types of submissions (e.g., post-market changes), the most complex and urgent submissions are typically related to market authorization throughout the entire product lifecycle.

2.1 Pre CTD: Uncontrolled Paper

For decades before 1990, submissions were often created with content prepared specifically for the agency or market to which they were being filed. There was limited consistency in submission structures, mainly driven by the practices of the individual sponsor, supporting service provider, or the preferences/guidelines of the target agency or reviewer. The content and the presentation of the content varied widely in order to maximize the real or perceived acceptance of the submission. These factors greatly inhibited opportunities for content reuse.

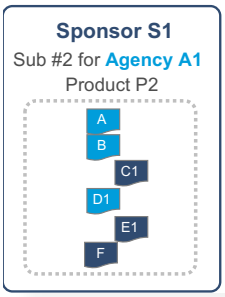
To illustrate this, we will incrementally introduce a set of four conceptual scenarios which we will re-use throughout the paper to enable comparison of submission practices over time. We will use two sponsors, creatively named **S1** and **S2**, submitting a total of four submissions for three separate products to two agencies, **A1** and **A2**.

1. First, **Sponsor S1 creates Submission #1 for Product #1** to be sent to **Agency A1.**
   There is a structure here, which represents a Table of Contents (ToC), but it was uncontrolled. This was implemented physically with paper documents (▭) using binders, tabs, and sections.
   However, this ToC is not the M1, M2 we are used to today because this is before the CTD was developed and adopted.



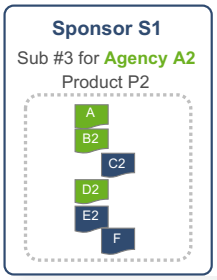
2. Now, the same **Sponsor S1 creates Submission #2 for Product #2** which is also to be sent to **Agency A1.**
   Again, there is a structure, but it is different from Sub #1.

   This might be because it was prepared by a different group within the sponsor organization, or was expected to be sent to a different reviewer within **Agency A1** who might prefer a different approach.



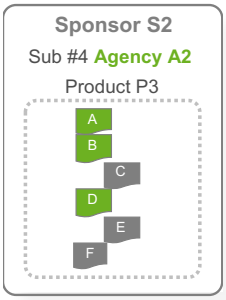
3. However, **Sponsor S1** then **creates Submission #3 for the same Product #2** for **Agency A2**.
   The structure is different from Sub #1 or #2.
   Again, there might be reasons for this, but was often due to different filing requirements across agencies, real or perceived.

   The content may also be different in some ways. The choice of what information to highlight, which studies to use and even how to phrase positions may vary, all leading to minimal document or content reuse, even if the core elements (e.g., chemistry, indications, composition) are largely the same.



4. Finally, the same pattern (or lack thereof) can be seen in Submission #4. A different sponsor (**Sponsor S2**) **has created Sub #4 for the Product #3** for **Agency A2**.
   Again, we have a different ToC for our collection of paper documents.

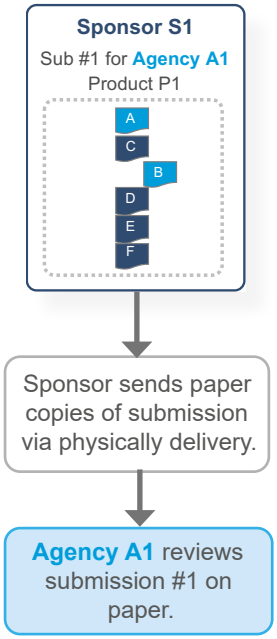
   Any included data is presented as tables within the paper document, complicating production and quality assurance by the sponsor and limiting opportunities for further agency analysis.



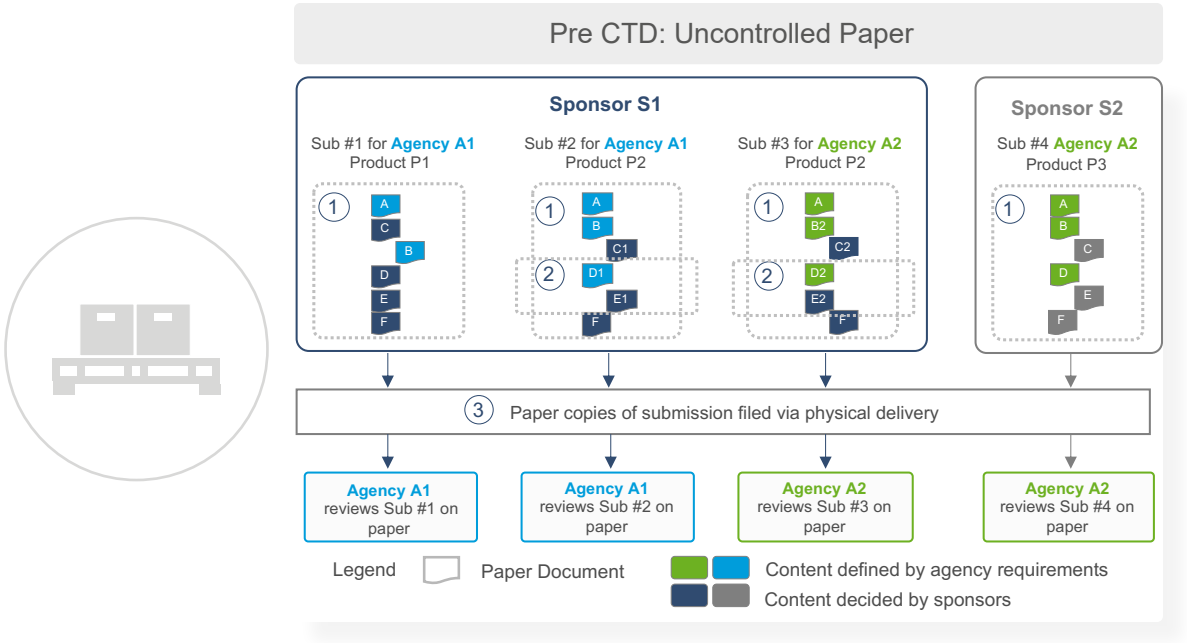
THE SUBMISSION PROCESS USES A "MONOLITHIC INITIAL FILING" APPROACH, where almost every part of the submission gets sent at once. There was always at least one copy of every document, typically sent in the initial filing, in order to have a clear official record. Portions of the submission might later be updated in pieces, usually using cover letters explaining what was being updated and why.

As can be seen in the accompanying diagram, **Sponsor S1** sends the entire submission #1 to Agency A1 in paper format, likely using a courier. This would have been a collection of binders (typically representing the structure) packed into boxes. Agency A1 reviewers would then review these paper documents.

OVER TIME THE NUMBER OF COPIES OF THE SUBMISSION FILED GREW to ensure more reviewers inside the agency had better access to the content. This might be complete copies or selected sub-sets. This helped to improve the review time (and therefore time to market) but of course required more paper. Eventually, many larger agencies had loading docks to make it easier for courier trucks to unload the pallets of paper coming in.



This submission approach was used by most agencies, leading to our composite picture below of the entire set of four scenarios.



We can summarize our observations using the diagram above:

1. **Submission structures (ToCs) are inconsistent** across sponsors, products and agencies. While the content filed was often similar, the ToC was not standardized. While today's readers might recognize "A" as CTD Module 1 content, such as a Cover Letter, this notation was not yet consistent, contributing to the randomness of the approach from a global perspective.

2. **Most documents are prepared uniquely for a given submission** according to sponsor's practices or agency specific guidelines. This leads to low content reusability and higher preparation and quality costs.

3. **Submissions are typically assembled as one large initial "monolithic" filing** with supplemental smaller filings over the life of the product in a given market. Submission documents are printed and typically multiple printed copies are delivered physically to each agency for review.

Even with these limitations, submissions generally accomplished their purpose. With some notable exceptions (e.g., see Thalidomide referenced on the ICH site), products were approved as appropriate for their target markets. However, the process was difficult to scale and very expensive to maintain in terms of training, preparation, and review effort.

As more companies became interested in achieving global markets for their products, and as many countries became more concerned with quality and efficacy of products in their domain, the need for an improved approach increased.

2.2 CTD: Emerging Structure

In 1990 the International Council on Harmonisation (ICH) was formed, led by several major agencies (US, EU & JP). They agreed to implement a standard approach to structuring major submission. From the ICH website:

> *Harmonisation of regulatory requirements was pioneered by the EC, Europe, in the 1980s, as the EC, Europe moved towards the development of a single market for pharmaceuticals. The success achieved in Europe demonstrated that harmonisation was feasible. At the same time there were discussions between Europe, Japan and the US on possibilities for harmonisation. It was, however, at the WHO Conference of Drug Regulatory Authorities (ICDRA), in Paris, in 1989, that specific plans for action began to materialise. Soon afterwards, the authorities approached International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) to discuss a joint regulatory-industry initiative on international harmonisation, and ICH was conceived.*

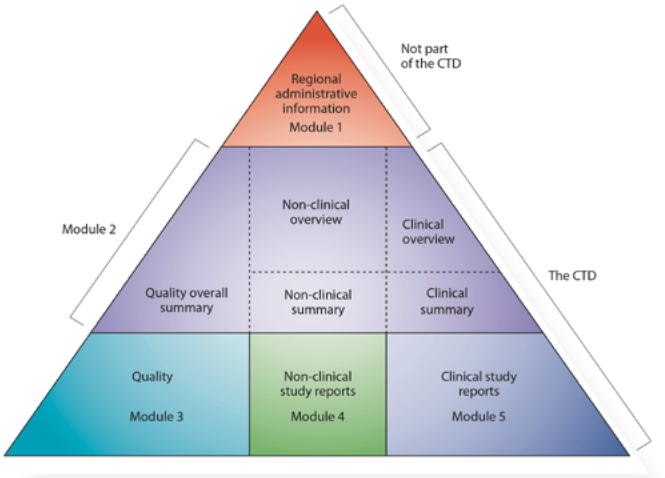
The ICH was not alone in pushing for standardization and several regional standards were developed in the 1990's, including early electronic formats. The Drug Application Methodology with Optical Storage (DAMOS) was a TIFF image-based standard for filing. It was used in certain drug regulatory agencies, such as the European Notice to Applicants (NtA). The eNDA format in the US is another early example.

However, the key accomplishment was when a working committee of the ICH was formed with participation of agency and industry stakeholders and developed what became known as the Common Technical Document (CTD). The CTD was initially focused on Safety, Quality and Efficacy and described the key parts of a registration submission structure, sometimes described as a Table of Contents (ToC). The famous CTD "triangle" diagram was developed to explain this structure, which also included necessary practical aspects such as Summaries and Region-specific content.

