Outlook into the Evolution of eCTD

Tim Powell - Director, Submission Sciences

17-Oct-2025

Introduction

- Chair of EFPIA eCTD Subgroup
- Industry SME in EU eCTD v4 Implementation Group
- PhRMA Regulatory IT Member
- ICH M8 EFPIA Deputy Topic Lead

The views and opinions expressed in the following slides are those of the individual presenter and should not be attributed to Biogen, its directors, employees, contractors, vendors, affiliates or any organization with which the presenter is affiliated.

Introduction

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- Industry SME in EU eCTD v4 Implementation Group
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Agenda

- A Brief History of eCTD v4
- Current Challenges and Opportunities in Regulatory Submissions
- Evolution and the Future of eCTD
  - Cloud Submissions
  - ICH Initiatives (M2/M8, SPQS, M4Q(R2), PQKM)

eCTD v4 History

- In 2005 FDA began a new project using Health Level Seven (HL7) to develop a next-generation submission format.
- eCTD v4, also known as NMV (Next Major Version) / RPS (Regulated Product Submissions) / HL7 v3 was approved by ICH to Step 4 in 2015
- PMDA (Japan) piloted first in 2021 and started to accept eCTD v4 in 2022 (mandatory in 2026)
- FDA (US) piloted in 2022-2023 and started to accept eCTD v4 in 2024 (mandatory in 2029)
- EMA (EU) pilots started late 2024 and are ongoing. Anticipate optional acceptance of eCTD v4 in late 2025 (MAAs only)
- Technical pilots expected in 2026 for Swissmedic, TGA & Health Canada

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Why did ICH implement eCTD v4.0 instead of continuing to update eCTD v3.2.2?

- Consensus decision across all parties in ICH M8 (Regulators and Industry Associations) in 2019 to continue with implementation of eCTD v4.0
- eCTD v3.2.2 is hardcoded and cannot be responsive to changes in the CTD (i.e., requires a DTD update)
- The primary focus is the implementation of eCTD v4.0 across all regions to incorporate new requirements instead of adding them to the existing eCTD v3.2.2
- The implementation of eCTD v4.0 has already started in major regions and is ongoing
- Updates for the regional implementation plans and timelines are available at the ICH website
- Implementation of eCTD v4.0 is the foundation for future developments and enhancements to eCTD
- ICH M8 agreed to defer all CTD changes to eCTD v4.0 implementation. Any new requirements are incorporated into eCTD v4.0 e.g., ICH M4Q(R2)

What are the most meaningful benefits of eCTD v4.0?

- **Document reuse**, this allows reuse of content (via UUIDs) across applications, independently of how submissions are stored at the agency. Allows ability to reuse data across different applications and regulatory bodies significantly reduce redundancy and workload on the regulators' and industry's side
- Updates on process and specification are managed via **controlled vocabularies**; eCTD v3.2 updates require a new DTD version causing version management challenges
- **Correction of metadata** (attributes, keywords) possible
- **Change of document granularity**/life cycle (one-to-many, many-to-one)
- **Grouping of documents** (via Group Title keywords) and **document ordering** (via Priority Numbers)
- The structure of eCTD 4.0 allows for more streamlined and efficient submission processes (e.g., **one XML exchange message**)

A detailed list of benefits can be found in the "Supplemental Documents for eCTD v4.0 Implementation Package", available at the ICH website

eCTD v4 Challenges

- Updated publishing and review software is needed
- The RPS format is significantly less human-readable than eCTD 3.2.2, and its nonhierarchical nature means that constructing a webpage “on the fly” is more complex
- eCTD 4.0 comes with a range of new or changed terminology that users will need to familiarize themselves with
- Long delay between standard finalisation and implementation has led to mixed opinions on the value of changing standards

Current Submission Challenges

- Still electronic paper (Document-driven)
  - Transition to data-centric approaches (Computable Data)
  - IDMP Compatibility (ISO IDMP, SPOR, PQ/CMC, ICH M4Q, SPQS, HL7 FHIR)
- Evolution of submission content
  - Large data sets, Real World Data / Real World Evidence
  - Growing scope & increasing volume of submissions
- Global reuse of documents & data
  - Global repositories, collaborative workspaces, global identifier, security approaches
  - Global harmonization of standards, terminology, metadata
  - Interoperability (APIs)
- Complex regulatory processes
  - Requirements, specifications, processes, legislation

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Erosion of original eCTD v4 value proposition

- FDA eSTAR format (electronic Submission Template And Resource) for Medical Devices
  - Does not use the RPS standard, more similar to NeeS
- IDMP Implementation in EU
  - eCTD v4 administrative information overlaps with EU IDMP for product and registration information
- CTIS (Clinical Trial Information System)
  - A different format / mechanism for assembling CTAs, not using an eCTD v3.2.2 or v4.0 backbone

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eCTD Evolution – Opportunities

Evolution *of submission formats and content, rather than revolutionary change*

Shift in Content Paradigm

// Combination of documents and structured data

// Shift towards more computer-readable information and less electronic paper

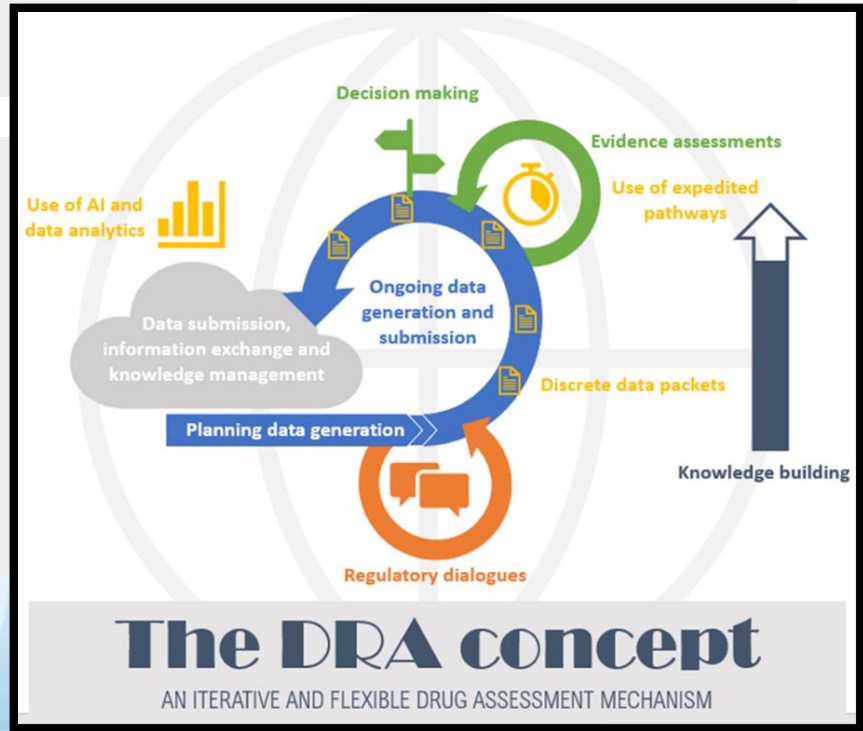
// Harmonisation and interoperability of content and standards (e.g., IDMP)

Regulatory Processes

// Incremental delivery of information (similar to rolling submissions but over a longer time period)

// Accelerated, coordinated and dynamic regulatory assessment

// Controlled vocabularies



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eCTD Evolution – Opportunities

