THE POWER OF DATA EXCHANGE, CMC INTEROPERABILITY AND A CLOUD-BASED ECOSYSTEM

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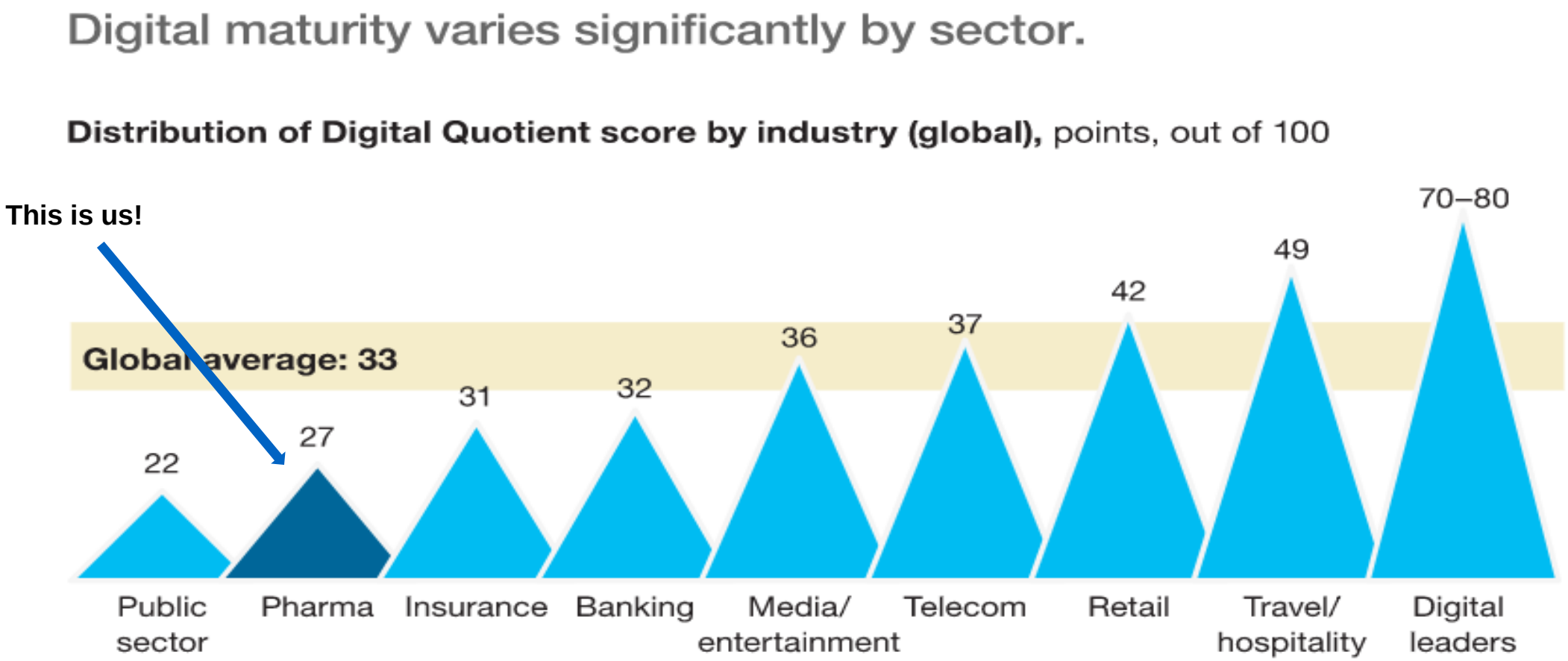
REGULATED INDUSTRIES AND DIGITAL MATURITY