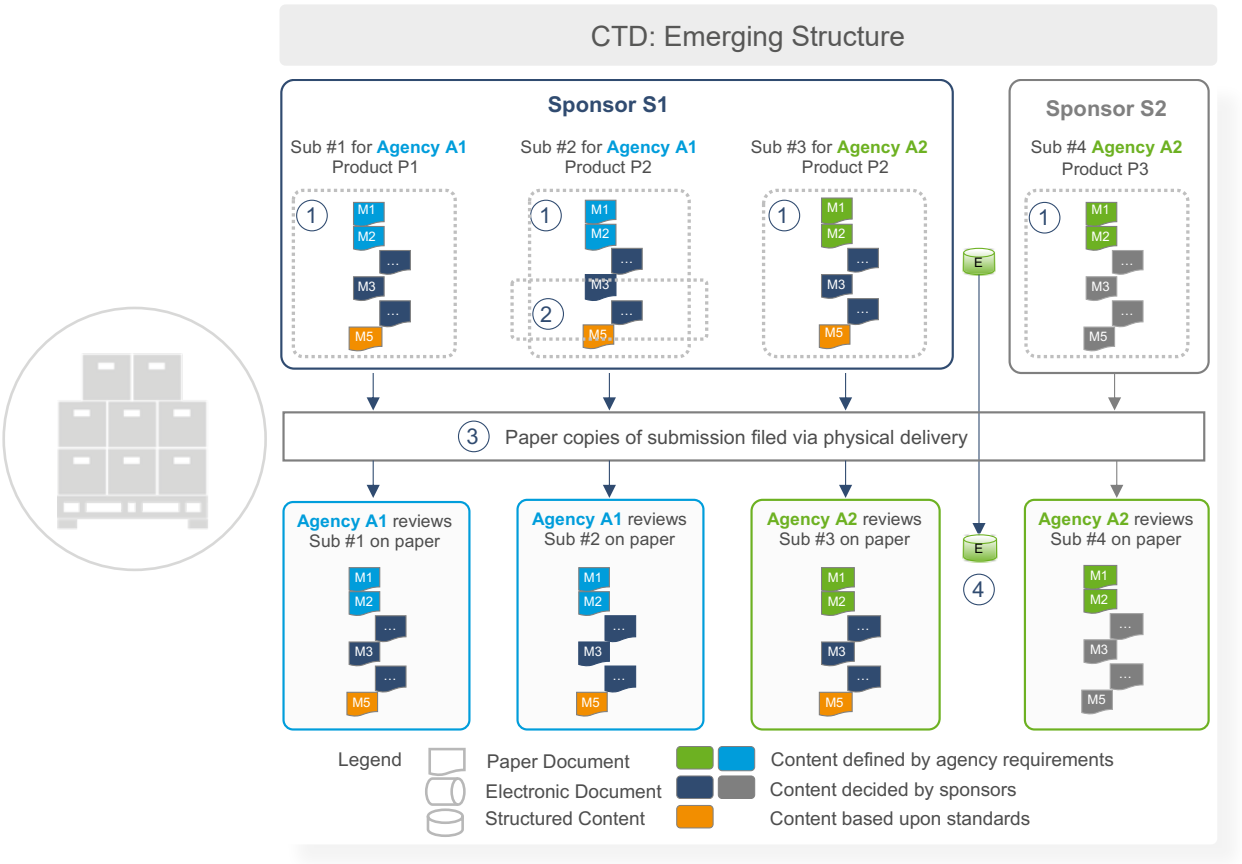
CTD was a critical improvement in terms of content organization but changed the overall process only in terms of standardizing the high-level submission structure. The rest of the submission process remained largely unchanged.

The following diagram illustrates CTD usage showing the same four scenarios as before. There are two different sponsors (**Sponsor S1** & **S2**) preparing four submissions for two different agencies (**Agency A1** & **A2**) involving three separate products (P1, P2 & P3). Each scenario includes the submission package created by the sponsor organization, the submission method, and the resulting package inside the agency. The internal structures now use the CTD Module terminology although this is shown in an abstract manner.

CTD Triangle



Source: CTD



As shown in the diagram:

1. **Submission structures are consistently based on CTD** across sponsors, products and many agencies. Key common topic areas ("Modules") are defined, including M1 with agency-specific information. Other modules are intended to be common across agencies although there are exceptions to this.

2. **More content is consistent across agencies** however most documents are still sponsor or agency specific. Content reusability is still limited.

3. **Submissions are typically assembled as one large monolithic filing** with supplemental smaller filings over the life of the product in a given market. Submission documents are printed, and typically multiple copies are sent to agencies for review using various delivery mechanisms.

4. **Most data (e.g., CMC, Study data) are provided as tables in paper documents** as the official copy. Occasionally however, electronic files are provided as working copies "on-the-side". These files were generally office documents such as spreadsheets (e.g., Lotus 1-2-3™) with their internal structures being jointly agreed to by a sponsor and an agency (or individual reviewer) on an *ad hoc* basis as opposed to an external standard.

Adoption of CTD started rapidly, with several major agencies adopting it early. For example, the CTD was harmonized in Japan in November 2000, and implemented in June 2001. Many sponsors implemented CTD quickly, recognizing the benefits of consistent submission structures in terms of lower preparation costs and higher submission quality. There were of course some sponsors which were slower to adopt CTD, perhaps because the agencies which were their primary market focus did not immediately request it.

The adoption of CTD as a submission structure by agencies raises a major point which is still relevant and sometimes under-estimated today. In general, agencies are limited in how much or how rapidly they can change their practices and procedures. Some aspects of these practices and procedures may be tied to actual laws, which are powerful but can obviously be very difficult to change in terms of time, political will, etc. Other changes are tied to rules and guidelines within the agency or its broader organizational structure such as the relevant Department or Ministry. While perhaps not as difficult or as useful as legal changes, these can still be worthwhile and yet be significant barriers to change for some agencies. Finally, many barriers in all organizations are based on historical practices. While these are less formal, they are no less real and require time, thought, and patience to overcome.

The Prescription Drug User Fee Act (PDUFA) is an example of the power of legislative change. This US legislation introduced in 1992 meant sponsors would have to pay to have their submissions reviewed by the US FDA but would benefit from the fact that the agency would have additional funds to build out internal support for review processes. PDUFA also led to the introduction of expected review timelines which gave sponsors more certainty in approval timeframes. All of this was assisted by the increasing standardization of the CTD-based submissions.

While the specifics varied, other countries implemented similar cost-recovery practices for their agencies, including associated performance management metrics, sometimes referred to by the broader industry term of Service Level Agreements (SLAs).

While the submission structure was standardized with CTD, even if not fully implemented globally, the submissions were still paper-based. This meant continued costs and time related to print production and shipping. This was exacerbated by the continuing tendency for submissions to increase in size. Agencies wanted more information to improve their review processes and the standardized submission structure made it easier to ask or require this from sponsors.

The ICH moved forward rapidly with efforts to move away from paper-based submissions.

2.3 eCTD: Electronic Paper

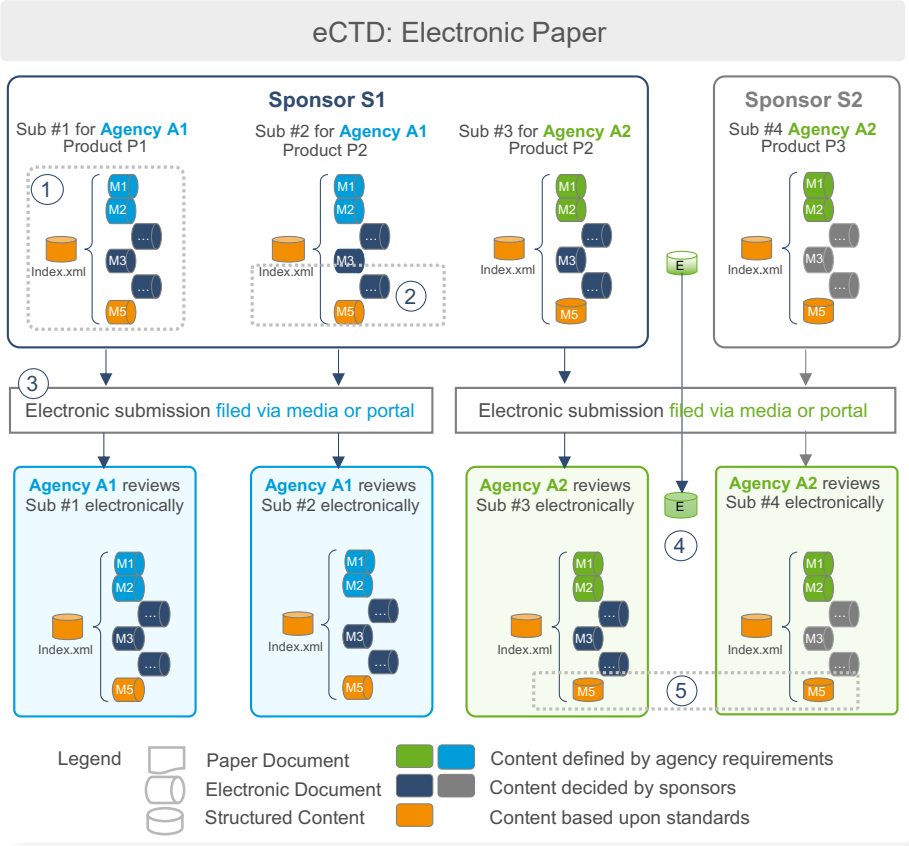
The ICH published the first public definition of an electronic CTD as eCTD v2.0 in early 2002 and it was quickly updated to v3.0 later the same year. The eCTD leveraged the CTD structure to define an electronic framework and related processes to allow electronic filing of submissions. The eCTD framework was implemented using index files, in what was at the time the relatively new eXtensible Markup Language (XML) format. These "backbone" files included file system based links to the individual documents, usually provided in Adobe's Portable Document Format (PDF) format. The eCTD index files also contained information about the overall filing and individual documents in the filing, introducing the term metadata to many people in the industry.

The eCTD framework was implemented using XML-based index files.

This is the process and structure the majority of submissions still use today.

THE SUBMISSION CONTENT AND STRUCTURE IS LARGELY UNCHANGED EVEN THOUGH THERE HAS BEEN AN OBVIOUS AND WELCOME MOVE FROM PAPER TO ELECTRONIC. The MA submissions are still filed as monolithic initial applications supplemented by updates. The content is largely in PDF, using it primarily as electronic paper with pages, unstructured text, inaccessible data tables, etc.

The diagram on the next page shows the evolution from the earlier approaches to the eCTD paradigm. The diagram shows the index.xml backbone file which serves as a CTD-based organizational tool for the electronic documents within. It uses the same four scenarios as above, however the internal structures now reflect electronic content ( ) vs paper content ( ).
We show a single index.xml to illustrate the various eCTD electronic tables of contents. The diagram is again conceptual in nature and not intended to reflect a specific or complete CTD or eCTD structure.



As shown in the diagram:

1. **Submission structures are consistently based on CTD** and this structure is now supported using standards-based xml files (e.g., index.xml). For example, agency modules (M1) typically have their own regional index files.

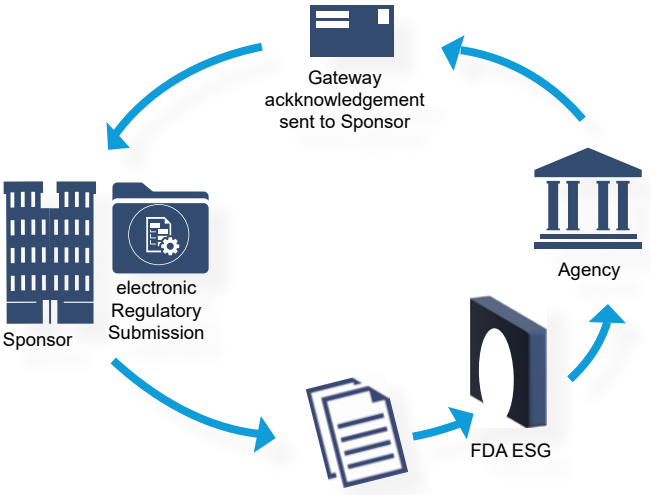
2. **More content is consistent across agencies** however many documents are still sponsor or agency specific. Content reusability is improving but still limited.

3. **Submissions are still typically done as one large initial filing** with supplemental smaller filings over the life of the product in a given market. Documents are sent in electronic form to agency for review. Documents are mostly PDF although other formats are allowed. Some agencies develop online portals to provide more effective common filing solutions.

4. **Most data (e.g., CMC, Study data) are still provided as tables in documents** as the official copy. Electronic files were initially common as working copies “on-the-side” in formats jointly agreed to by a sponsor and an agency, but this practice has decreased in recent years.

5. **Later, some agencies began allowing some structured content** within the eCTD structure such as Study Tagging Files at the FDA (M5). This also led to the decrease in “on-the-side” working files as discussed above.

In the early days of eCTD, sponsors would send their submissions to the agencies using media (magnetic or optical disks). As the volume of electronic content increased along with the overall size of submissions, what started out as one CD-ROM now required many. Some agencies introduced portals where sponsors could securely upload their submissions, e.g., the FDAs Electronic Submission Gateway (ESG).



THE eCTD ALSO INTRODUCED THE CONCEPT OF A FORMAL SUBMISSION LIFECYCLE to the industry. The eCTD lifecycle provides clarity on what content is "up-to-date" without compromizing the evidentiary record. It was normal in the past to file new documents on their own as opposed to the obvious waste of re-printing and re-sending the entire submission. New or updated printed documents were sent with a suitable cover letter explaining where they fit into the overall application. While eCTD filings still retain the cover letter, eCTD also uses document lifecycle operations Add, Replace, Delete and the often confusing Append.