Collaborative Workspace

// Globally accessible cloud platform for information exchange
// Global reuse of submitted data (e.g., global repositories, global UUIDs)
// Secure environment (access control, data protection, data integrity, data privacy)

Vendor Participation

// Early involvement of vendor community
// Increasing reliance on and use of technology
// Perhaps other Vendors than in the past – Vendor selection criteria

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The Future of eCTD – ICH Perspective

Joint ICH M2/M8 Working Group on “eCTD Evolution”

- Working group was created in mid-2023 and active until end of 2024
- Will be restarted in Q4 2025 (led by EMA)

Goal

- Maximize the life span of eCTD v4 by addressing evolving requirements with incremental changes to the specification and/or process of exchanging content

eCTD Evolution

- The goal is to maximize the life span of eCTD v4.0 addressing evolving requirements with incremental changes to the specification and/or process of exchanging the content between Regulated Industry and Regulators. The evolution aims to address the following pain points:
  - Transition towards data-centric approaches; combination of documents and computable data
    - Transformation from narrative text to structured data whenever possible
    - Use of exchange messages (e.g., FHIR) within the eCTD v4
  - Use of metadata to reflect structure
  - Allow eCTD message to reference external content (outside of sequence folder)
  - Improve IDMP compliance and compatibility
  - Reduce burden of duplicate entries of metadata between electronic forms, eCTD, delivery files, IDMP, etc.

eCTD Evolution Recommendations

- Creating a *Shared Environment* will address many of the pain points and serve to *incrementally update eCTD* as regulatory business processes change and technology enables the resulting regulatory product submission process.
  - Step 1: A Single (e.g., Module-specific) Shared Environment
  - Step 2: Single Comprehensive Shared Environment
  - Step 3: Single Integrated Industry Shared Content Environment
- The Shared Environment will be predicated on the following two activities:
  - Continued *Vendor Group Engagement*, which will inform ICH M8 about implementation barriers and opportunities as new business requirements evolve for the Shared Environment
  - *Standardisation of eCTD Module Content* (i.e., structured, computable data) by ICH Experts (e.g., Module 2/3 revisions by M4Q) and inclusion in eCTD

Joint ICH M2/M8 Working Group

- Prepared a Briefing for the ICH MC regarding eCTD Evolution
  - Scope and Objectives, Milestones, Feedback and Endorsement
  - FAQs created to address any misunderstandings about eCTD Evolution replacing eCTD v4.0
    - **eCTD v4.0 is REQUIRED as the foundation for any evolution to take place**
- Additional Steps Explored
  - Creation of an EFPIA eCTD Subgroup on “eCTD Evolution”
  - Consultation and coordination with PQ KM Task Force
  - Engage the Vendor community to address requirements for a shared environment
  - Consultation of Global IDMP Working Group (GIDWG)

eCTD Evolution – Outcomes

eCTD Evolution Concept Paper

// Create Value Proposition of the business benefits

Discuss and align on life span for eCTD v4.0

Joint discussion with M4Q

// To understand the technical aspects of quality related activities and potential implications on eCTD

Monitor FHIR development

// Review current implementation and maturity state of FHIR, consider implications on eCTD

Discuss and align on time frame for ICH support for eCTD v3.2.2

// ICH support will be limited in time, also for Non-ICH Regions

Monitor Emerging Technologies development

// Information Security approaches, Cloud Technology, AI, etc.

Cloud Submissions

FDA PRISM (DNA Nexus)

Accumulus Synergy

ICH PQKM (Product Quality Knowledge Management)

PROJECT PRISM

A Regulatory Cloud Collaborative Initiative

precisionFDA Regulatory Information Service Module
FDA-Industry Research Collaboration Agreement
(Public-Private Partnership)

ABSTRACT OF THE RESEARCH PLAN:

- ***This research collaboration will demonstrate the feasibility of collaborative regulatory review and submission validation utilizing FDA's production regulatory cloud platform, known as PrecisionFDA. The project will utilize actual regulatory data previously submitted to the FDA, as well as third-party tools that FDA currently uses for eCTD and study data review / validation.***
- *Practical use cases will test the essential functions of collaborative review, receipt and archive of information against current solutions, utilizing novel interactive tools and technologies that will enable enhanced communication between the two parties. Exchange and use of large submissions will be evaluated, a challenge that continues to grow. The collaborators are expected to gain important foundational insights into cloud-based solutions and processes that can improve the submission, review and ease of communications for drug and biologics applications to FDA.*
- *Use of PrecisionFDA will allow FDA and collaborators an understanding of the benefits of production regulatory cloud with the intent of informing future solutions, without incurring unnecessary costs for the parties.*
- *Learnings gained from this collaboration will be published after each phase, and can be utilized by others in industry and global regulatory authorities to leverage technologies / processes that offer greater review efficiencies.*

Vendor collaborators	Industry collaborators
DNAnexus, Lorenz,	Boehringer Ingelheim, Bayer, Merck KGaA/EMD
Veeva, Pinnacle, Weave	Serono, Takeda, Bristol Myers Squibb, Gilead, Biogen

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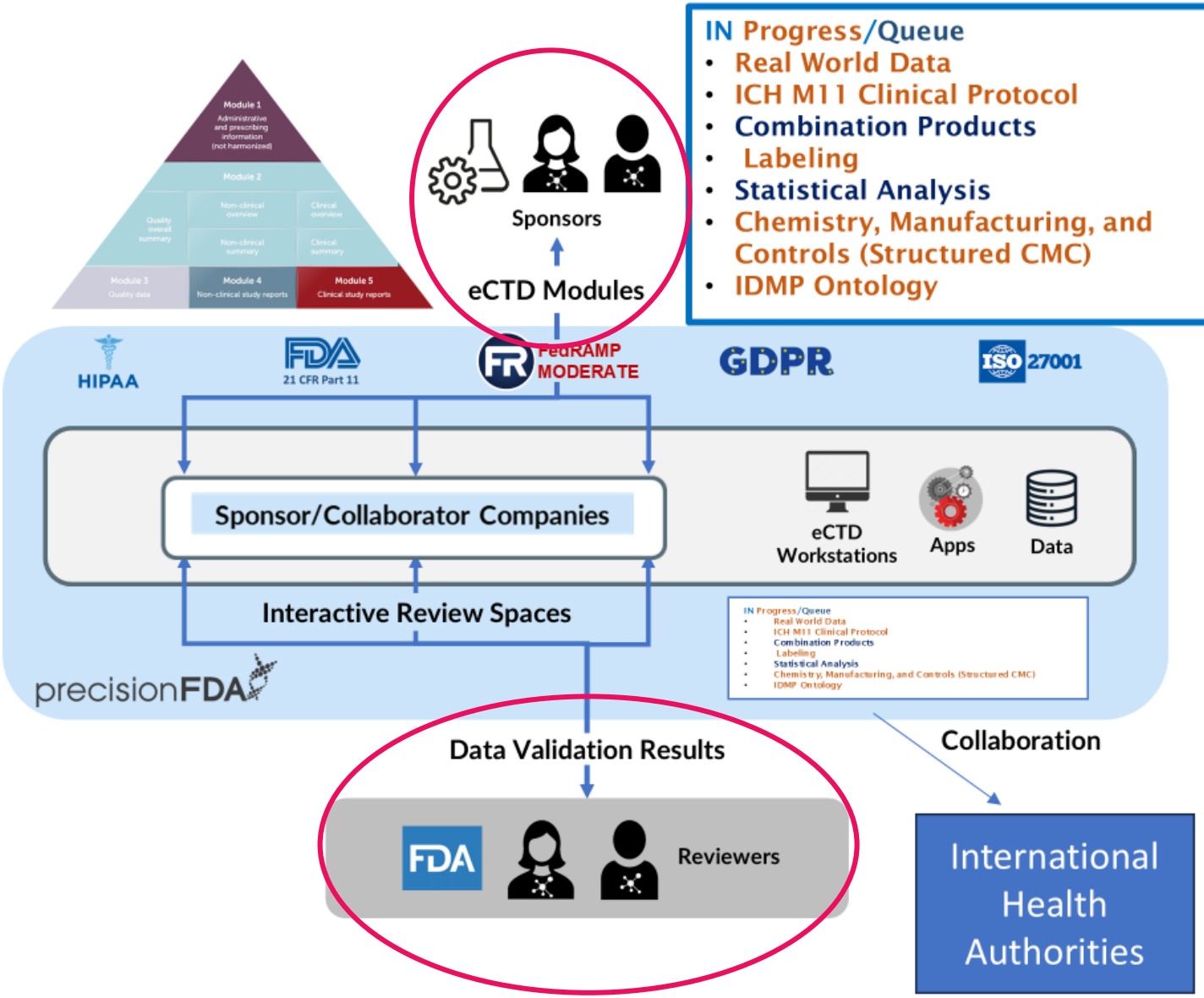
PRISM Phase 1 – Interactive/Collaborative Communication