Source: www.mckinsey.com/industies_closing the digital gap in pharma

CURRENT CMC DATA MANAGEMENT AND SUBMISSIONS

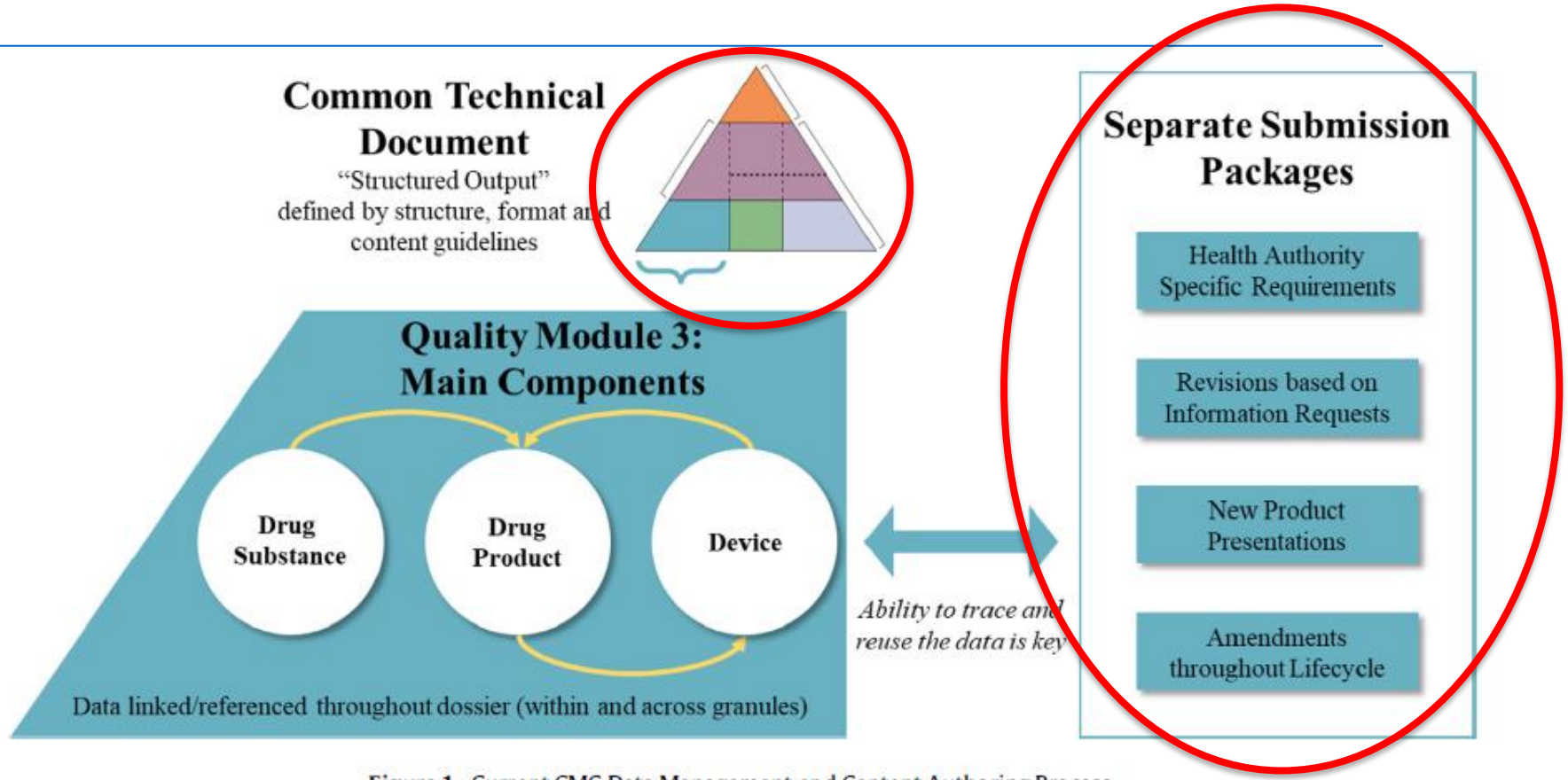
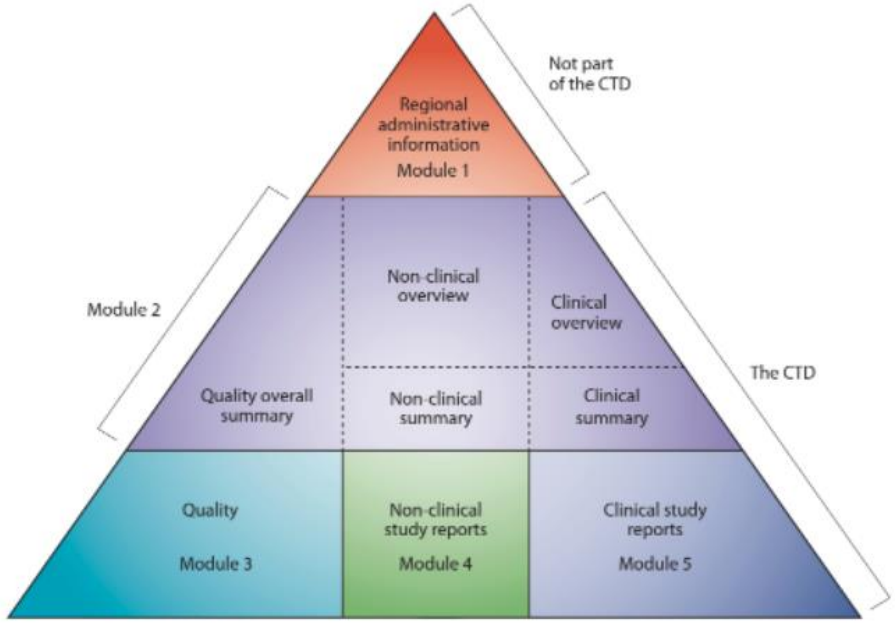


Figure 1. Current CMC Data Management and Content Authoring Process.

Current CMC data management processes are time consuming, create potential for transcription errors and data integrity issues, and require multiple reviews and verification steps.

Reference: https://doi.org/10.1016/j.xphs.2021.09.046

STRUCTURED CONTENT FACILITATES THE TRANSITION FROM DOCUMENT-LED TO DATA-DRIVEN DIGITAL FILINGS



eCTD guidelines provide a basic structure for dossier organization, but individual nodes are unstructured and subject to regional interpretation, introducing potential for significant heterogeneity