Further complicating the situation, eCTD versioning is done at the filing (the "sequence") level and applied to documents within (a "top-down" approach) as opposed to the more common document management approach of document level versioning ("bottom-up"). The conceptual benefits were clear but the implementation was difficult for many to understand and apply effectively in the early stages.

The complexity of the eCTD lifecycle, along with the novelty of XML and the lack of supporting tools, likely slowed the overall adoption of eCTD.

The complexity of the eCTD lifecycle, along with the novelty of XML and the lack of supporting tools, likely slowed the overall adoption of eCTD (see Timeline in section 2.5). This can be seen in the long timeframes between when agencies began accepting eCTD to when it became the primary expected submission format. For example, Health Canada first published their eCTD M1 format (a key prerequisite for eCTD filing) in 2004 but did not make eCTD mandatory until 2019 when there was full confidence that this requirement would not be a major impediment for sponsors.

THE eCTD ADOPTION DELAY CAN ALSO BE SEEN IN THE POPULARITY OF OTHER ELECTRONIC FORMATS PERCEIVED AS SIMPLER THAN eCTD. These can be broadly categorized as Non-eCTD electronic Submissions (NeeS) and there are many variations of this approach still in use in globally. A key hallmark of NeeS formats is that they are less complex compared to eCTD, primarily in terms of lifecycle operations and required metadata.

The version of eCTD currently in use is version 3.2 although version 4 has been under discussion for many years. Version 4 has only recently gained final approval at ICH and only a few countries have indicated they plan to adopt it in the near term. It provides some improvements, including easier content reuse and greater flexibility in terms of internal metadata

based on Controlled Vocabularies (CVs). However, it retains the index-and-PDF-file approach and the eCTD lifecycle approach. It remains to be seen whether the incremental improvements of eCTD 4.0 will be enough to encourage widespread adoption.

THE eCTD SUBMISSION PROCESS REMAINS FOCUSED ON THE MONOLITHIC "BUILD & SUBMIT" MODEL but there are a growing number of situations where expedited processes are used. Sometimes termed parallel- or rolling- reviews, these processes allow for the possibility that an initial filing, while still monolithic, may be deliberately incomplete and provided to allow the reviewers to start work immediately while additional content is prepared. Similarly, some early work has been done with shared agency reviews, whereby Agencies review content collaboratively, sharing views and results as appropriate. This will be further discussed in the next chapter.

The use of PDF is increasingly seen as a limitation in terms of content reuse, quality & risk management, all contributing to higher costs and reduced potential benefits.

And while eCTD allowed the submission of almost any "document" format, it is still today primarily focused on PDFs, which are essentially electronic paper. The use of PDF is increasingly seen as a limitation in terms of content reuse, and quality & risk management, all contributing to higher costs and reduced potential benefits. As eCTD usage became more widespread, some agencies began supplementing their PDF-centric eCTD requirements with standards-based structured content such as CDISC, SPL, etc. Other agencies began implementing structured data submission solutions outside of the eCTD such as EMA with xEVMPD filings. This will be discussed in the next section.

2.4 Structured Content: Moving from Text to Data

> *Structured Content is "structurally rich and semantically aware, and is therefore automatically discoverable, reusable, reconfigurable and adaptable". Rockley Group 2010.*

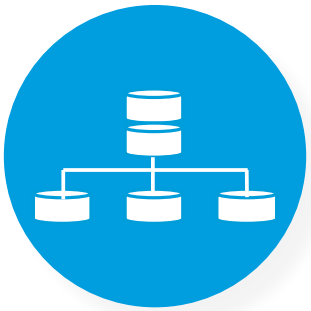
The use of structured content is increasingly common in pharmaceutical submissions and vital to future improvements. The classic definition above is a reasonable starting point, but in our context, we would refine this to say that it must use an industry-wide standardized format and shared metadata to allow for effective processing of the content within. These days, in our world, this is usually using standards based on XML which continues to be a convenient and suitable baseline.

STRUCTURED CONTENT INCLUDES BOTH DATA AND TEXT. Structured data is relatively well understood and there are numerous standards that exist or are evolving for pharmaceutical regulatory data such as CDISC. Structured text is more challenging, as those who have used Structured Product Labeling (SPL) can attest. The key to success is to provide a relatively granular text structure (e.g., paragraphs, ingredient names, corporate identifiers) which have implicit or explicit metadata to describe their purpose within the larger submission.

Metadata for structured content relies heavily upon controlled vocabularies (CVs) which are managed lists of terms with associated codes and other

Metadata for structured content relies heavily upon controlled vocabularies (CVs).

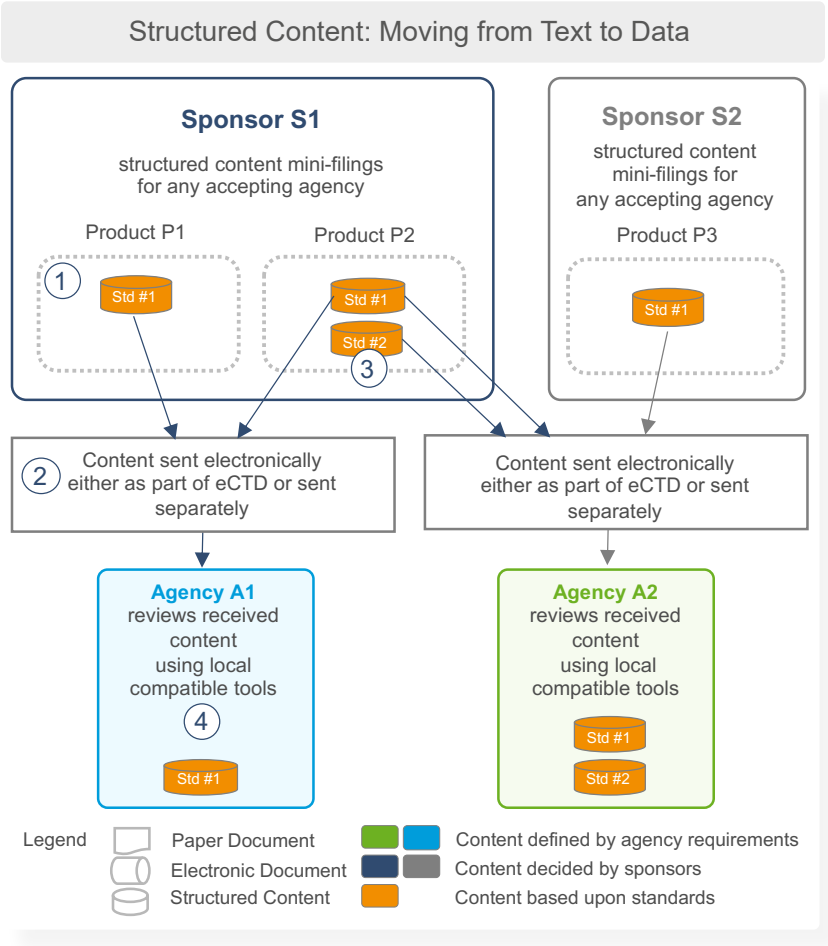
useful values such as display names (ultimately multi-lingual), alternate values (preferred vs non-preferred), currency status (valid <from> and <to> dates), etc.



Supporting this trend is the increased adoption and sophistication of Regulatory Information Management (RIM) systems. These systems, which are currently very broadly defined, capture data-based content relevant for regulatory materials and associated processes. While capabilities vary, some of these systems can support the evolving structured data submissions.

THE PROCESS FOR PREPARING, FILING, AND REVIEWING STRUCTURED DATA CURRENTLY VARIES WIDELY. As shown in the following diagram, it is generally used today for providing specific required content to meet a specific but narrow regulatory purpose or to support a larger primary submission (e.g., SPL, CDISC, IDMP).

The diagram shows scenarios based on the ones used before. Sponsors **S1** & **S2** are preparing content for two different agencies **A1** & **A2** involving three separate products (P1, P2 & P3). Now however, instead of the monolithic filing, the structured content is a set of smaller supporting filings.



As shown in the diagram:

1. **To date, Structured Content submissions are small and often separate from the primary filings.** They are typically either subsets of the traditional MA-type applications or supplemental filings to support MA maintenance in a given region. Submission formats are usually standards-based but different agencies may use different standards or supporting reference data.

2. **Submission content is sent electronically to the agency for review** either included in the eCTD such as the Canadian XML Product Monograph (XML PM) or separately for example the xEVMPD process currently in use in the EU.

3. **The same content may potentially be sent to multiple agencies** although different submission methods may be used. This allows true content reuse to occur leading to greater efficiency.

4. **Agencies typically review the content using their own tools** as opposed to shared or sponsor-provided technology.

THE BENEFITS OF STRUCTURED CONTENT SUBMISSIONS INCLUDE FINALLY BREAKING THE PAPER PARADIGM, giving the agency the opportunity to readily review data as opposed to relying solely on sponsor analyses and enabling the rapid population of internal databases with high-quality data for further use. Examples of this include US FDA's use of CDISC data as well as the IDMP standard (discussed in the next chapter) which is gaining acceptance globally. Another use is to support broader access to the content, such as the publishing of SPL labels through the DailyMed website.

However, the current approaches are typically fragmented, meaning each standard is targeted to a small number of use cases. Many of the standards rely upon CVs which may not always be the same from one agency to another, although there is significant effort being made in some areas to map or consolidate CVs such as the GSRS & SPOR substance models. Translations and process-related metadata can also be a challenge in developing global standards.

New, more all-encompassing submission standards are emerging which have the potential to remedy some of these situations including Fast Healthcare Interoperability Resources (FHIR). Use of the FHIR message model has the potential to make it easier to implement broader, more global, standards without breaking the underlying technical models required for system developers in the vendor community.

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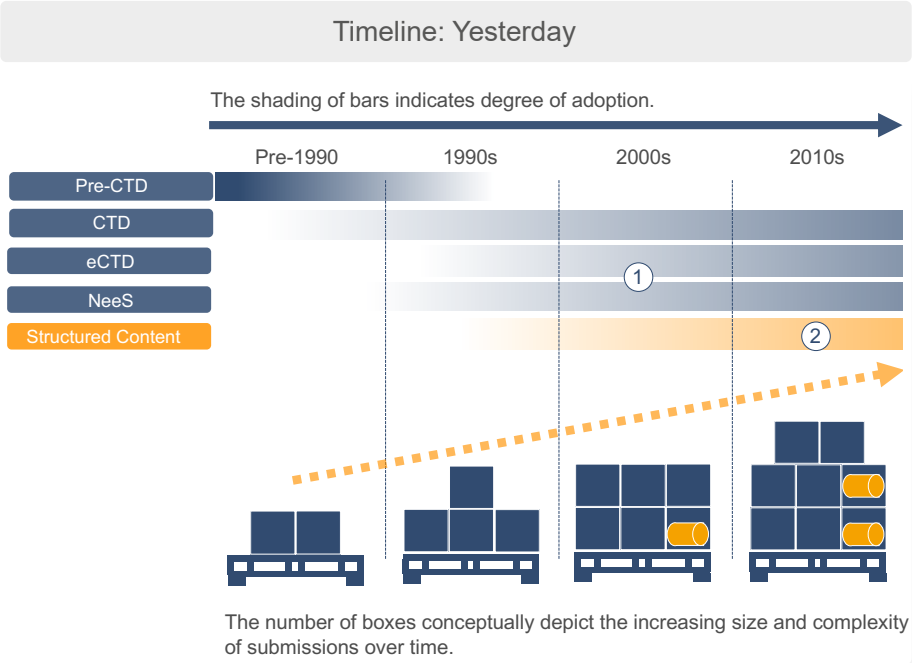
Another challenge to broader acceptance of structured content for many agencies is the difficulty of working with it in their (sometimes constrained) technology environments. The technology required for the current PDF-based world, with all its limitations, are widely available at a relatively low cost. Working with structured content can start simply, such as viewing an HTML rendering of an SPL XML file or using a SAS dataset viewer, but increasingly requires more sophisticated systems to get the full value of newer standards. For many agencies these systems are often expensive to acquire, implement and maintain.

2.5 Observations and Timeline

There are several observations we can make based on the previous discussion.