Sponsors share eCTD modules 1, 4 and 5 using Shared Interactive Review Spaces.

Using 21 CFR Part 11-compliant precisionFDA Workstations Sponsors validate their data using FDA-managed applications.

Sponsors and Reviewers work in their **Private Spaces** and share and comment on the data validation results in the **Interactive Review Spaces.**

Reviewer/Sponsor data sharing and validation activities, and inter-party communications and interactions are captured in an **Interactive Review Report**.

Accumulus Synergy Vision

Accumulus Synergy is a global, non-profit organization founded in 2020 that is developing a transformative data exchange platform to enable collaboration, efficiency, and deeper insight generation between biopharmaceutical companies and global health authorities

Our Vision

We dramatically accelerate critical therapies to citizens of the world

Our Mission

We reimagine the interaction and information exchange between stakeholders in the healthcare ecosystem to streamline the regulatory lifecycle

Current Stakeholders

Sponsor Biopharma Companies

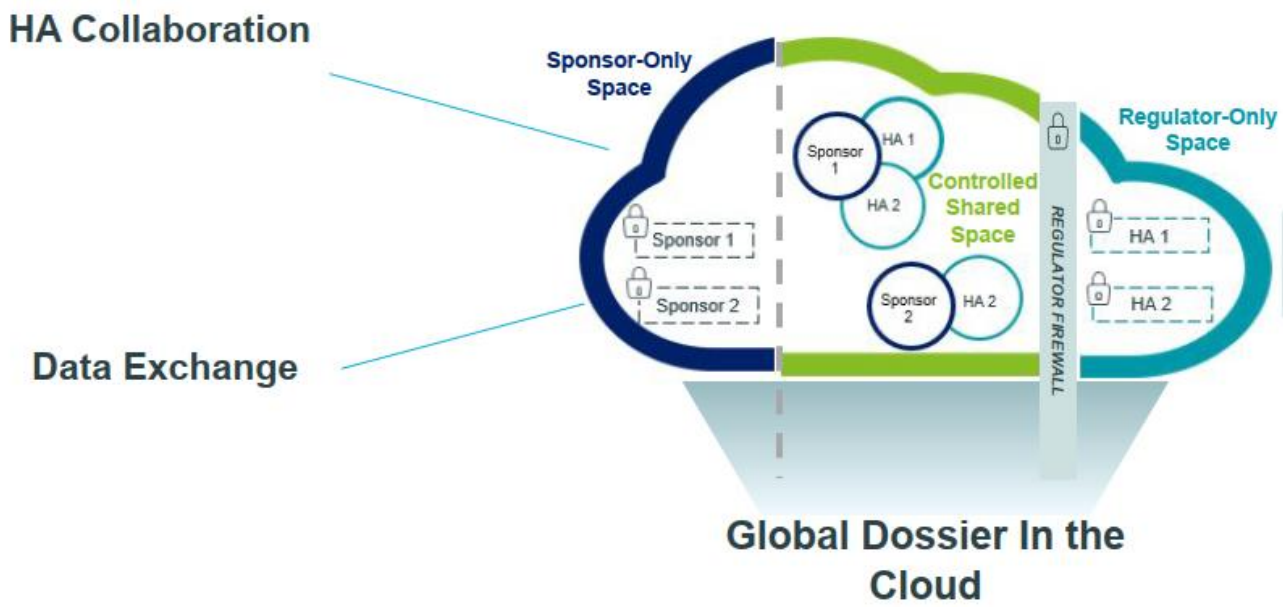
- Amgen
- Astellas
- AstraZeneca
- BMS
- GSK
- J&J
- Lilly
- Merck
- Pfizer
- Roche
- Sanofi
- Takeda

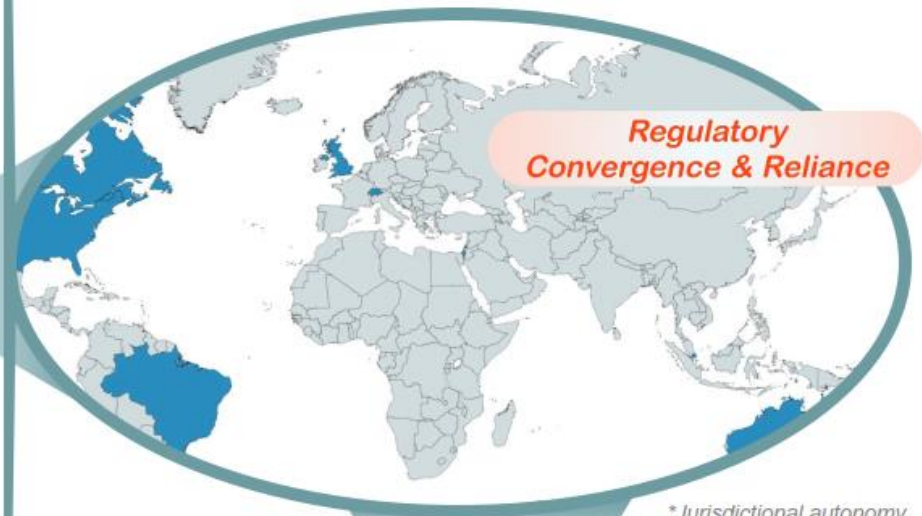
Engaged Health Authorities

Conducted dozens of meetings across eleven different health authorities

Cloud Technology Enabling Regulatory Convergence and Reliance

A reimagined information exchange between stakeholders in the healthcare ecosystem can streamline the regulatory lifecycle and facilitate real-time, simultaneous collaboration between various entities