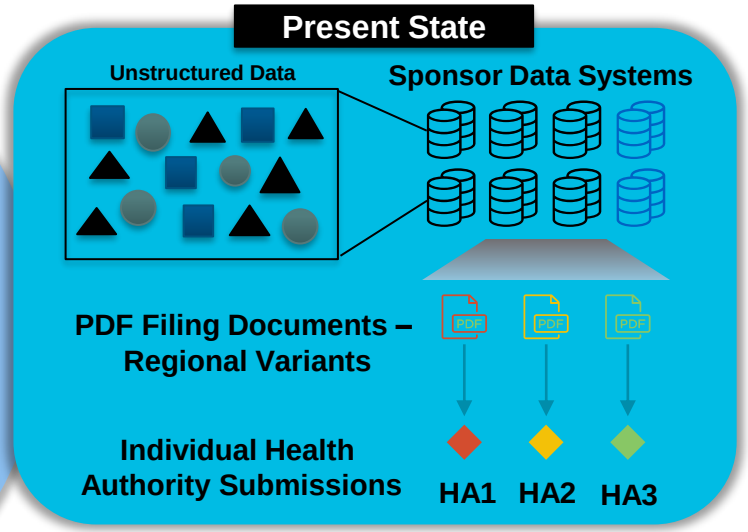
Unstructured Content

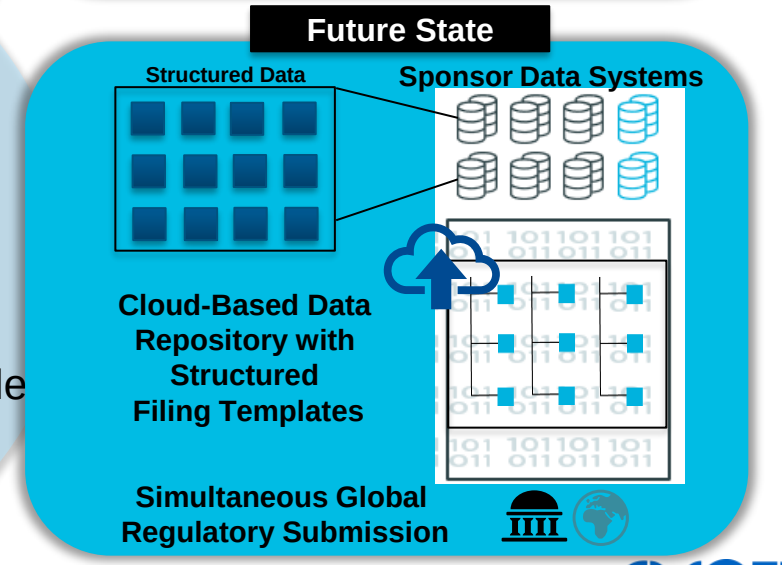
- ❑ Difficult to keep updated
- ❑ Time consuming to format
- ❑ Limited scalability
- ❑ Not predetermined

vs

Structured Content

- ✓ Independent from submission
- ✓ Defines metadata and ontology
- ✓ Human & machine readable
- ✓ Individual building block
- ✓ Predetermined





How does the biopharmaceutical industry evolve and transform from current state to a more innovative technological CMC regulatory filing and review future state?

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ICH INITIATIVES

1 Revision of M4Q(R1)

Reorganize application to align with quality assessment platforms and towards a more structured and standardized application

2 Structured Product Quality Submissions (SPQS)

Guideline identifies CMC information/data to be standardized into structured data formats

3 ICH Q12

Strategies for implementing harmonized regulations for post-approval change management throughout lifecycle

Procedures to encourage unification of post-approval submission requirements across regions

Opportunities to incorporate SCDM key elements

SCDM solution to track ECs and Post-Approval Change Management Protocols optimizes global maintenance and evolution of the product lifecycle management (PLCM) document

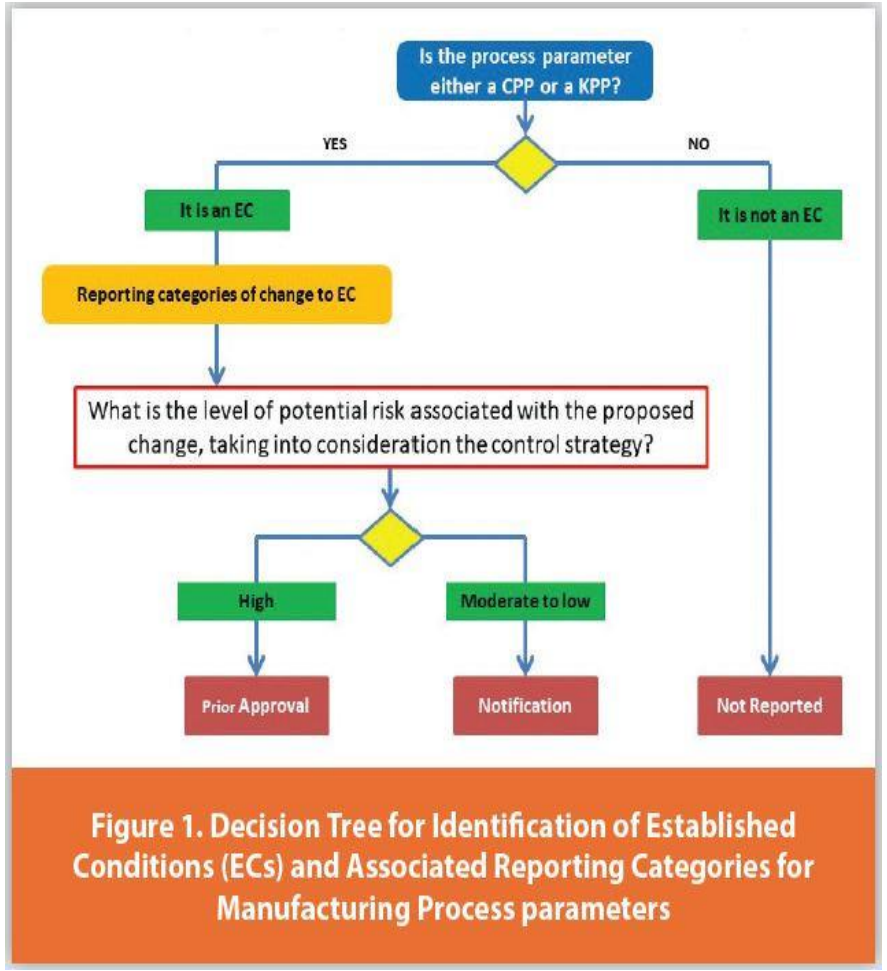

Figure 1. Decision Tree for Identification of Established Conditions (ECs) and Associated Reporting Categories for Manufacturing Process parameters

https://www.americanpharmaceuticalreview.com/Featured-Articles/358866-Does-the-International-Council-for-Harmonization-Offer-a-Solution-via-ICH-Q12/

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EMA INITIATIVES – SPOR ISO IDMP & IRIS