- Introducing new submission standards or processes takes time for all stakeholders, but especially agencies.
- Submissions continue to grow in size and become more consistent in structure.
- The traditional paper-paradigm is a constraint on future regulatory needs.

The first two points are conceptually depicted in the diagram below.



As shown in the diagram:

1. We can see that eCTD took a long time to become fully accepted, reflecting legal and business challenges to its adoption. By contrast, NeeS was accepted and became common quite rapidly due to its simplicity and lower barrier to use.

2. While structured content has always been used to some extent it is rapidly becoming much more widespread. Early submissions were unstructured text (prose) with some images of data. Future submissions will be mostly structured processable content (including data) linked with a minimum amount of prose to “tell the story” and hold the submission together.

Agencies are looking for other scenarios to allow them to achieve the benefits of structured content within their budgetary and legal frameworks. In the next chapters, we will review some of the trends and drivers that underlie these scenarios and lay out a possible next step in the evolution of submission processes.

3. Trends & Drivers

3.1 Introduction

The global pandemic has become the perfect catalyst to enable change, pushing the entire industry to think outside the box and re-examine ways of working to deliver life-saving medication to patients faster. While increased efficiencies, process optimization, data standardization and technology modernization have been goals for the healthcare industry for years, the need for these changes and improvements has never been more apparent. COVID-19 vaccines have been able to make it into patient's arms in record time only by working outside the norm to break barriers and make the impossible possible.

The global pandemic has become the perfect catalyst to enable change, pushing the entire industry to think outside the box and re-examine ways of working to deliver life-saving medication to patients faster.

Data transparency, work-sharing, collaboration, and a shift from sequential to parallel processes have been critical in enabling rapid and effective product development, clinical trials, application approvals and post-market monitoring. These improvement trends are not new and many have been evolving for years. However, the learnings from COVID-19 put a spotlight on critical gaps and opportunities. This section will focus on the trends and drivers that could have the biggest impact on the evolution of change as it relates to the regulatory filing and product approval processes.

3.2 Global Health Agencies Collaboration

Collaboration amongst global health regulators has existed for some time but has been spurred on by the need to respond to the global pandemic. It has never been more apparent that sharing information, leveraging skill sets, and collaboration in decision making is of benefit to the health of the global population. Agencies and health organizations have banded together to approve a COVID-19 vaccine, leveraging established partnerships to aid in decision making.

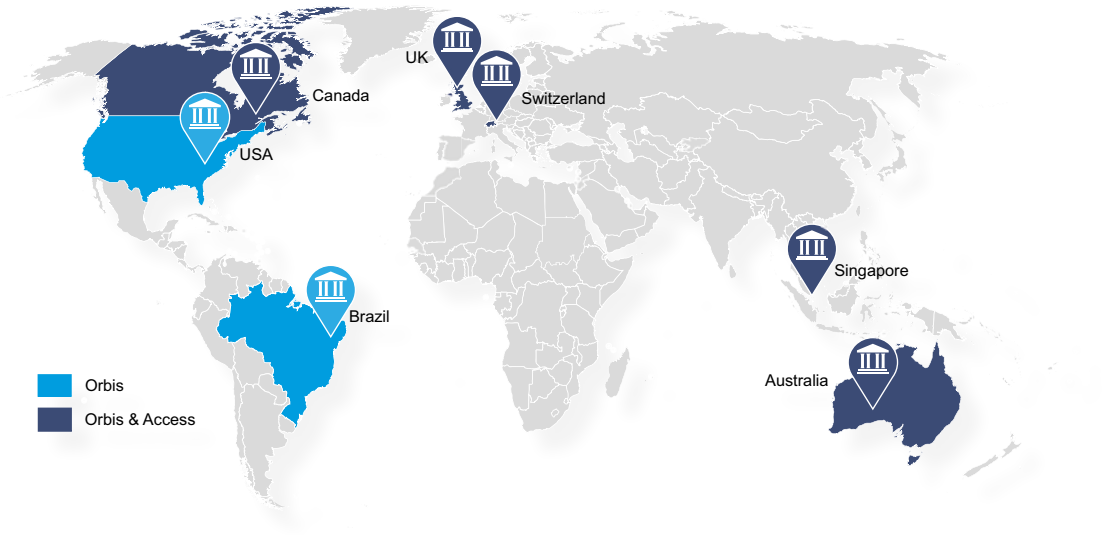
Some partnerships are a natural part of the political landscape, such as EMA and the various National Competent Authorities (NCAs) within the EU. Other partnerships have been formed over the years to provide mechanisms for collaboration, information exchange, and joint reviews through work-sharing efforts. Further information is available in the links below, but examples include the Access Consortium, established in 2007 and the FDA Oncology Center of Excellence Orbis project, established in 2019. Member countries are shown on the accompanying map.

PROJECT ORBIS

ACCESS CONSORTIUM
AUSTRALIA
CANADA
SINGAPORE
SWITZERLAND

Source: Orbis, Source: ACCESS

Orbis & Access Member Countries



COVID-19 HAS ALSO PAVED THE WAY FOR ADDITIONAL COLLABORATIONS such as the EMA OPEN Project and extended scope of work for the International Coalition of Medicines Regulatory Authorities (ICMRA). The EMA OPEN Project is a pilot established in December 2020 with Health Canada, TGA, and Swissmedic, focusing on evaluations of the COVID-19 vaccines and treatments. The ICMRA is a coalition of regulatory authorities

Source: ICRMA

including the World Health Organization (WHO) to address current and emerging regulatory and safety challenges in human medicines. ICMRA expanded its scope to provide a global approach for regulators to COVID-19 treatments and vaccines. While an individual regulatory agency is always ultimately responsible for the approval decision for a health product in their jurisdiction, expanded evaluation insights and skills from other global partners are invaluable assets, and ultimately serve the patient population better.

In addition, the ability to run parallel review activities with downstream Health Organizations / Government partnerships such as Health Technology Assessment organizations (HTA's) and Advisory Health organizations enables faster decision making and ultimately will bring products to markets faster. These partnerships and work-sharing trends will continue to evolve and grow, potentially pushing the industry to work together in new and exciting ways.

3.3 Evolving Submission Procedures

3.3.1 Increased Rolling Review Practices

ROLLING REVIEWS HAVE BEEN USED FOR YEARS IN SEVERAL JURISDICTIONS using various names, such as Dynamic Regulatory Assessments. Some agencies adopted these practices early like the FDA who implemented it in 2012 to support new legislation with their Fast Track, Breakthrough therapy and Accelerated Approval initiatives. Other agencies implemented it more recently to deliver on expectations from the public for the COVID-19 vaccine approvals.

A rolling review allows drug companies to submit sub-sections of the application and data as it becomes available to share with the agency which enables a faster overall approval process. Today, this process is often only available in emergency or breakthrough therapy situations for serious conditions.

Rolling reviews have been used for COVID-19 vaccine approvals at the EMA and other agencies including Health Canada, who implemented interim orders to enable expedited review practices. It is still unclear how this trend will evolve over the next five to ten years.There are multiple questions that come to mind as we think about the future use of rolling review practices, including:

Questions	Answers
Will rolling reviews become the trend for a broader range of medicinal products?	1 *We believe this is possible. It seems feasible to think that governments will continue to prioritize health emergency use medications, and those critical need or high-demand products such as oncology, biodefense, orphan drugs or breakthrough medications.*
Can data standardization, technology advancements and new policies create opportunities for global agencies to expand this flexible drug approval approach?	2 *We believe yes. However, significant investment and collaboration will be needed, and it will take many years to implement.*
How might this be standardized and how can technology enable easier transition of information and two-way communication?	3 *We have already seen the development and use of more data exchange standards (e.g., FHIR) using relatively new underlying technologies, such as Cloud-based IT infrastructure. We believe these patterns will continue to be applied going forward to support and enable standards-based data sharing using two-way communication.*

How might rolling reviews support simplification of global submissions?	4	*As rolling reviews and similar processes become more common there will be increasing pressure on agencies to harmonize their submission content and filing standards. While agencies will always have significant challenges changing their legal frameworks, the pandemic has clearly demonstrated the benefits of cooperative reviews, which will provide motivation and support.*
How will rolling reviews impact technical requirements such as improved data governance and status tracking?	5	*Currently, rolling review and other shared review processes have a large amount of administrative overhead built in to manage the process. As these become more common, solutions will be sought to streamline that process. This is likely to include improved data governance and status tracking which will ensure the regulatory status of submission content is clear as well as knowing who has reviewed what piece of content.*

3.3.2 Real World Evidence

The expanding use of technology in our world is increasing the availability of relevant information which can support regulatory decision making. This data may be included in a formal submission or may be obtained through a post-market activity. Real world evidence (RWE) currently includes sources like electronic health records, patient-generated data, and data from wearable devices.

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Leveraging real world evidence based on specific study design protocols has been in use over several years and is growing in popularity globally. Currently, most data are buried in PDF documents and summaries making it harder to see global patient outcomes. However, by designing clinical studies leveraging available technology like wearables and tapping into electronic health records to collect a large volume of data, regulators can make better decisions and defend them with more transparency.

WE ANTICIPATE THAT THE SCOPE AND USE OF REAL WORLD EVIDENCE FOR REGULATORY DECISION MAKING WILL CONTINUE TO EXPAND. This information might include non-traditional information beyond what is provided in the sponsor's submissions while providing an opportunity for the analysis of this information to be challenged by the sponsor. This data collection will be supported by emerging practices such as the FAIR data model which is "intended to provide guidelines to improve the Findability, Accessibility, Interoperability, and Reuse of digital assets". Agencies will continue to invest in modernizing their tools and practices to enable greater use of real world evidence.

3.3.3 Changing Submission Pathways and Processes

Another aspect of modernization is how information is being exchanged between sponsors and health agencies. This is also enabling agencies to open alternative methods outside of gateways and eCTD to submit information. We see this with an increased use of portals for information exchange. This is not a new concept (as discussed above) but reflects a continuing trend and there are newer examples such as the EMA's IRIS portal and the European Commission EUDAMED database for medical devices. The use of portals and other alternative pathways is supporting increased data standardization and compliance. This further increases submission quality but also increases pressure for data governance and data asset management.

The use of portals and other alternative pathways is supporting increased data standardization and compliance.

Another new submission pathway being discussed is the *Dynamic cloud* or the *Dossier in the cloud*. This concept started to evolve in 2020 and picked up momentum due to COVID-19. There are some newer initiatives associated with this trend. The first is the Dynamic Dossier in the Cloud project which is a joint venture with academia (including Harvard Medical School), other partners, and the the US FDA, performing proof of concepts on selected selective medication types. The second is Accumulus Synergy, a newly formed non-profit group formed in 2020 which is a collaboration among some large pharma and technology companies, health agencies, and data standards organizations. Their vision is to have a centralized global shared space that is accessed by sponsors and health agencies with the ability to take in continuous data from multiple global sources. They are working towards this goal one use case at a time, with a vision of a full advanced integrated regulatory eco system by 2035.

3.4 Data Standardization and Modernization

Changes in the scientific landscape are driving innovation in drug development, for medications like gene therapies, genomics, and just in time use products. The digitalization of regulatory practices is helping agencies look beyond conventional sources of evidence to support decision making for these new therapies. However, a lot of effort will be required to assess big data sourcing, the quality of these sources, and its application to regulatory review.

On-going efforts like the HMA-EMA Joint Big Data Steering Group will provide a mechanism to assess data sources across the product life cycle; standardize the data landscape, regulatory practices and

policies; and ensure high-quality data to enforce competent evaluation of regulatory submissions. In preparation for this digital transformation, some agencies are actively working on implementing technology modernization plans and data standards strategies to create technical infrastructures that will be able to support the benefits of new technology and polices. Some of those include the US FDA Technology Modernization Action Plan (TMAP), CBER-CDER Data Standards Program Action Plan and EU Data Standards Strategy At the heart of this evolution is structured data.