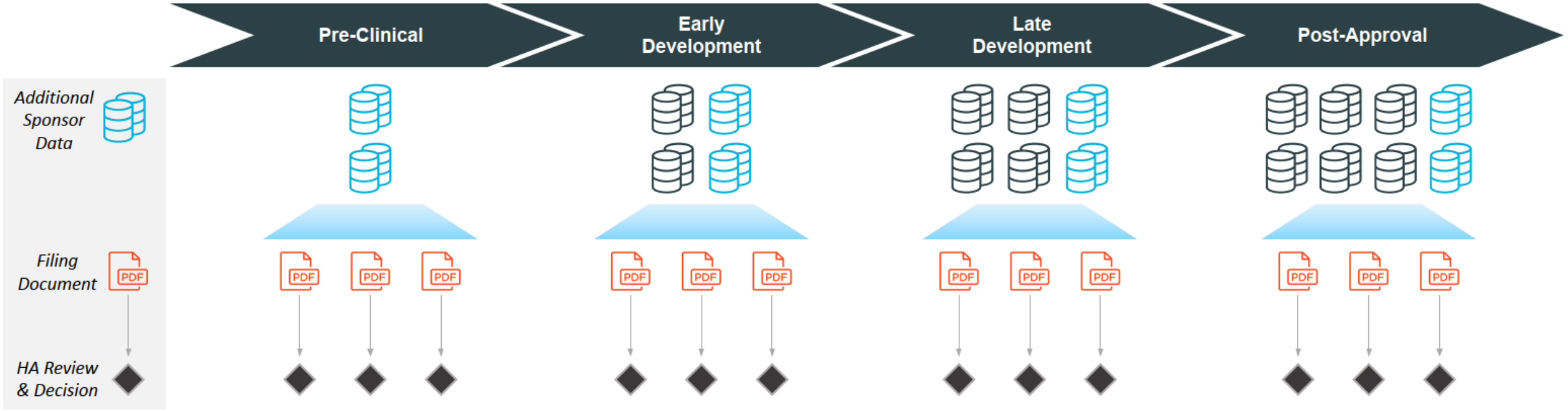
*Jurisdictional autonomy will be maintained

We dramatically accelerate critical therapies to citizens of the world

Current State: Submission-Focused and Document-Led Transactions

While data grows throughout product lifecycle, today's submissions continue to be isolated events that lock content in static documents and require a lot of manual manipulation by reviewers

ILLUSTRATIVE



Key Challenges

- Most content is **shared in PDF format**
- Review is currently **heavily narrative-driven**
- Hard to construct a **regulatory history** for a single product and for regulators to share knowledge /see trends across product reviews
- Content must be **replicated and reformatted** across different jurisdictions
- Content exists in **different systems** across organizations
- Regulatory process revolves around the **submission event**

Long Term Future Direction: Towards Data-Centric Reviews without changing the risk/benefit expectations for approvals

Data submission, review, and assessment will evolve over a multi-year time frame towards a more dynamic interaction that is consistent with how the data is generated in real time and aids regulatory assessment as reviewers access richer content

ILLUSTRATIVE

Pre-Clinical → **Early Development** → **Late Development** → **Post-Approval**

Future Direction Considerations

This requires design of a new engagement model and standardization, both which will be a multi-year, multi-stakeholder discussion.

Additional data beyond company data (e.g., wearables, EHR) are expected to inform reviews over time

Accumulus synergy

*Data will be uploaded as it is made available by Sponsors and will reside in **Sponsor-only, shared, or HA-only spaces** depending on **security and privacy permissions** granted by the data owners*

Health Authorities have **instant and user-friendly access** to all data and analysis/ insights for review, **facilitating regulatory decisions** (examples below), Reviewers would have a full line of sight as data on product accumulates, technology would **enable efficiencies on more routine work** to allow reviewers to **focus on value-add aspects of review**