ISO IDMP

IRIS

Regulatory Submission Portal

- **Orphan designation**
- **Parallel distribution notifications**
- **Briefing meetings**
- **Research Product Identifier requests**
- **Scientific advice questions**

International Organization for Standardization (ISO) for the identification of medicinal products (IDMP)

https://iris.ema.europa.eu/ https://www.phlexglobal.com/idmp

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FDA INITIATIVES – KASA & PQ/CMC

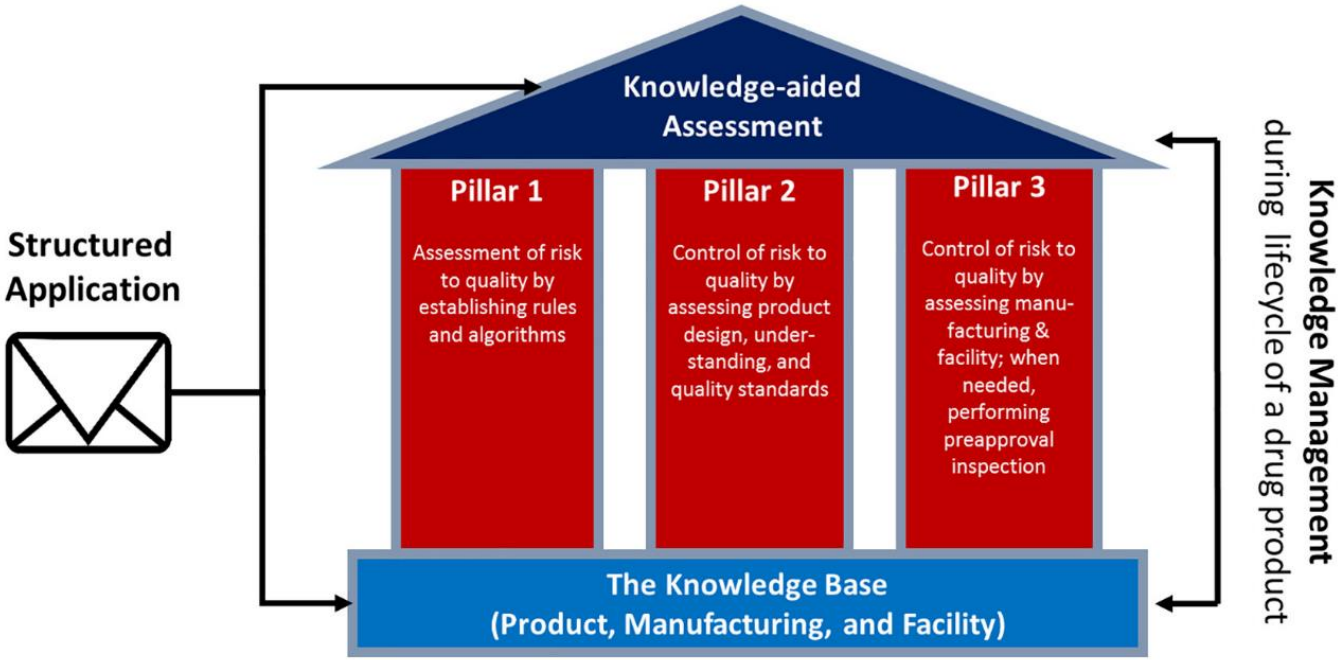
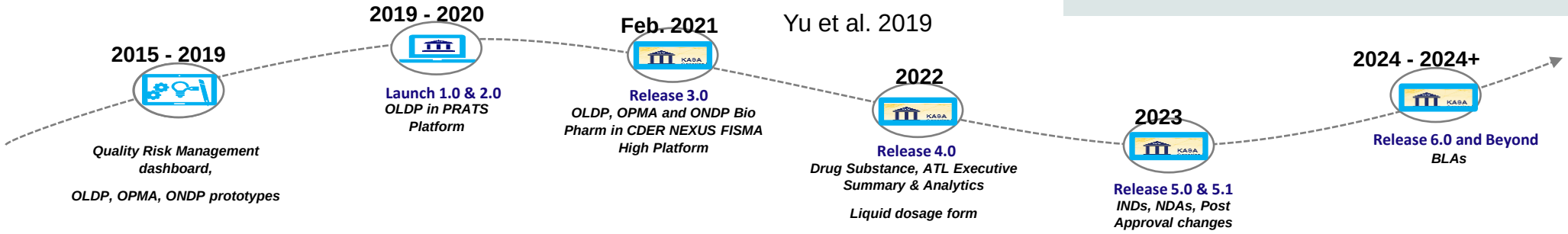


Fig. 1. Knowledge-aided Assessment & Structured Application (KASA) system.

Yu et al. 2019



For a structured application, sponsor needs to know:

What information is submitted and how is it organized?

ICH M4Q(R1) Revision (R2)

How is data structured?

Pharmaceutical Quality/CMC

↓

Standardized Data with XML format
FRN published Q2, 2022
Draft Guidance 2022; Likely limited to “Specification,” “Batch Analysis” and “Stability”