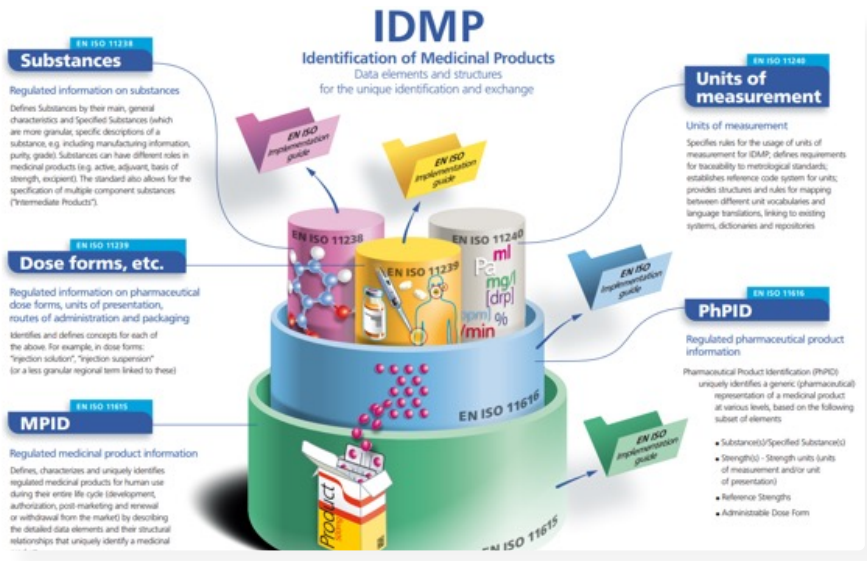
Agencies are actively working on implementing technology modernization plans and data standards strategies.

CRITICAL SUCCESS FACTORS FOR TRANSFORMING DATA INTO INTELLIGENCE INCLUDE identifying data sources, standardizing data, clean-up and migration of legacy data, and management of data. Continuous evolution from electronic documents to structured data is happening and actions plans like the FDA Data Modernization Plan (DMAP) will overhaul the agencies approach to technology and data. In preparation, global agencies must address topics such as assessing the big data landscape from a regulatory perspective, standardizing data with supporting policies, deploying new data systems, enabling consistent and repeatable data practices, digitalization of processes, ensuring data security, investigating new AI technology, analysis capability, and the capacity to guide, analyze and interpret the data.

Even with the perfect conditions for change it takes time to evolve. The evolution of regulatory submission formats explained in section 2.4 and the on-going efforts to implement IDMP are good examples of what typically has been the slow pace of digitalization change in the healthcare industry. Technology continues to offer more advancement, but that is only one piece of the puzzle. Prerequisite work such as data standard definitions, structure, and quality are key elements required as the industry moves towards a data-centric approach to support regulatory submissions and decision making through a product's lifecycle.

THE INTRODUCTION OF THE FIVE ISO IDMP STANDARDS IN 2012 created an internationally accepted framework to uniquely identify and describe medicinal products. This supports a variety of regulatory activities related to the development, registration and lifecycle management including pharmacovigilance and risk management. These standards, and global agency defined controlled vocabularies, are slowly being integrated into RIMS solutions, further supporting structured submission content to agencies. The IDMPstandards are often shown using the "wedding cake" diagram shown here.

ISO IDMP Standards



Source: IDMP

Other initiatives such as the DIA's Regulatory Affairs Community RIM Working Group are developing a RIM Reference model. This framework would aid organizations in structuring the complex matrix of global data identification, ownership, quality management and maintenance and will further support standard data structuring.

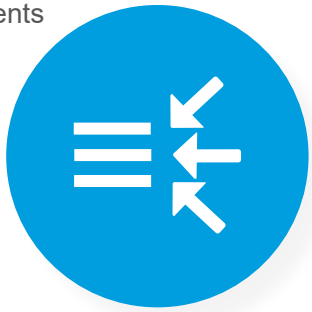
In addition to data standards, increased structure and diversification information exchange methods are being introduced. We anticipate application structure increasing with further adoption of CDISC plus on-going work by the US FDA with the PQ-CMC (Chemistry and Manufacturing Controls). This is further supported by the US FDA's structured regulatory review practices leveraging their KASA (Knowledge-Aided-Assessment and Structured Application) enabling more consistent intelligence sharing and decision making by the regulators.

Source: CDISC Core

Beyond the technical standards, there are organizational changes required to support this modernization. For example, we are seeing an increased emphasis on roles such as Enterprise Data Governance to ensure integrity and quality of corporate data assets supporting product lifecycle and regulatory filings. Data to support a product through its lifecycle is critical and is typically produced by many groups, both internal and external. The data must be properly managed to be fit for purpose (e.g., Strategic, Organizational, Regulatory, Legal, Environmental, or Risk Management). Properly structuring an organization to manage its data is a key success factor in being able to move into a more structured data submission format, and support the technology that will enable the exchange of information.

3.5 Summary

The COVID-19 pandemic has identified opportunities for improvements in global regulatory frameworks. Some of these opportunities are process-related such as rolling reviews and joint agency collaborations. Others are more technology driven, such as the increased use of structured data, diverse data sources, and increased use of cloud platforms to simplify content exchange.



THESE TRENDS ALL REFLECT THE NEXT STAGE IN THE EVOLUTION OF SUBMISSIONS, WHICH WE REFER TO AS DYNAMIC SUBMISSION MANAGEMENT. They should not be viewed as isolated events, but as extensions of the historical trends described earlier which now support or build on one another to create a new modernized regulatory framework. This is unlikely to occur as a "big bang" singular solution, but rather as an iterative collection of improved solutions, many of which are dependent on the other foundational changes described above. All of this is to achieve the larger goal of bringing medicines to patients faster by supporting more dynamic collaboration.

4. Dynamic Submission Management

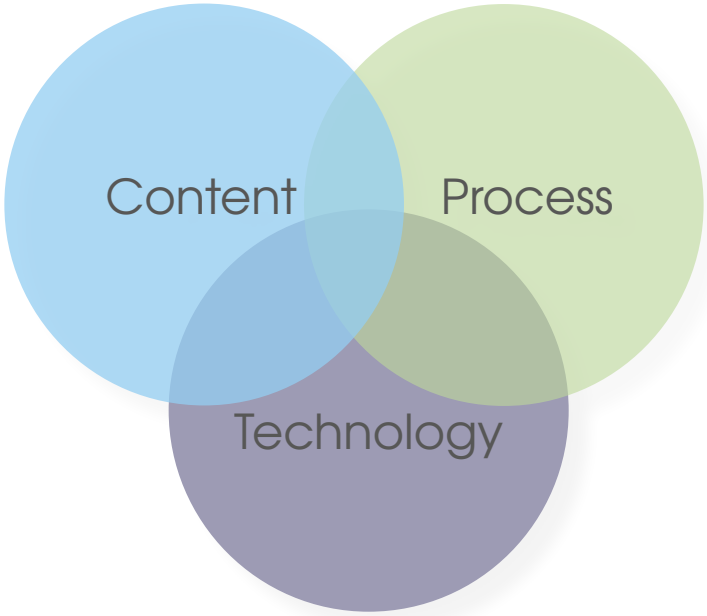
The trends and drivers discussed above reflect the start of an exciting journey ahead in the evolution of submissions. It is expected that more flexibility will be required to deal with changes to the scientific landscape and innovative drug development. We believe the industry is moving towards what we describe as Dynamic Submission Management (DSM). The key word "Dynamic" is critical in explaining the variety of ways the healthcare industry will adapt to future digital transformations, increased structured data and content, secure information exchange, and submission filing process changes.

4.1 Defining DSM

We envision DSM as a collection of processes and supporting technical capabilities which covers the entire lifecycle of Submission Management from product conception to end-of-life, and is flexible in terms of content and process. We will proceed to discuss what DSM is, how it will be applied, and the impact on various stakeholder groups. We will then discuss the anticipated timeline for this and various challenges and opportunities.

DSM is a collection of processes and supporting technical capabilities which covers the entire lifecycle of Submission Management from product conception to end-of-life, and which is flexible in terms of content and process.

THE ENVISIONED CHANGES FROM DSM OCCUR IN THE OVERLAPPING AREAS OF PROCESS, CONTENT, AND TECHNICAL CHARACTERISTICS. We can use this pattern to help organize and develop the DSM attributes including the new approaches and capabilities, based on the trends discussed above. These characteristics will be applied to more specific scenarios by key stakeholder groups.



4.1.1 Content

In this section we will cover DSM characteristics related to the content, format, and structure of the submission-related materials.

More submission content will be based on standardized structured data as opposed to prose text. Data will be increasingly interpreted using advanced modeling and visualization tools including systems using Artificial Intelligence (AI) and Machine Learning (ML). Documents which can be standardized such as clinical study reports, will increasingly use consistent formats and structured content to gradually improve both the creation and review processes.

Reviewers will more often use non-submission provided data, such as sponsor source data, real world evidence, post-market, and other related materials as opposed to relying mostly upon content in the specific submission being reviewed.

All organizations will increase their use of metadata metadata to manage documents and other regulatory content. This metadata will progressively move from being manually verified text to relying on CV-based content to ensure clarity, accuracy, and global shareability.

4.1.2 Process

In this section we will cover DSM characteristics related to the processes being used by various parties. This is primarily driven by the agencies, but of course other stakeholders will need to adapt their processes in order to comply.

Submissions will move away from being mostly monolithic point-in-time to an increasing use of incremental or partial filings. More regulatory activities may occur in parallel, with multiple concurrent activities requiring multiple filings.

Submission related processes will become shared across multiple stakeholders including agencies, industry, and other organizations including academia, Contract Research Organizations (CROs), and consultants.

Organizations will use improved Data Asset Management and Quality Governance to manage the increased complexity.

4.1.3 Technology

In this section we will cover DSM characteristics related to the technology being used to support the content and processes.

Data storage and computing platforms will move towards shareable Cloud-based models as opposed to mostly local and private. This pattern is already apparent in many areas and will be used to support secure collaboration models, providing better opportunities for smaller and diverse organizations.

Improved content management and workflow capabilities will be required to ensure the basis of legal decisions is always consistent and clear to all stakeholders.

Advanced data management capabilities, from full-text search to AI/ML, will provide opportunities for improved review but provide challenges for quality and permissions management as well as validation and auditability.

4.2 Applying DSM

This section will explore what we anticipate Dynamic Submission Management will mean to different stakeholder groups based on customer insights, industry trends, and technology needs.

4.2.1 DSM for the Regulators

We see the regulators as the primary enablers of changes in the DSM evolution. While the industry is shaping and influencing, the regulators will control and enable the supporting process and legislative framework to implement many of the key DSM aspects and achieve the broader benefits. The following list illustrates drivers for DSM modernization within the regulator's world:

- **Increased international agency collaboration:** DSM technology and processes will allow for secure information exchange and effective cross-agency work-sharing practices. For example, we would anticipate further improvements to Access Consortium and Project Orbis submission approval practices, and the development of similar initiatives.

- **Faster product to market via parallel activities and rolling review practices:** DSM technology and processes will better support parallel submission activities and the ability to submit sub-sections of an application to reduce approval times.

- **Increased investment in technology and data standard modernization:** DSM will enable consistent use of data standards and modernization of technology platforms to support faster decision making. For example, further development and implementation of action plans such as the US FDA's Data Standards Program Action Plan and Technology Modernization Plan.

- **Increased opportunity for applying data intelligence:** DSM will improve access to regulatory data to enable advanced tools and processes, such as artificial intelligence and machine learning to create opportunities for faster regulatory decisions. For example, greater use of Real World Evidence (RWE), along with improved regulatory decision support and post-market intelligence.

4.2.2 DSM for the Industry Sponsors

Implementing DSM technologies will require significant investment and effort. Larger pharma companies with big portfolios and global presence will benefit the most from the DSM evolution, due to the economies of scale. However, all sponsor companies can benefit by leveraging the consistent data standards and processes to allow them to expand to additional markets at a lower cost. Ideally, the legislative changes required to support DSM modernization will also lead to opportunities to improve regulatory support for new classes of innovative therapeutic products. The following list illustrates drivers for DSM modernization within the sponsors' world:

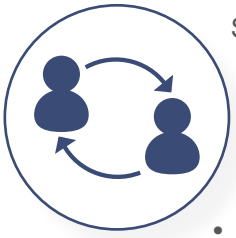
- **Increased opportunities to lower costs, leverage content re-use and improve time-to-market:** DSM technology, processes and consistency in data formats will better enable content re-use and increase efficiencies to support global dossiers.