First-In-Human

Phase 3 Start

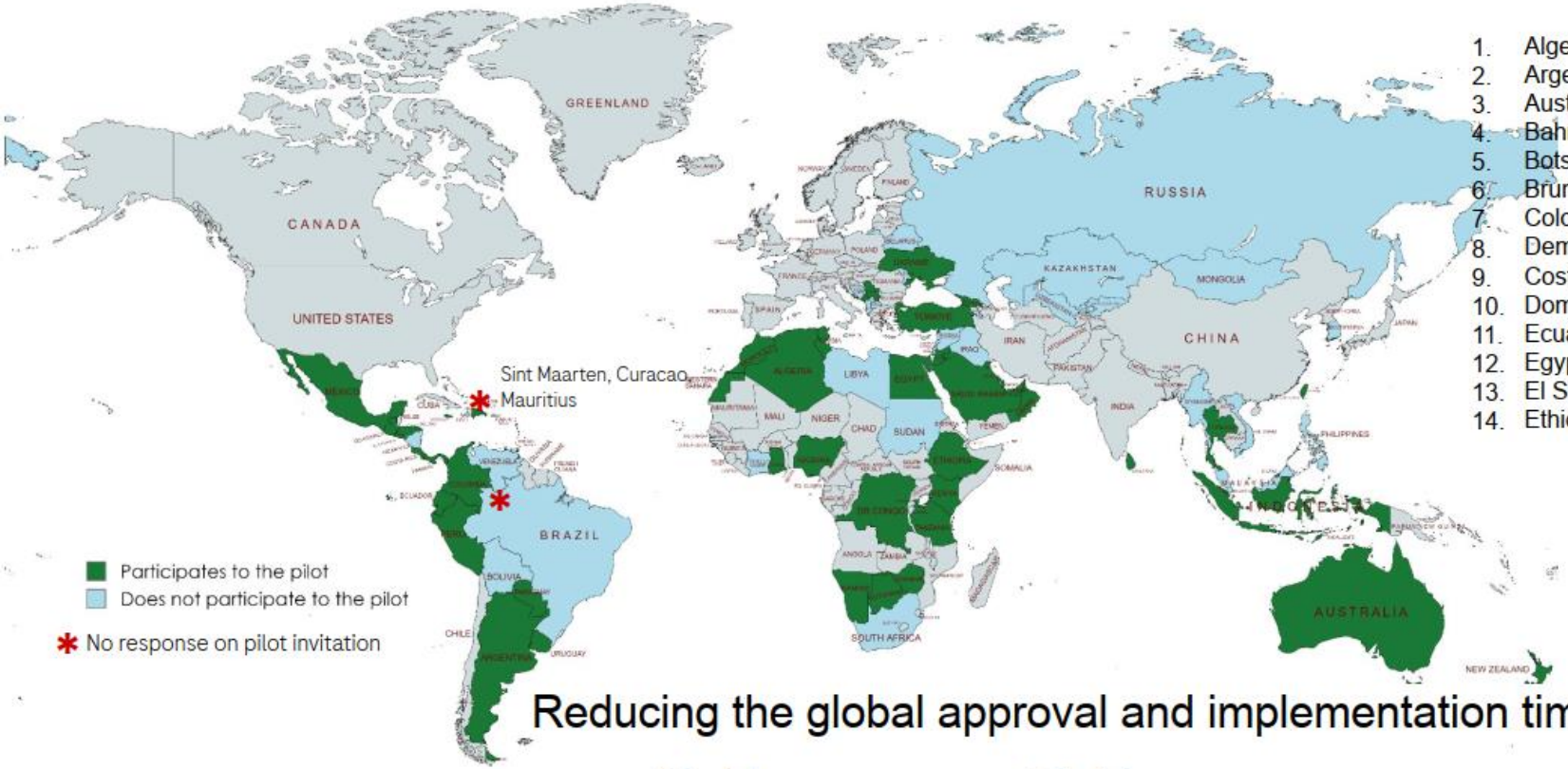
Marketing Application Review

Roche PAC Reliance Pilot - Participating Countries

84 COUNTRIES IMPACTED BY THE CHANGE

48 COUNTRIES AGREED to participate in the pilot

57%
Acceptance Rate

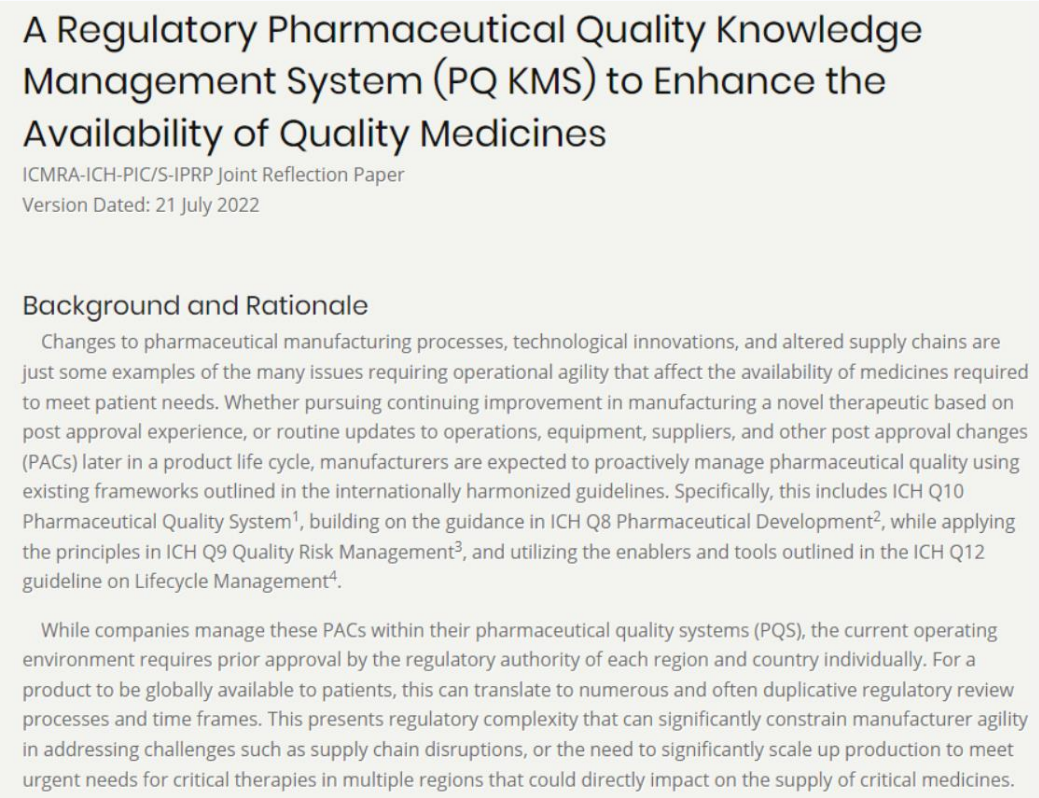


1. Algeria
2. Argentina
3. Australia
4. Bahrain
5. Botswana
6. Brunei
7. Colombia
8. Dem. Rep. of Congo
9. Costa Rica
10. Dominican Republic
11. Ecuador
12. Egypt
13. El Salvador
14. Ethiopia
15. Georgia
16. Ghana
17. Guatemala
18. Honduras
19. Indonesia
20. Israel
21. Jamaica
22. Jordan
23. Kenya
24. Kuwait
25. Mexico
26. Montenegro
27. Morocco
28. Namibia
29. New Zealand
30. Nigeria
31. Oman
32. Panama
33. Paraguay
34. Peru
35. Qatar
36. Saudi Arabia
37. Serbia
38. Sri Lanka
39. Taiwan
40. Tanzania
41. Thailand
42. Trinidad and Tobago
43. Tunisia
44. Türkiye
45. Ukraine
46. United Arab Emirates
47. Uruguay
48. Zimbabwe

Reducing the global approval and implementation timelines

From 2.5 YEARS to 6.5 MONTHS to ensure continuous supply to patients

ICH PQKM (*Product Quality Knowledge Management*)



A Regulatory Pharmaceutical Quality Knowledge Management System (PQ KMS) to Enhance the Availability of Quality Medicines

ICMRA-ICH-PIC/S-IPRP Joint Reflection Paper
Version Dated: 21 July 2022

Background and Rationale

Changes to pharmaceutical manufacturing processes, technological innovations, and altered supply chains are just some examples of the many issues requiring operational agility that affect the availability of medicines required to meet patient needs. Whether pursuing continuing improvement in manufacturing a novel therapeutic based on post approval experience, or routine updates to operations, equipment, suppliers, and other post approval changes (PACs) later in a product life cycle, manufacturers are expected to proactively manage pharmaceutical quality using existing frameworks outlined in the internationally harmonized guidelines. Specifically, this includes ICH Q10 Pharmaceutical Quality System[1], building on the guidance in ICH Q8 Pharmaceutical Development[2], while applying the principles in ICH Q9 Quality Risk Management[3], and utilizing the enablers and tools outlined in the ICH Q12 guideline on Lifecycle Management[4].

While companies manage these PACs within their pharmaceutical quality systems (PQS), the current operating environment requires prior approval by the regulatory authority of each region and country individually. For a product to be globally available to patients, this can translate to numerous and often duplicative regulatory review processes and time frames. This presents regulatory complexity that can significantly constrain manufacturer agility in addressing challenges such as supply chain disruptions, or the need to significantly scale up production to meet urgent needs for critical therapies in multiple regions that could directly impact on the supply of critical medicines.

Background

Agility to maintain:

- Robust supply chains
- Continually update manufacturing processes

Aims

Leverage information sharing on pharmaceutical quality between regulatory agencies

Align on regulatory requirements (post-approval setting)

- Data submissions and regulatory assessments
- Inspections

Goals

Regulatory reliance, agility, effectiveness, and efficiency

Harmonization: data submissions, regulatory expectations, assessments, inspections

Acceleration of global availability of quality medicines

ICH established a PQKM Technology Platform Task Force in **March 2024**, to understand the foundation needed to establish and govern a standardised technology platform for PQKM

ICMRA Pilots:

Collaborative pilot programs (Collaborative Regulatory Assessment and Collaborative Hybrid Inspection) are extended through the end of 2025 to gather more data and experience with these regulatory approaches