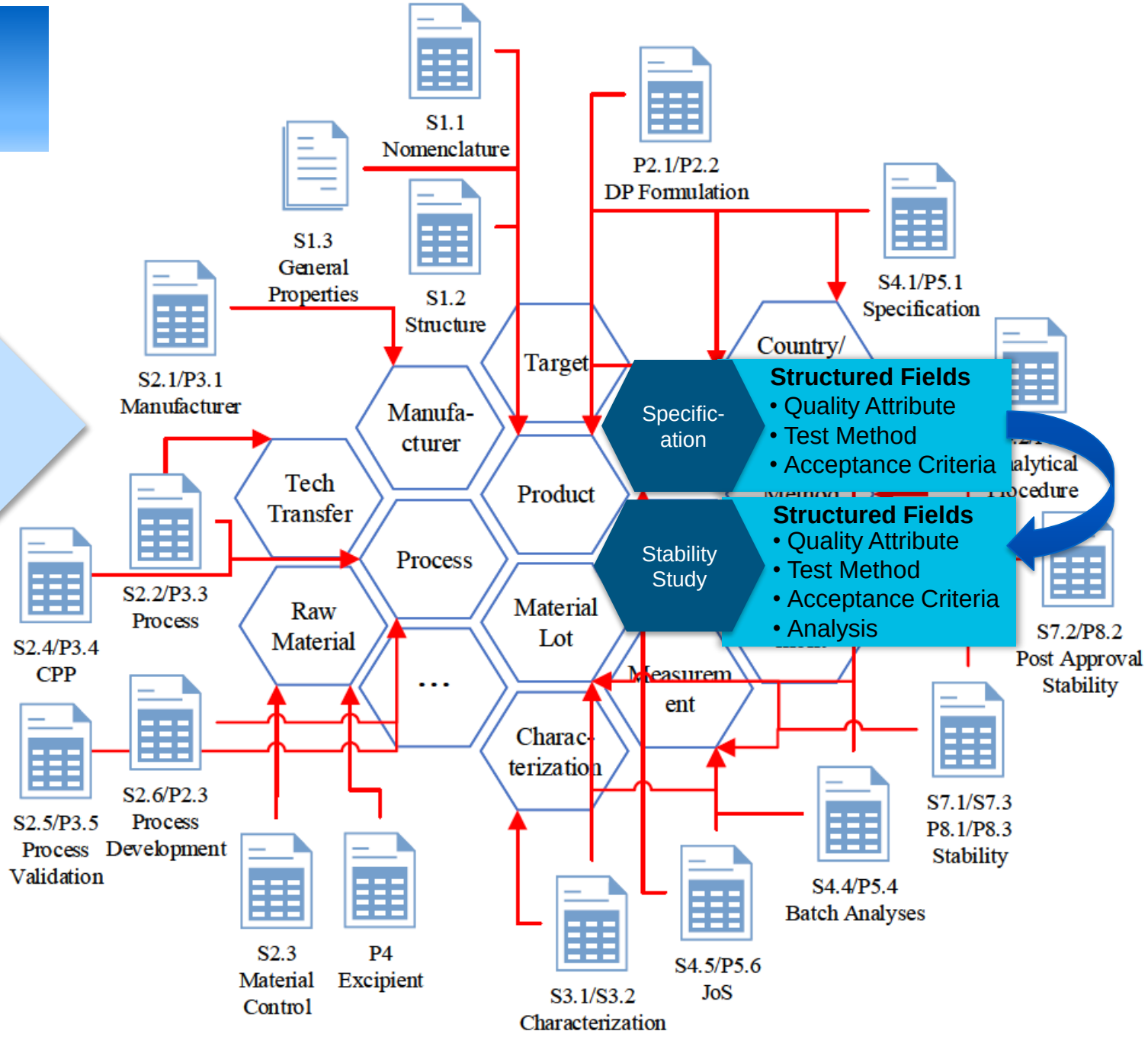
Schmuff, DIA 2021

SPONSOR CMC UNIFIED DATA MODEL (UDM)

Key Points:

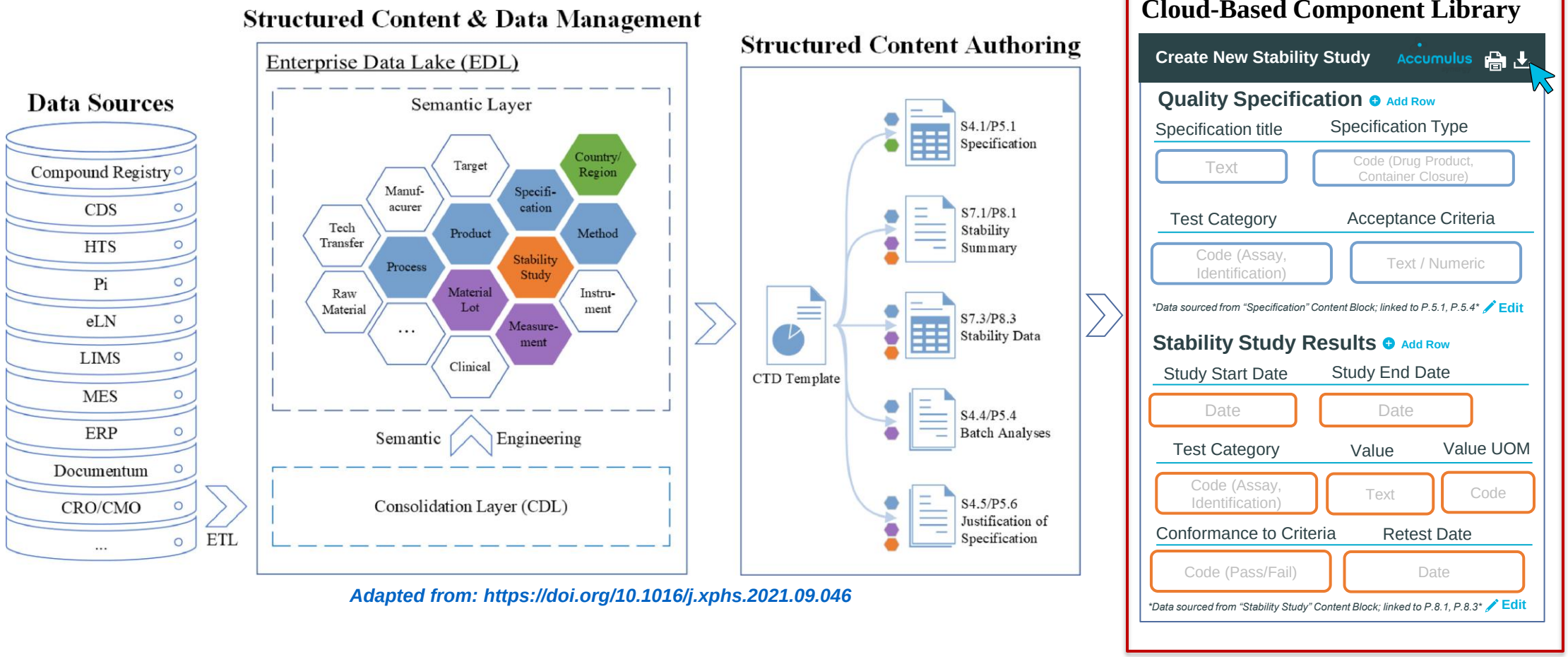
- Flexible data domains can be extended to promote reuse, lifecycling, and “smart” data management
- **<u>Ideal Scenario</u>:** Harmonized UDM structure and standardization across industry to facilitate consistent submission assembly and review