- **Increased collaborations and partnerships:** DSM technology and processes will better enable collaboration between companies, technology, and academia to develop and manufacture products faster. To illustrate this, we would expect to see more collaborative product development, similar to the Pfizer BioNTech collaboration which led to a COVID-19 vaccine.

- **Leveraging global data transparency to support product development and decision making:** DSM technology and processes could enable integrations to support transparency of non-clinical and clinical data via common technology and company partnerships. We are already seeing early examples of this in Transcelerate's DataCelerate solution.

- **Data management governance to support increased structured submission formats:** DSM technology and processes will support improved data asset management across the full product lifecycle. We are seeing early examples of this in some RIMS-type products; however, we expect this to be improved and become more pervasive.

4.2.3 DSM for Service Providers



Service providers such as CROs, third-party publishers, and API manufacturers, often perform the same regulatory activities as industry organizations. However, in addition they must perform these activities as agents for multiple organizations which creates unique requirements. The following list illustrates drivers for DSM modernization within the service providers' world:

- **Enhanced data governance:** DSM technology and processes will need to enable a secure and flexible structure to manage a high volume of various client data, with the ability for secure and selective sharing across organizations.

- **Flexible offerings and functionality:** DSM technology and processes will need to support evolving variations of submission filing, including non-classic review processes, and new standards. As agents for global sponsors, vendor organizations must stay abreast of a wide range of evolving submission requirements and technologies, which will be more challenging in a DSM environment.

- **Support various secure and transparent exchange platforms:** DSM technology will enable exchange of content and data, including sponsor-to-agency and agency-to-agency as new DSM practices become more popular. Service providers will need to integrate into these exchanges on behalf of their clients, for instance supporting multiple platforms and tracking regulatory status and activities.

4.2.4 DSM for all Stakeholders

While most of the characteristics described will apply to all stakeholders to some degree, others are clearly common to all. The following list illustrates drivers for DSM modernization amongst all stakeholders:

- **Flexible integration capabilities:** DSM technology, standards and global practices will enable flexible options to integrate with technology solutions to support the full product lifecycle.

- **Flexible application of data standards:** DSM technology will support evolving global data standards to support the full product lifecycle. This will include not only the standards themselves, but also regional variations, whether controlled vocabulary choices, implementation technology differences, or other differing interpretations of how the standard is to be used.

- **Modern use of automation, artificial intelligence, and machine learning:** DSM technology will apply evolving AI and machine learning capabilities. These intuitive algorithms will leverage structured and unstructured content (primarily data) to support regulatory decision making.

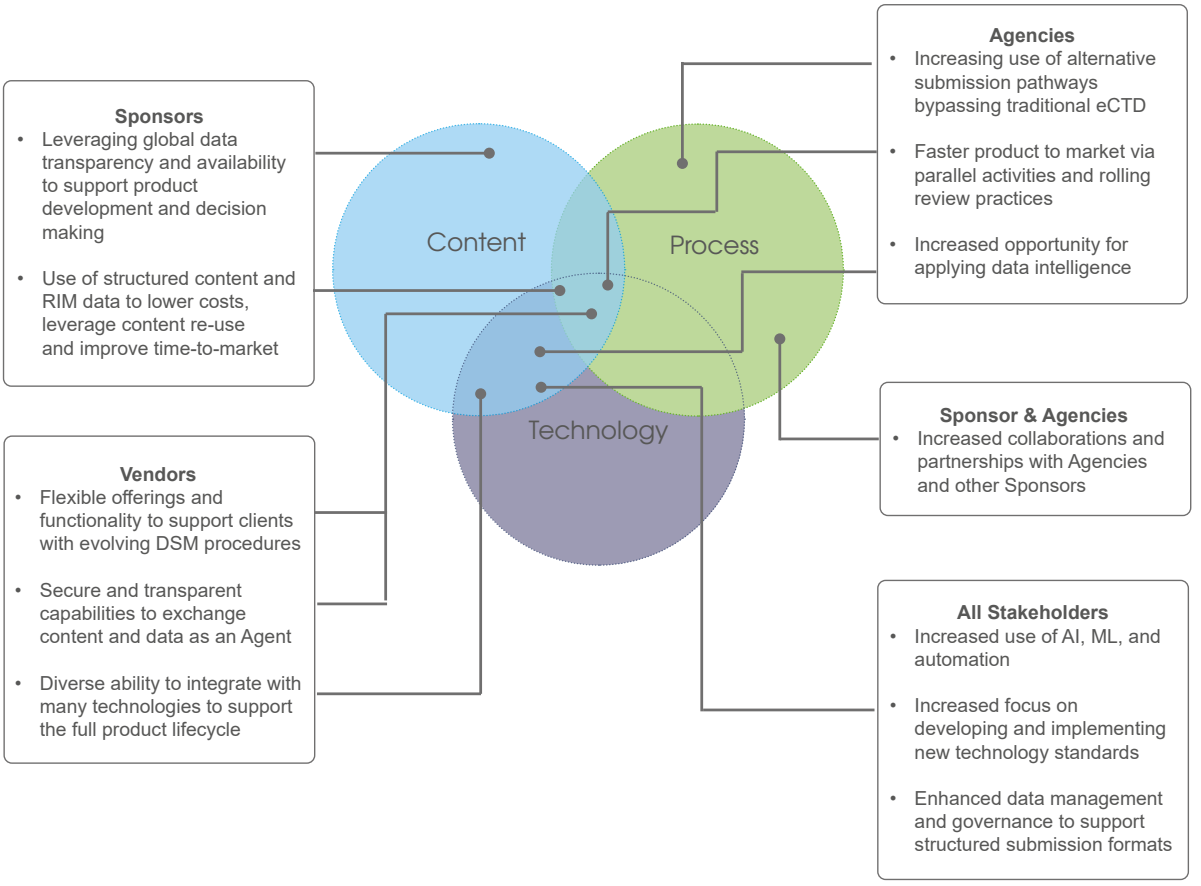
- **Enhanced data reusability:** The improved data management and governance characteristics of DSM-enabled RIMS systems will enable a lower level of granularity of reusable content and data, as well as improved intelligence regarding how and where the data has been applied. Today we often see reusability at a document level. Going forward DSM will enable more reusability of individual data points, while tracking usage.

- **Data compliance and validation:** DSM technology will enforce compliance and validation of data against published regulatory authority rules and guidelines.

- **Cost effective ways to keep up with technology modernization:** All of these new trends will require seemingly endless changes to underlying technology and systems. While larger organizations may have the ability to "keep up", many others will have challenges and will need standardization, sharing, and economies of scale to enable them to keep pace.

The following diagram summarizes these DSM drivers and characteristics. We have provisionally positioned them according to our Content-Process-Technology pattern as well as stakeholder impact or interest.

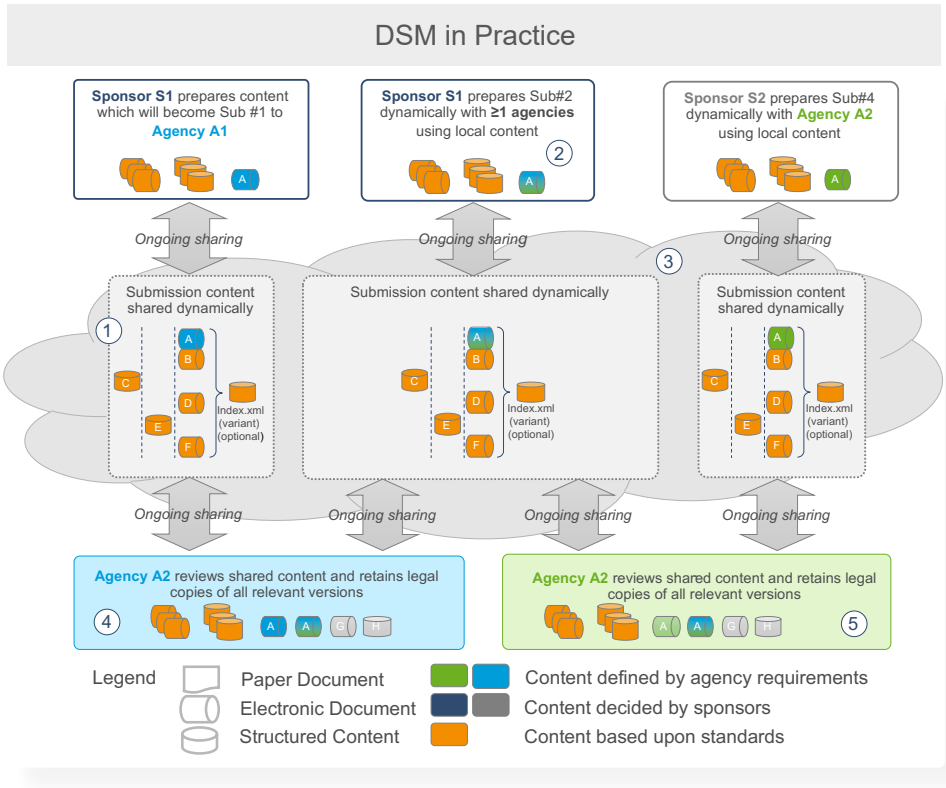
DSM Drivers, Characteristics, and Stakeholder Interests



4.2.5 DSM in Practice

In combination, these new DSM characteristics enable different regulatory practices to what are commonly used today. As discussed above, many of them are already happening to some extent somewhere in the regulatory arena. We would also expect many, if not most of, the existing processes to still be active for an extended period while DSM is established (see updated Timeline below).

The following diagram illustrates DSM in practice using a variation on the scenarios used earlier in chapter 2. 0As before, there are two sponsors (**S1** & **S2**) preparing “submissions” for two different agencies (**A1** & **A2**) involving three separate products (P1, P2 & P3). The scenarios use dashed streams to indicate parallel or incremental filings.



As seen in the diagram:

1. **Submission structures will be standards-based however they may be assembled on-the-fly** as opposed to being built in advance. Also, different agencies may use different standards or have slightly different implementations. An example is CV usage, which will be very prevalent but agencies may occasionally differ on which CVs are used for the same purpose except where there is a joint agency review. Note that the dashed lines (swim-lanes) are intended to denote incremental sharing of content over time.

2. **Submission content will be primarily standards-based, structured, and electronic**, with even scanned images being limited to necessary documents, such as certain clinical trial records or legal materials. Agency-specific content will decrease and some agencies may even agree to harmonize their specific content. This provides many opportunities for efficient content reuse.

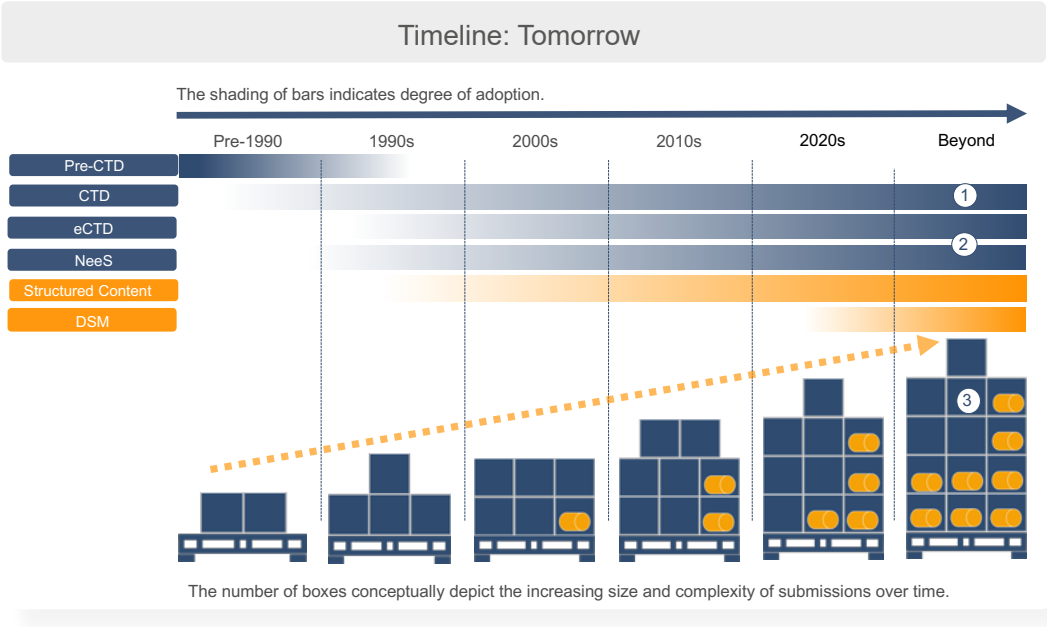
3. **Submission content will be sent to (or shared with) one or more agencies piece-by-piece** based upon pre-determined agreements. Object-level versioning, permissions management, and access security will be critical to ensure the correct content is only visible to the correct persons at the correct stage of the process.