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ICH PQKM

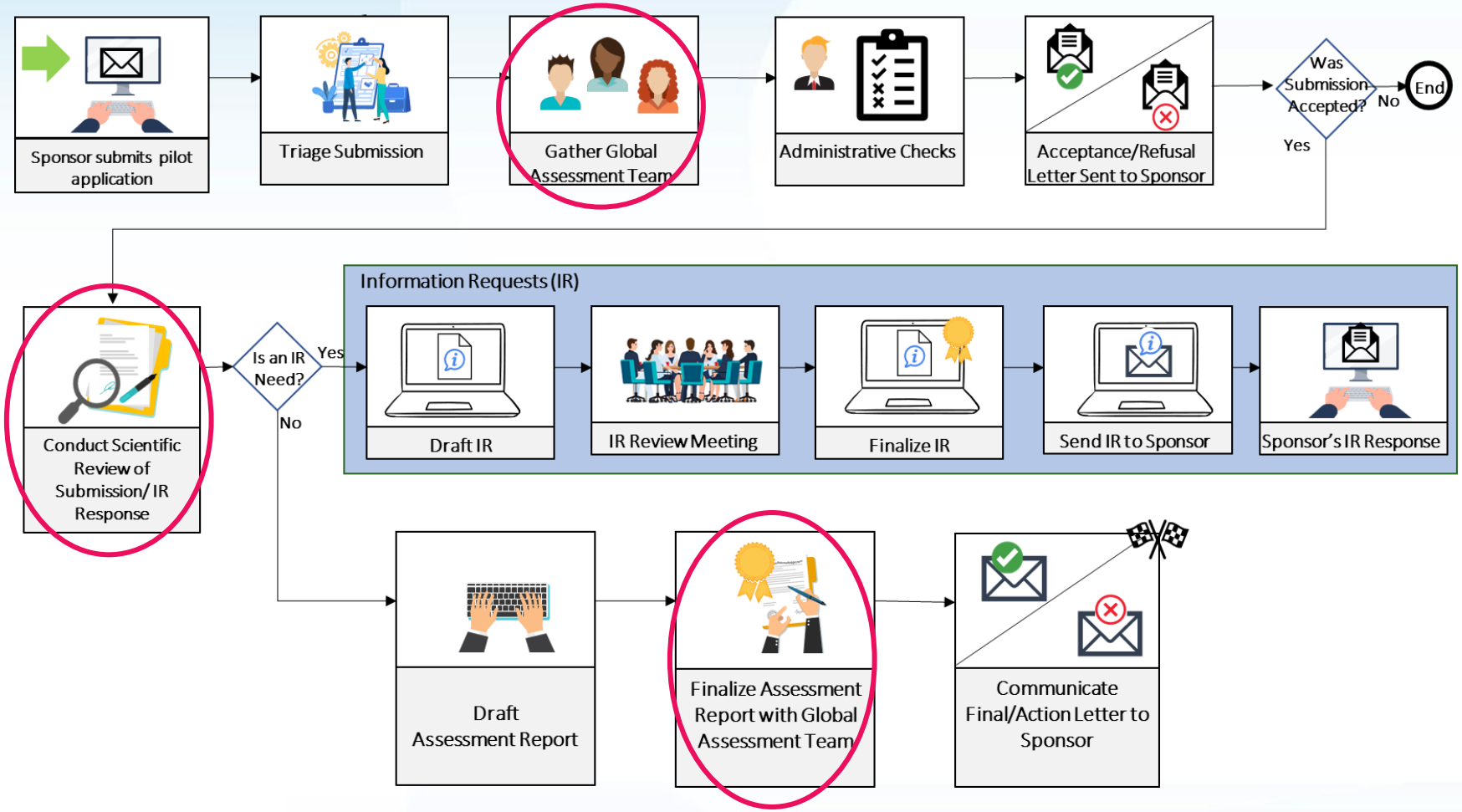
(*Product Quality Knowledge Management*)

Future Proposal

GRACE (*Global Regulatory Assessment and Collaborative Evaluation*)

This would include specification of a “Global Pathway” for collaborative regulatory assessment with established timeframes for collaborative review among regulators and the interactions with application submitters.

Overview of the Piloted ICMRA Collaborative Assessment Process



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ICH M4Q (R2) EWG

Focusing on the revision of CTD Quality sections in Modules 2 and 3

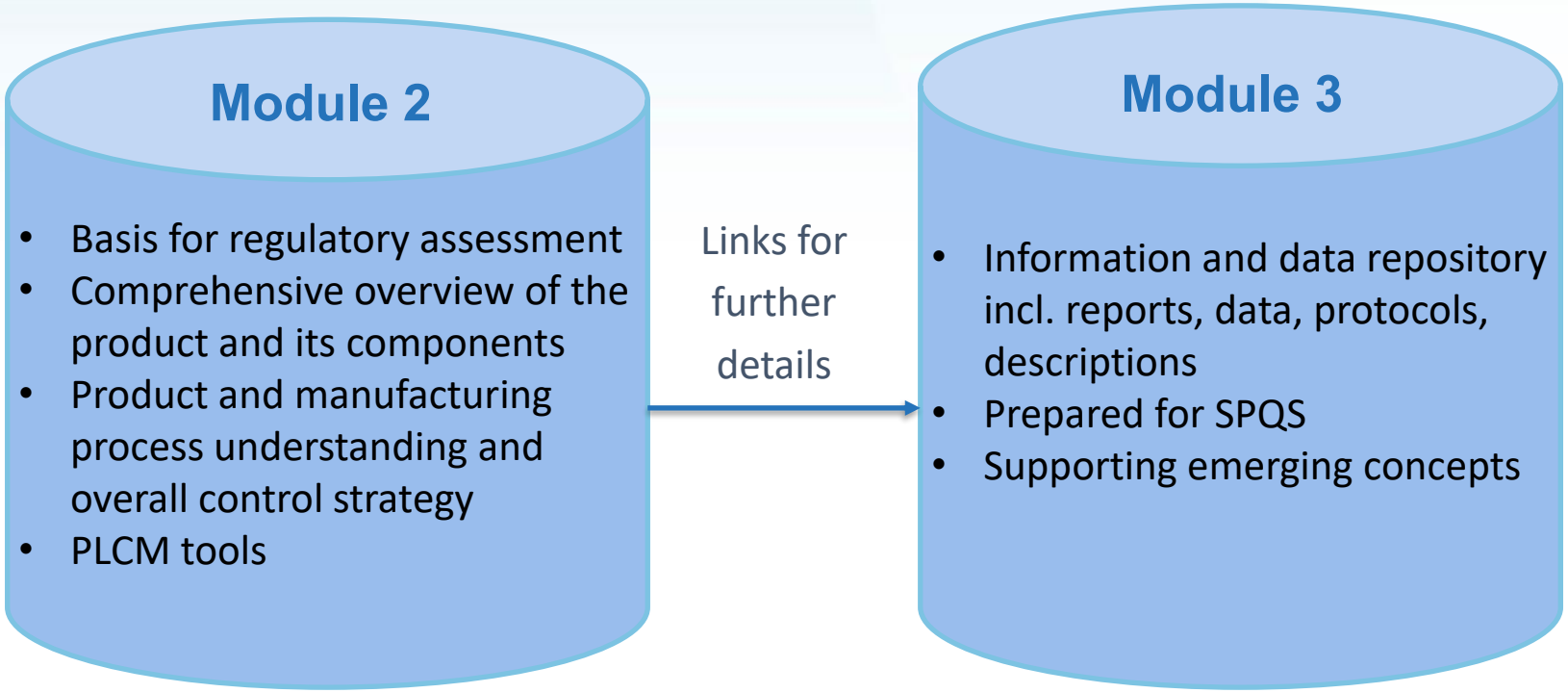
- Organizing product and manufacturing information in a suitable format for easy access, analysis, and knowledge management
- M4Q (R2) will consider, but will not work on implementation of structured data
  - ICH is setting up a new EWG to support this (SPQS)
- Whenever possible, terms and logic aligned to ISO IDMP to facilitate future move to SPQS
- Step 2 Sign-off and release for Public Consultation planned Jun 2025

M2/M8 Subgroup is working with M4Q (R2) subgroup

- Consider whether and how much eCTD v4.0 can currently handle the revised model
- Assess the feasibility of implementing metadata and hyperlinking requirements of M4Q (R2)
- Consensus decision, to implement changes in eCTD v4.0 only