About the Figure:
- Hexagon = Data Domain
- Neighboring hexagons are semantically connected
- The model is 3D



Adapted from: https://doi.org/10.1016/j.xphs.2021.09.046

CMC UDM AND CLOUD TECHNOLOGIES ENABLE A DIGITAL OPERATING MODEL FOR REGULATORY SUBMISSION AND REVIEW



Adapted from: https://doi.org/10.1016/j.xphs.2021.09.046

Accumulus synergy

Introducing Data Exchange: A CMC Application Using Structured Data and a Cloud-based Ecosystem

Accumulus Synergy Vision

Accumulus Synergy is a non-profit organization dedicated to creating innovative solutions that can make regulatory review times more efficient and transforming global data exchange

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
- Pfizer
- Roche
- Sanofi
- Takeda
- Merck

Engaged Health Authorities

Conducted dozens of meetings across eleven different health authorities

Accumulus is Prioritizing Development of a CMC Data Exchange Solution

Accumulus Synergy's initial focus areas include:

Submission Review and Collaboration (SRC)

Intuitive platform communication tools will centralize and streamline Health Authority to Health Authority and Biopharma Company to Health Authority interactions

INITIAL FOCUS

Multi-HA reviews (FDA's Project Orbis)
Single-HA reviews (Labeling Negotiations)

Data Exchange (DataX)

An interoperable platform with the capacity to link data, visualizations, and narrative while leveraging existing and future standards

INITIAL FOCUS

CMC Data (Major Manufacturing Changes)

Data Analysis

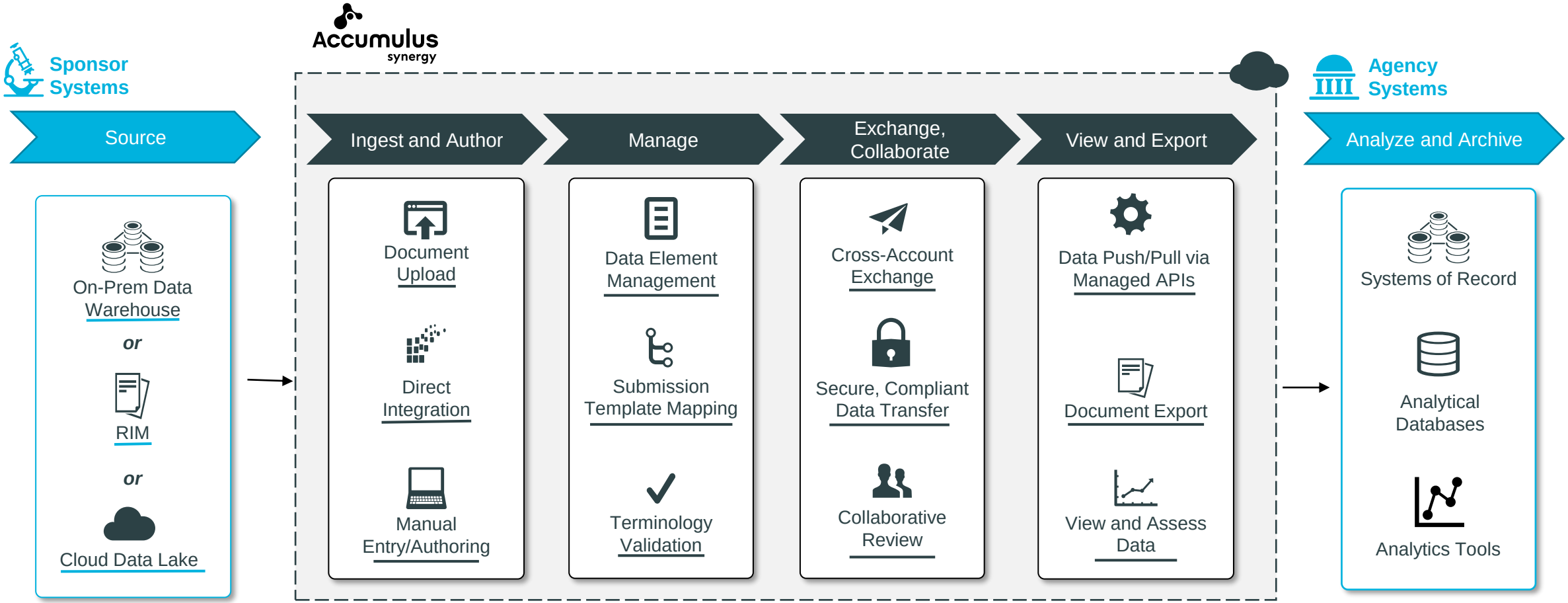
An objective, validated, and unbiased analytical toolkit that supports and enhances human decision-making

INITIAL FOCUS

Clinical Content (Automated TLF Generation)

Platform Vision

Accumulus provides a managed platform for sponsors and regulators to securely exchange and collaborate on structured regulatory information



A Structured CMC Content Model Enables Future State Interoperability

Present State

Based on stability results available to date, a shelf life of XX months is proposed for drug product stored at the recommended storage condition of X°C to X°C (referred to as X°C). The secondary packaging effectively protects the drug product vial from light exposure.