4. **Structured content will be increasingly common**, with even some supporting text being semi-structured (e.g., SPL). The CTD structure will remain useful as an organizing structure but eCTD (and its associated lifecycle) may eventually be replaced by more flexible FHIR-type messages.

5 **Agencies will increasingly make use of other relevant content for review,** (i.e., from beyond the "official" submission) including other MA submissions, external "real-world" data, other agency content, post-market reports, etc.

4.3 DSM Timeline

How does the advent of DSM impact our timeline? The following diagram extends the previous one in section 2.5.



As shown in the diagram:

1 **The fundamental CTD structure will continue** to be used as the baseline ToC for the foreseeable future. How this is managed, and the format of the content within will continue to evolve.

2 **Whether eCTD will survive long-term is debatable.** eCTD took a long time to become fully accepted, reflecting the many legal and business challenges to its adoption. However, going forward, eCTD may well be replaced by other more flexible message structures such as FHIR. This is true even for eCTD4 given the limitations of the complex lifecycle and sequence-based versioning. We expect NeeS will survive for a longer time due to its simplicity and low barrier to use.

3 **Structured content will become the primary format,** as we go from "prose with supporting data" to "data with supporting prose." Where the early submissions were primarily unstructured text (prose) with some tables or images of data, future submissions will be mainly structured content (including data), linked with a minimum amount of prose to establish context, tell the story, and hold the ultimate submission together.

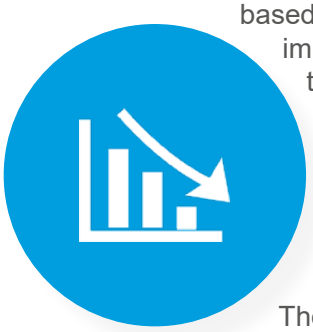
4.4 DSM Opportunities and Challenges

4.4.1 Opportunities

DSM provides many opportunities, in terms of efficiency, risk-reduction and accessibility. These can lead directly to improved market access and timing and support improved global access to medication.

The efficiency is provided by increased shared content (including RIM), more flexible communications and automated processes, and faster reviews. This in turn leads to the possibility of faster overall time-to-market and potentially lower regulatory costs.

The risk-reduction opportunity comes from broader content usage, data transparency, joint reviews and the use of advanced data management tools such as AI and rules-based analysis. This will hopefully improve public confidence in the regulatory process as drugs move from relatively simple chemistry to advanced genome-based therapies aimed at small population subsets.

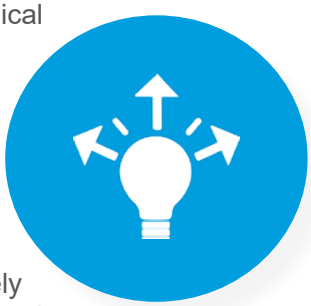


The accessibility aspect is exemplified by the use of cloud-based technologies and shared review procedures. While some agencies already work together to share resources, these changes will reduce the barriers further and increase this trend.

There is also an opportunity to apply DSM processes and supporting technologies to improve the overall transparency of regulatory activities. Increasingly, accelerated regulatory processes are being used to deliver novel therapies to the market more quickly, such as mRNA vaccines. Having a transparent process with systems-based data may help to alleviate some of the public concerns which arise.

4.4.2 Challenges

While there are some technical challenges in DSM, we anticipate the primary challenges to be on the business side. This will include harmonization and implementation of new data standards and key processes but will largely consist of the challenges faced by each agency to officially change their core procedures, which may even require legislation which is complicated and time-consuming.

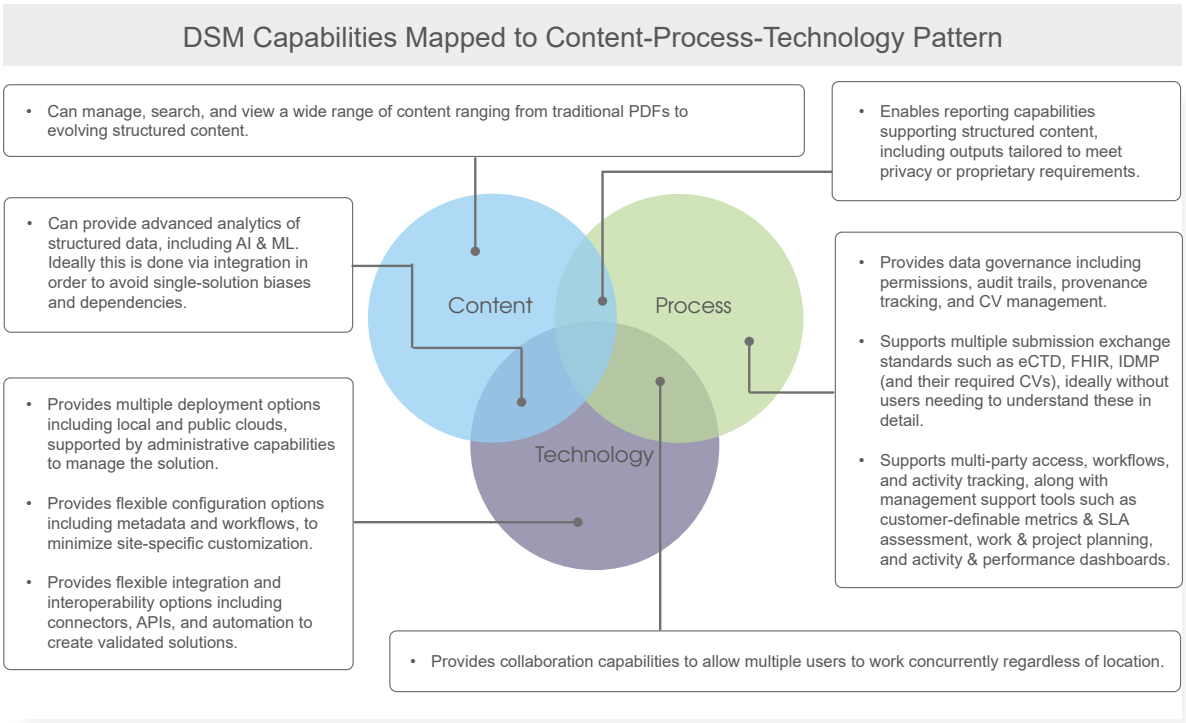


Getting agreement on what to do will also be challenging in a global political context. It is quite possible that some regions will not want to adopt standards developed elsewhere. One way to mitigate this is to, wherever possible, involve broader communities as early as possible but this has its own challenges in terms of logistics, languages, etc. Industry may well have a significant role to play in terms of encouraging adoption of global DSM standards.

We do see that the recent pandemic may provide opportunities for many agencies to begin to have these discussions, as the global experience has clearly demonstrated the benefits of the changes discussed above. It is quite possible that the new DSM changes will initially be restricted to certain areas of need (e.g., vaccines), or specific processes (e.g., joint reviews). We still believe that these challenges can and will be met, and that DSM will be widely-used and become the de facto method for most pharmaceutical regulation.

4.4.3 Solutions

The diagram below provides an initial list of DSM solution capabilities. While most reflect technology-based solutions, we have done a preliminary organization in terms of where they could fit in terms of our Content-Process-Technology pattern.



5. Conclusion & Next Steps

5.1 Summary and Perspectives

We have shown in chapter 2 the historical trend towards increased size, complexity, and standardization of regulatory submissions. There is also a clear move towards increased submission of structured content, whether data or text. In chapter 3 we have identified a wide variety of activities involving agencies and industry which are driving these changes from a business perspective. Finally, in chapter 4 we have defined and illustrated this pattern as the emerging area of Dynamic Submission Management. We have described the characteristics, impacts, timelines, and challenges of this exciting new concept.

We recognize that there are inevitably different views of yesterday and more trends of today than what we have included here. However, we feel that the points presented are representative of key factors influencing the decisions for tomorrow. We believe that they provide a basis for a reasonable concept of what the future could look like.

We have discussed this paper and our DSM perspectives with some industry thought leaders to get their views. We would like to thank them for their comments which are included below.

> *In the last decade, all regulatory stakeholders have seen continuous improvements in IT approaches for submission processing and evaluation practices. Unfortunately, this leads to new process and technical requirements, which often require a legal background to implement. It takes time to adapt to these new approaches and therefore has an initial burden on industry, requiring a constant investment into infrastructure, technology, and training.*
>
> *As we work in a collaborative way to develop common European procedures, we should also work towards international standards supporting a global harmonised regulatory environment. The availability and exchange of important information in a structured format will pave the way to more patient safety worldwide. The pandemic situation has shown us the importance of communicating on a global level.*
>
> ***Dr. Andreas Franken German Medicines Manufacturers' Association (BAH)***

> *LORENZ continues to share their thought leadership by reviewing the past 20 years to set the context for the near and longer term future as submission management transitions from a static to dynamic model. They intertwine the regulatory shift from documents to data, growing product development collaboration, and health authority evolution to rolling submissions and data standards which requires advanced data management. A must read for Regulatory and IT professionals.*
>
> ***Steve Gens, GENS & Associates Inc.***

> *Health Products and Food Branch at Health Canada has a number of initiatives underway looking at how we can better enable international collaboration through modern technologies and standards. We are excited to be working closely with LORENZ on DSM capabilities to support structured product monographs and implementing a cloud-based web environment, leveraging LORENZ's docuBridge product, to support collaborative reviews through the ACCESS Consortium.*
>
> ***Shannon Laforce, Health Canada***

> *The paper provides an excellent overview of the evolution of submissions and introduces the ambitious dynamic submission management; a future that includes 'structured data for advanced internal analysis,' projected by the industry and by (and between) Health Authorities. The paper focuses on the next steps after 'electronic paper eCTDs' with an excellent overview of structured content process, evolving submission procedures, recognizing that 'current approaches are typically fragmented.'*
>
> *As per the paper, COVID-19 has propelled an exciting revolution in collaboration for a global regulatory framework that necessarily opens doors for dynamic submission management. I believe the speed of change/evolution is directly proportional to the demands of Health Authorities, patients, and sponsor companies. We have seen an amazing acceleration in working differently induced by the recent pandemic for speed of medicines reaching patients. We could go backwards, or events may propel us to better deliver on patient expectations for data exchange, transparency and delivery in unexpected and revolutionary ways.*
>
> ***David Ross, AstraZeneca***

> *In the past, communication and collaboration was always time-consuming, resource-intensive, and slow. Today, we are moving towards centralized solutions and European regulations for the benefit of research, patients, and healthcare professionals. The new Clinical Trials and Veterinary Regulations are examples of the way forward: centralized cloud-based systems covering the entire lifecycle of a medicinal product which supports innovation and research as well as collaboration between regulators and industry partners/sponsors.*
>
> *The Covid-19 pandemic has shown us the advantages of using cloud services within the regulatory environment. This shift allows us to go back to our roots: Scientists can focus on their work, and a fast and intense collaboration between all parties – including regulators, academia, and industry – is easier than ever thanks to the advantages of using cloud services.*
>
> ***Harald von Aschen, BfArM***

> *A cloud-based regulatory framework for submission management would enable a dynamic and more fluid exchange of information between industry and regulators allowing agencies to perform more sophisticated analysis across disparate studies, applications, and reviews. Dynamic practices that create opportunities for data exchange in real-time could help us learn about new diseases faster and approve treatments faster.*
>
> ***Dr. Max Wegner, Bayer AG***

5.2 Next Steps and Closing

Organizations that want to participate in this evolution should get involved with related initiatives. This involvement will improve overall DSM visibility and helps to develop common language, standards, use cases, issues, acceptance, etc. There are many choices but for most organizations we believe it is better to be more involved with a small number of initiatives rather than try to keep up with all of them. There will be different specific opportunities and challenges with each, but the larger trends and opportunities will be seen in most of them. There may also be consideration given to selecting technology solutions which are well positioned to meet future DSM needs.