M4Q(R2) EWG REPORT TO THE ASSEMBLY

M4Q(R2) Establishes Module 2 as the Basis for Regulatory Assessment, Supported by Module 3



- M4Q(R2) should enable efficient, effective, patient-centric and globally harmonised submissions, assessment and life cycle management, and minimize dossier redundancies
- Suitable for various types of submission and product modalities

AGREEMENT REACHED ON STRUCTURE OF MODULE 2

2.3.I Introduction

2.3.OCS Overall Control Strategy

2.3.D Development summary and justifications *(supportive) - scientific justification*

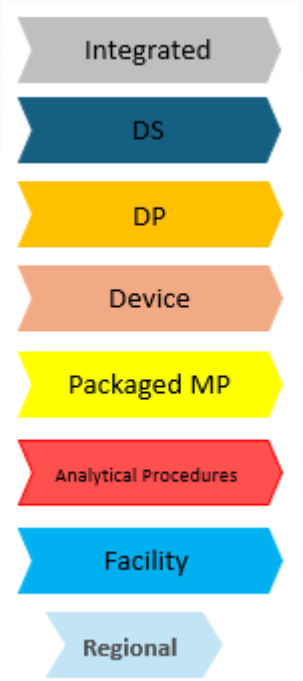
2.3.C Core Quality Information – *may trigger post-approval change*

2.3.L Product lifecycle management document (optional)

- Established Condition identification (optional)
- Alternate reporting categories and regulatory justifications (optional)
- Post-approval change management protocols (PACMP)
- Post-approval CMC Commitments

2.3.6 Conclusion which may contain Quality Benefit Risk

Module 3 is supportive and only amended as a result of post-approval changes



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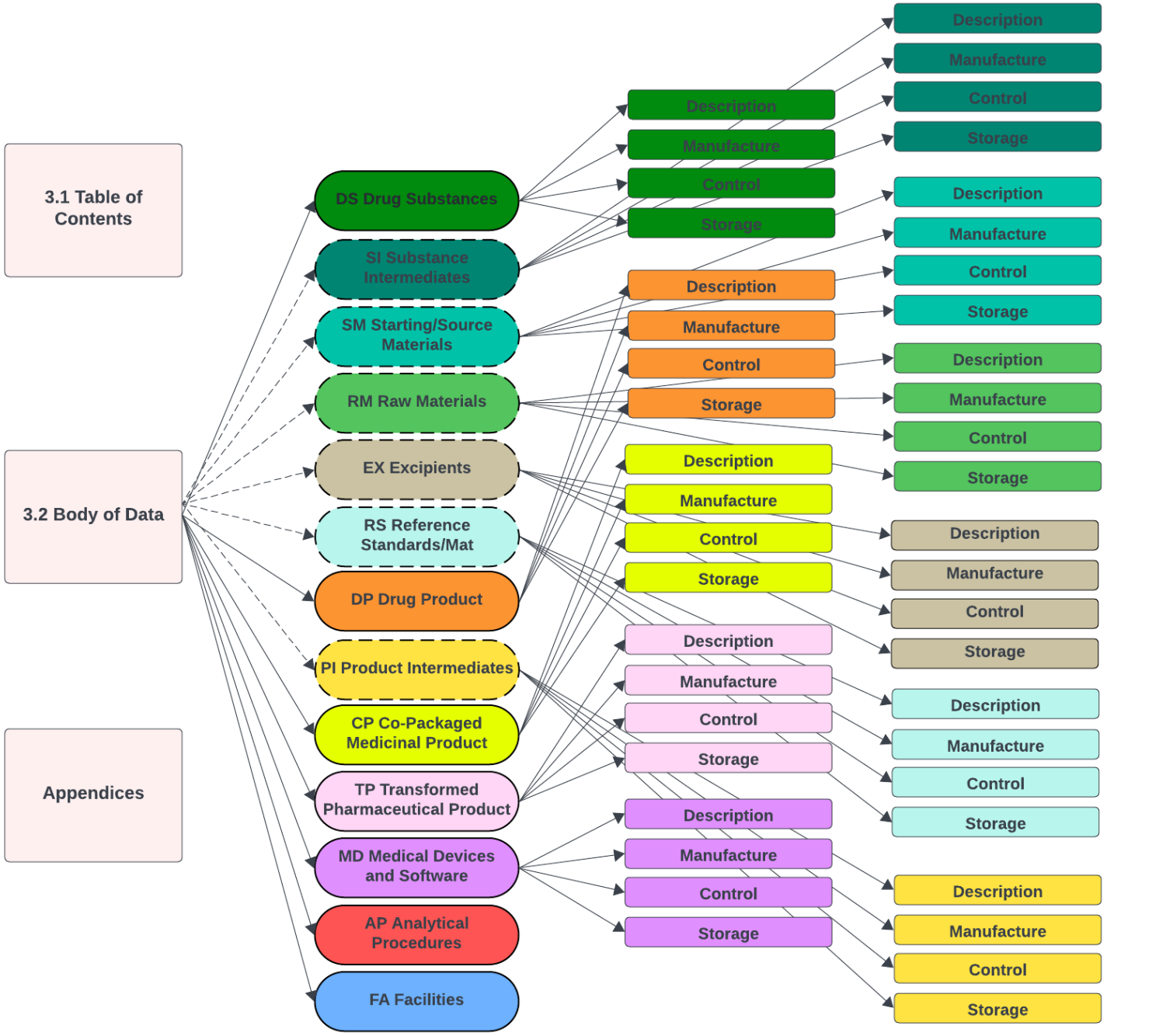
STRUCTURE OF 3.2

Module 3 follows the same structure as the Core Quality Information section



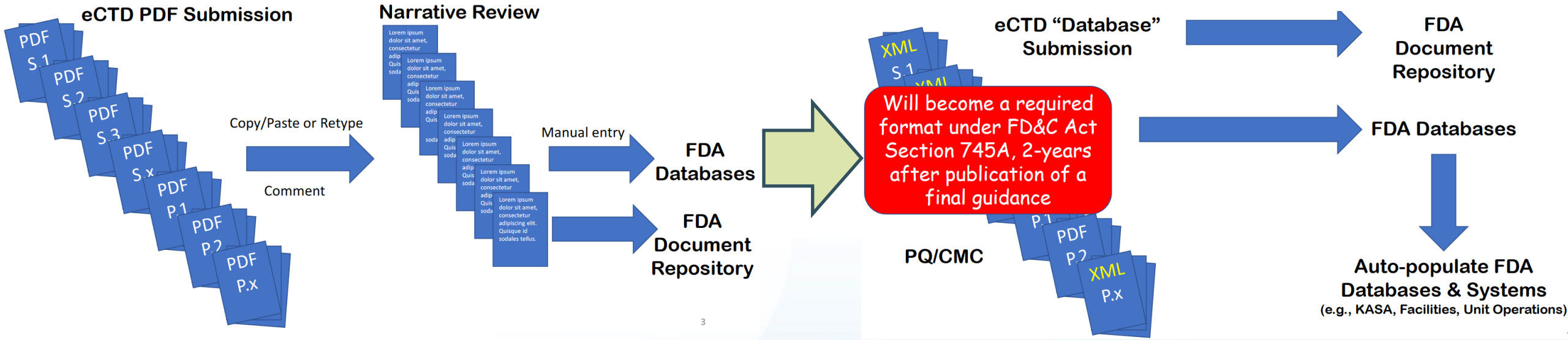
ICH M4Q (R2) Timelines

- Proposal endorsed by ICH Assembly in May 2020
- Concept Paper approved in April 2021
- Step 2 consultation document released in June 2025, public comments due back via industry associations by 24th October
- Step 3 (Regulatory Experts sign-off) planned in June 2026
- Step 4 (Adoption of Final Guideline) expected in June 2027