1. Lot Information

Two presentations were manufactured for clinical development and will be used for commercial production: XXX mg (XX mL) and XXX mg (XX mL) single-use vials containing XX mg/mL AMG XXX. The 2 presentations are considered to be equivalent, differing only in fill volume and container size. The results from the XXX mg and XXX mg drug product presentations were combined to support product shelf life, and at least 1 lot from each presentation was assessed for all evaluations.

A summary of the drug product lots in the stability program is provided in Table 1. The drug product stability program consists of 14 lots stored at the recommended storage condition of X°C. The overall program includes supporting, primary, and production lots. Comparability has been demonstrated between clinical and commercial sites (3.2.P.2.3, Product Comparability). All lots in the stability program were used to establish the proposed shelf life.

Transition State

Core Data Element	Sub-Element 1	Definition (Source)	PQ/CMC?	Data Type
Drug Product Identification				
Product Names & Identifiers				
Product Name		Name as authorised by a Medicines Regulatory Agency Note 1 to entry: This may be either an invented name, not liable to be confused with the common name, or a common or a scientific name accompanied by a trade mark or any other applicable descriptor (ISO IDMP 11615)	N	Text
	Product proprietary name	The exclusive name of a drug substance or drug product owned by a company under trademark law regardless of registration status with the Patent and Trademark Office (PQ/CMC & FDASOPP 8426)	Y	Text
		A name unprotected by trademark rights that is entirely in the public domain. It may be used without restriction by the public at large, both lay and professional (PQ/CMC 2021)	Y	Text
Strength StrengthNumericNumerator, StrengthNumericDenominator		The content of an active ingredient expressed quantitatively per dosage unit, per unit of volume, or per unit of weight, according to the pharmaceutical dosage form. This should be the strength as listed on the label (PQ/CMC, adapted from NCI EVS C53294) — The quantity of the substance contained in a Manufactured Item or Pharmaceutical Product. The strength (quantitative composition) shall be provided based on a	Y	Numeric

Accumulus Future State

Create New Stability Study – Drug Product *(P.8.1, P.8.3)*

Drug Product Information Add Row

Product Proprietary Name	Product Non-Proprietary Name	Strength	Strength UOM
ACCUMULIXIMAB	AMG XXX	XXX	MG

Data sourced from "Product" Content Block; linked to S.1.1, P.1 Edit

Batch/Lot Information Add Row

Batch/Lot Number	Batch Size	Batch Size UOM	Batch Utilization	Manufacturing Site	Manufacturing Date
ATO352810XX	500	KG	Stability	ATO	05/04/2022

Data sourced from "Batch/Lot Information" Content Block; linked to P.5.4 Edit

Container Closure System

Primary Packaging Component Add Row

Container Closure System Description	Container Type	Container Size	Container Size UOM	Container Fill	Container Fill Unit	Closure Type
Amber, opaque, single-use glass vial	Vial	5	mL	2	mL	Child-resistant, metal

Secondary Packaging Component Add Row

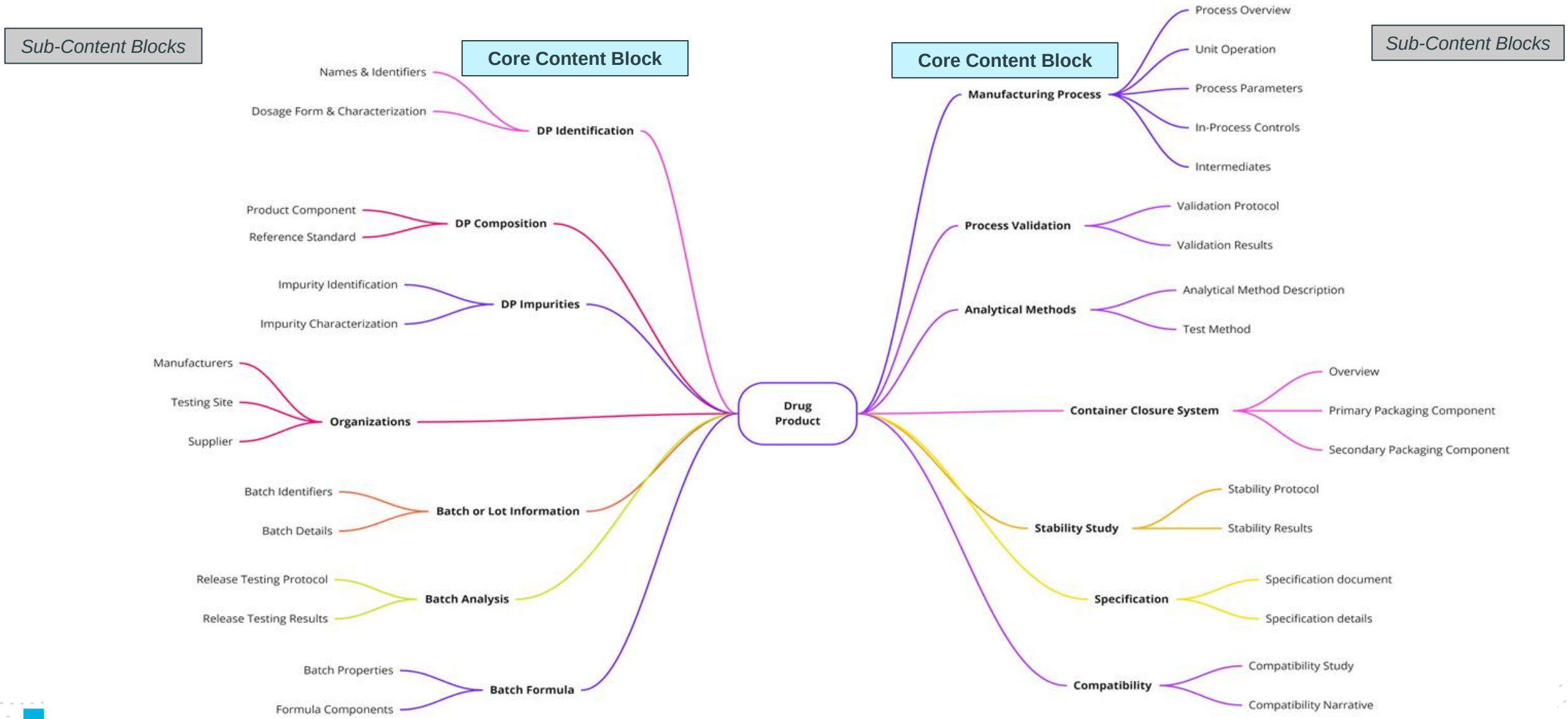
Container Closure System Description	Container Type	Container Size	Container Size UOM	Container Fill	Container Fill Unit	Closure Type
Aluminum canister, protects from light	Canister	10	mL	5	mL	Roll-on, metal