For most organizations we believe it is better to be more involved with a small number of initiatives rather than try to keep up with all of them.

We would especially encourage smaller organizations to get involved, including agencies and industry stakeholders. While some of the DSM evolution will inevitably be defined by the larger organizations we feel the smaller players need to be involved. This will help to ensure maximum benefits for everyone, especially the patients who are benefitting from improved medications and treatments.

We have initiated some thoughts based on where we believe we are today. Many ideas will evolve over the next few years, as we observe global agencies and organizations digest the learnings and opportunities accelerated through the COVID pandemic response.

5.3 Contact LORENZ

LORENZ is excited as we move forward, evolving our products towards a DSM evolution and we look forward to traveling with you on this journey. We would love to explore DSM further with you. Please feel free to contact us so we can exchange ideas and strategies. We have included a link below for easier convenience or send a note to dsm@lorenz.cc.

Click here to contact us

6. Additional Information

6.1 People

6.1.1 Authors

Lorelle Leonienco, PMP
Corporate Development and Account Manager at LORENZ Life Sciences Group

Lorelle has been with LORENZ for the last five years. In her current role she supports product strategy insights and agency account and project management activities. Over her 17 years of experience within large global brand and generic pharmaceutical companies, she has held various roles supporting and leading transformational business changes. Starting early in her career she supported the global implementation of a LIMS system, modernizing paper processes to compliant technology practices to further drive efficiencies within commercial release and R&D laboratories. In following years, she spent time in clinical project management and IT project management delivering on various technology improvements across Regulatory Affairs, Medical Affairs, Clinical and other R&D functions.

Charles Mathis
Requirements/Solution Engineer, LORENZ Life Sciences Group

Charles has worked in different roles for LORENZ at intervals since 2007, including QA and Development roles. He is currently a solutions architect consulting primarily on agency needs and internal product architecture. He has worked in various types of regulated environments since 1989 and designed and implemented his first electronic regulatory filing system using structured content in 2003. He participated in the early implementation of FDA's SPL and designed a supporting authoring system. In addition, he has been IT Manager for a regulatory agency and a Senior Enterprise Architect with a major Canadian bank. In his spare time, he likes to sing with his champion Barbershop chorus, the Toronto Northern Lights.

6.1.2 Thought Leaders

We are grateful to the following people for their insights on the topic of DSM.

- **Dr. Andreas Franken**; Member of Working Groups M8 (eCTD) and M2 (ESTRI) at ICH-International Council for Harmonization and ISO TC 215 (Health informatics), German Medicines Manufacturers' Association, Bonn (BAH)
- **Steve Gens**; Managing Partner & Founder, Gens & Associates Inc.
- **Shannon Laforce**; Executive Director, Transformation and Business informatics, Resource Management and Operations Directorate (RMOD), Health Products and Food Branch (HPFB), Health Canada
- **David Ross,** Director Global Regulatory Operations (RIM), Strategy and Change Management, AstraZeneca. GSO IRISS Lead, PhRMA IT Knowledge AZ
- **Harald von Aschen**; IT, Research & Development, Strategic Planning, Federal Institute for Drugs and Medical Devices, Germany (BfArM)
- **Dr. Max Wegner**; Senior Vice President, Head Regulatory Affairs Bayer AG

6.2 Organizations

The following list of organizations are either referenced in the document or may have a role to play in DSM development. The list should not be considered complete.

6.2.1 Regulators / Health Authorities

- Austria (AT), Agency for Health and Food Safety (AGES↗)
- Australia (AU), Therapeutic Goods Administration (TGA↗)
- Brazil (BR), Brazilian Health Regulatory Agency (Anvisa↗)
- Canada (CA), Health Canada/Santé Canada↗
- China (CN), National Medical Products Administration (NMPA↗)
- Czech Republic (CZ), State Institute for Drug Control (SUKL↗)
- Europe (EU), European Directorate for the Quality of Medicines & HealthCare (EDQM↗)
- Europe (EU), European Medicines Agency (EMA↗)
- Germany (DE), Federal Institute for Drugs and Medical Devices (BfArM↗)
- Germany (DE), Paul-Ehrlich-Institut (PEI↗)
- International Coalition of Medicines Regulatory Authorities (ICMRA↗)
- Ireland (IE), Health Products Regulatory Authority (HPRA↗)
- Japan (JP): Pharmaceuticals and Medical Devices Agency (PMDA↗)
- Poland (PL), Office for Registration of Medicinal Products, medical Devices and Biocidal Products (URPL↗)
- Singapore (SG), Health Sciences Authority (HSA↗)
- Slovenia, Republic of (SL), Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP↗)
- Switzerland (CH), Swissmedic↗

- United Kingdom (UK), Medicines and Healthcare Products Regulatory Agency (MHRA↗)
- Thailand (TH), FDA Thailand (TFDA↗)
- United States of America (US), Food and Drug Administration (FDA↗)
- World Health Organization (WHO↗)

6.2.2 Other Organizations

- Accumulus Synergy↗
- Clinical Data Interchange Standards Consortium (CDISC↗)
- Drug Information Association (DIA↗)
- Health Level Seven International (HL7↗)
- International Council for Harmonisation (ICH↗)
- International Organization for Standardization (ISO↗)
- Regulatory Affairs Professionals Society (RAPS↗)
- TransCelerate↗

6.3 References and Additional Reading

This section is organized based upon the structure of the main document. These links are either referenced or considered as useful additional information.

6.3.1 Evolution of Regulatory Submissions

- Artificial Intelligence (AI↗)
- Common Technical Document (CTD↗)
- Drug Application Methodology with Optical Storage (DAMOS↗)
- Electronic Common Technical Document (eCTD↗)
- EMA; Electronic Product Information (ePI↗)
- EMA; Extended EudraVigilance medicinal product dictionary (xEVMPD↗)
- Health Canada; Implementation of SPL via XML Product Monograph (XML PM↗)
- Health Canada; Regulatory Enrolment Process (REP↗)
- HL7; Fast Healthcare Interoperability Resources (FHIR↗)
- HL7; Structured Product Labeling (SPL↗)
- Identification of Medicinal Product (IDMP↗): a collection of five ISO standards.
    - MPID – Medicinal Product Identification (ISO 11615↗)
    - PhPID – Pharmaceutical Product Identifier (ISO 11616↗)
    - SubID – Substance Identification (ISO 11238↗)
    - Dosage Form and Route of Administration (ISO 11239↗)
    - UoM - Units of Measurement (ISO 11240↗)
- Japan eCTD: The implementation of eCTD in Japan↗ (2011) by Hiroji Emoto and Masami Tamura.
- Japan eCTD 4.0: The Japanese eCTD and electronic submissions↗ (2016) by Masami Tamura and Hiroji Emoto.
- Journal of Pharmaceutical Sciences, Volume 109, Issue 4, April 2020↗. Transitioning Chemistry, Manufacturing, and Controls Content With a Structured Data Management Solution: Streamlining Regulatory Submissions. Algorri, Cauchon, Abernathy.

- Market Authorization (MA↗): An approval to market a medicinal product, typically associated with a single market / region.
- Machine Learning (ML↗)
- National Competent Authorities (NCA↗): within Europe, organizations that have the legally delegated or invested authority, or power to perform a designated function, normally monitoring compliance with the national statutes and regulations.
- Non-eCTD Electronic Submissions (NeeS): A generic term for a variety of electronic submission types which usually have an XML-based index file but generally do not have the complex metadata or lifecycle used in eCTD. This link↗ is illustrative of NeeS usage for European markets.
- Structured Content: Early definition and discussion (c. 2010) by Rockley Group↗
- US FDA; Electronic Submission Gateway (ESG↗). Also used by Health Canada since 2013 and called Common Electronic Submission Gateway (CESG↗) in that context. The European Medicines Agency (EMA) also has several gateways↗.
- US FDA; Global Substance Registration System (GSRS↗).
- US FDA; Implementation of SPL resources↗. Also see DailyMed↗.
- US FDA; Prescription Drug User Fee Act (PDUFA↗)

6.3.2 Global Health Agencies Collaboration

- Access Consortium: A group of agencies (AU, CA, CH, SG, UK ↗) collaborating on selected regulatory approvals.
- EMA; Covid-19 response↗; Working with EU and international partners
- EMA; Cooperation↗ with Health Technology Assessment (HTA) organizations
- EMA OPEN↗: An agency collaboration pilot project which includes non-European agencies.
- EMA; Parallel↗ consultation with regulators and HTA organizations
- Health Canada's regulatory response to Covid-19: International engagement↗
- Health Technology Assessment organization (HTA↗)
- US FDA Project Orbis: A group of agencies led by the US FDA collaborating on selected oncology product review.

6.3.3 Evolving Submission Procedures

- Dynamic Dossier in the Cloud: A Sociotechnical Architecture for a Real-Time and Metrics-Based Data Tracking System with Gene and Cell Therapies as a Case Study; SpringerLink↗, October 2020
- Dynamic Dossier in the Cloud: NEWDIGS Jan 2019↗ publication
- Drug Discovery Volume 19, June 2020↗; Cloud-based data systems in drug regulation: an industry perspective
- EMA; Electronic Product Information (ePI↗)
- EMA; IRIS Portal ↗
- European Commission↗; European Database on Medical Devices (EUDAMED)
- EMA; Use of Rolling Review↗ for covid-19 vaccine
- FAIR data principles↗
- Health Canada; Interim orders↗: Authorization pathways for covid-19 drugs and vaccines
- Orphan Drugs↗: a pharmaceutical agent developed to treat medical conditions which, because they are so rare, would not be profitable to produce without government assistance. The conditions are referred to as orphan diseases.

- Real World Evidence (RWE↗): evidence obtained from real world data, which are observational data obtained outside the context of randomized controlled trials and generated during routine clinical practice.
    - Real World Evidence, Health Canada: Optimizing the Use of Real World Evidence↗ to Inform Regulatory Decision-Making
    - Real World Evidence, US FDA: Use of Real World Evidence↗ to Support Regulatory Decision-Making for Medical Devices
- US FDA; Rolling Review and Accelerated Pathways↗ (Fast Track, Breakthrough, Accelerated)

6.3.4 Data Standardization and Modernization

- DIA; RIMS Reference Model Working Group↗
- Digitization, Digitalization & Digital Transformation. Forbes ↗ April 29, 2018.
- EMA; DADI (Digital Application Dataset Integration (DADI↗)
- EMA; European medicines agencies network strategy ↗ to 2025
- EMA; IDMP↗ implementation (SPOR↗)
- European Commission; Turning FAIR Data into reality↗
- HMA-EMA; Joint Big Data Steering Group↗
- Journal of Pharmaceutical Sciences; October 2, 2021↗; The Future of CMC Regulatory Submissions: Streamlining Activities Using Structured Content and Data Management
- RAPS; Article November 2021↗; FDA taking incremental approach to launching KASA (Knowledge-aided Assessment and Structured Application) reviews
- US FDA; CDER Data Standards Program↗
- US FDA; Data Modernization Plan (DMAP↗)
- US FDA; Data Standards Program Action Plan↗
- US FDA; IDMP implementation↗
- US FDA; Technology Modernization Action Plan (TMAP↗)

6.3.5 Dynamic Submission Management

- Contract Research Organization (CRO). A life sciences company that provides support to the pharmaceutical, biotechnology, and medical device industries in the form of research services outsourced on a contract basis. This Forbes article from April 2021↗ gives a perspective on CROs and where they are going.
- Pfizer/BioNTech; COVID-19 Vaccine partnership↗
- TransCelerate; Toxicology Data Sharing↗

6.3.6 Graphic and Image References

- Access↗ Consortium logo
- CDISC Core↗ logo
- CTD Triangle
- ICRMA↗ logo
- ISO IDMP↗ Standards
- Project Orbis ↗ logo

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