// **IMPORTANT: These revisions will only be available in eCTD v4.0**

ICH M16 SPQS (Structured Product Quality Submissions)

- Will focus on implementation of structured data, starting with Quality information
  - ICH is currently seeking nominations for a new EWG to support this
  - Whenever possible, terms and logic will be **aligned to ISO IDMP** to facilitate future move to SPQS
- US FDA has a similar initiative with PQ/CMC (additional info here):

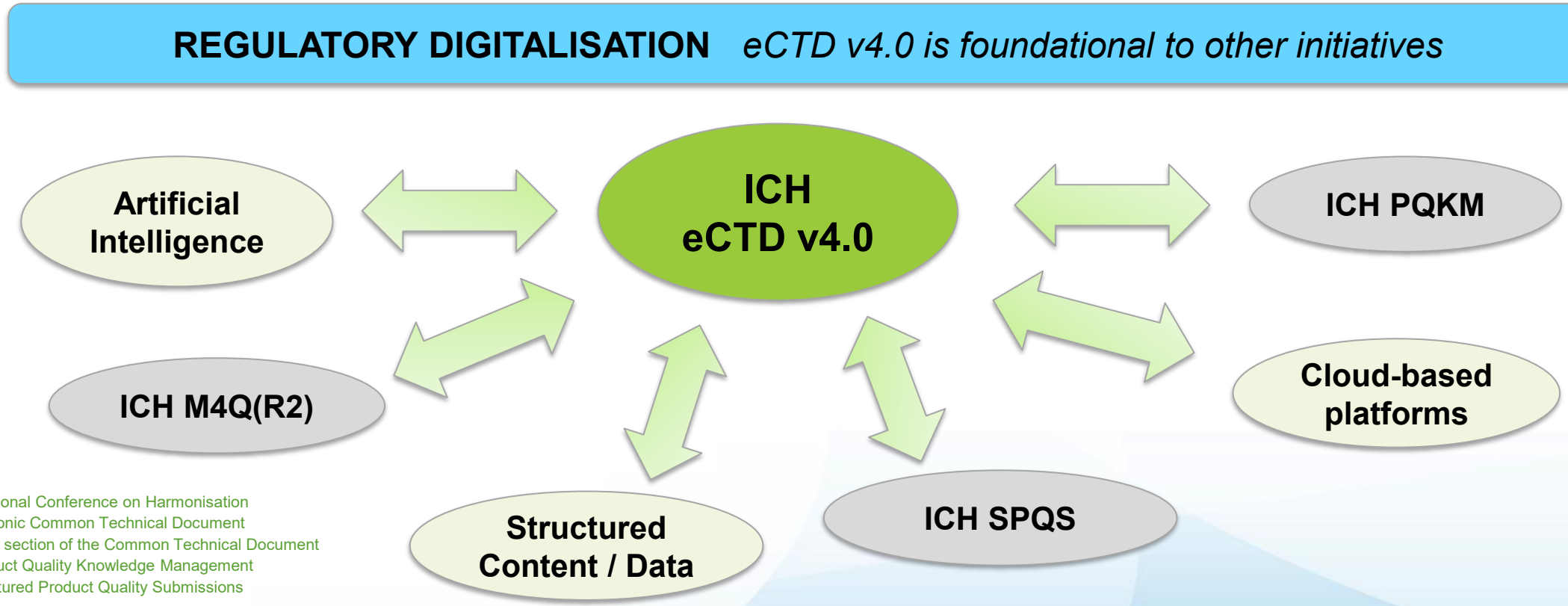


ICH Supports a Transition from a Document-Centric to a Data-Centric approach for Regulatory Submissions

- eCTD v4.0 is a more versatile message standard that can support the exchange of modern data standards or message formats, such as the following that are currently being developed and implemented by ICH Work Groups:
  - The ‘eCTD Evolution’ subgroup is working on a plan to support the incremental transition to a data-centric approach, such as the secure standardized technology platform for exchange of regulatory information that is being proposed by the PQKM Task Force
  - A new ICH working group, M16 Structured Product Quality Submissions (SPQS), is tasked with standardizing product quality data
  - M11 Clinical electronic Structured Harmonised Protocol (CeSHarP) guideline will provide comprehensive clinical protocol organisation with standardised content
  - ICH Guidelines are reflecting the need for Real-world data and modern technology approaches (e.g., AI)

ICH ECTD V4.0

- Whilst acknowledging that eCTD v4 has some limitations, it is viewed as a foundational step forwards in modernisation and a way to support future digital innovations and initiatives
- This standard is also an enabler for Regulatory reliance pathways thanks to the harmonisation across ICH regulators and beyond



ICH = International Conference on Harmonisation
eCTD = electronic Common Technical Document
M4Q = Quality section of the Common Technical Document
PQKM = Product Quality Knowledge Management
SPQS = Structured Product Quality Submissions

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How Can You Be Prepared?

- Carefully consider how and when to start submitting in eCTD v4
- Where possible, participate in pilots of new technologies / processes
- Regularly provide feedback to regulators on pain points and opportunities
- Discuss ideas and concepts with colleagues, peers, industry networks
- Take advantage internally of changes required externally (e.g. IDMP data)

Conclusions / Predictions

- The eCTD v4.0 Implementation train is running and gaining speed
  - Industry and Regulators need to see eCTD 4.0 strategically, as one step in a transformation to a more data-centric regulatory practice
- Industry and software vendors need to collaborate with Regulators to shape the future and advance initiatives that can improve and streamline how we exchange information
- What does the future hold?
  - Expect to continue submitting eCTD v4 for foreseeable future, with nature of content changing and scope reducing over time
  - eCTD v4 will evolve step-wise as new technologies and processes are developed
    - Collaborative cloud platforms, transition from documents to structured data, globally aligned data standards, use of AI
    - E2E regulatory processes including rolling submissions and reliance pathways

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EVOLUTION OF ECTD AND SUBMISSIONS ROADMAP

Transforming Sponsor/Regulator and Regulator/Regulator collaboration
- **Dynamic Regulatory Assessment – E2E Dossier**
- **Increased reliance and worksharing – One Global Dossier, One Approval**
- **Cloud Submissions** (Accumulus Synergy/PRISM/PDUFA VIII)
- **AI in drug/device development affecting submission content**

Data-centric, streamlined processes for regulatory reviews
- Data submissions, Data Analytics Support, KASA, UNICOM
- Leveraging digital technologies, automation, to improve processes
- Connect and centralize siloed information

Submission of Big Data
- **EMA Patient-Level Raw Data (Clinical)**
- EMA Nonclinical + CMC Data Submissions
- EMA RWD / RWE Submission for Regulatory Decision-Making

Structured information / ICH initiatives
- IDMP + SPOR + PQ-CMC + M4Q
- Structured Product Quality Submissions
- Structured content management

International eCTD expansion / new regulations: Many new regions set to come onboard with eCTD in 2024-2030. Harmonization of specifications and standards to ICH and handling different versions (3.2.2/ 4.0) plus explosion of new regulations

Biogen