The CMC Content Model provides an initial "instruction manual" for bringing together:

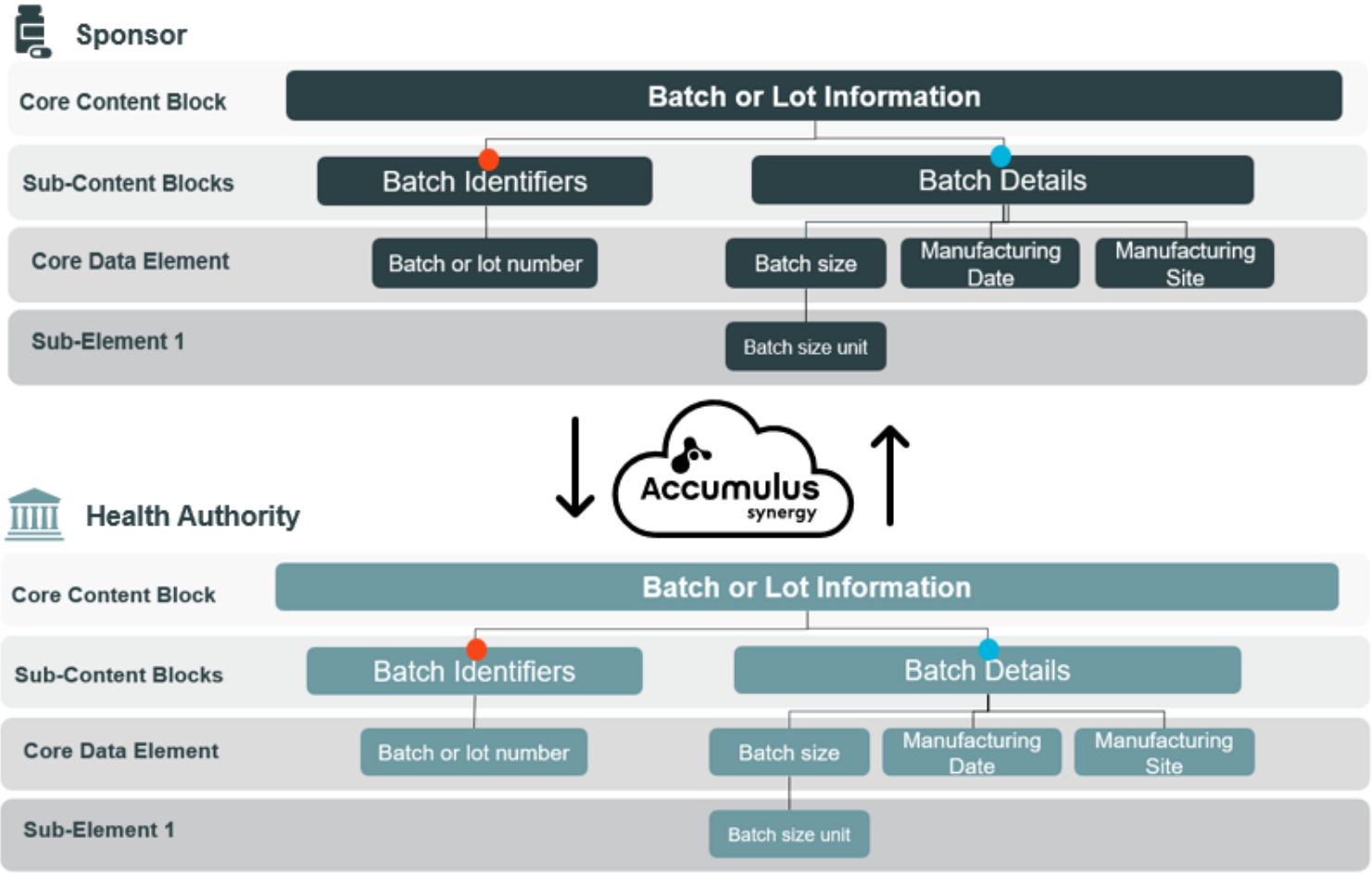
ISO IDMP · SPOR · PQ/CMC · eCTD* · ICH Q12 · HL7 FHIR

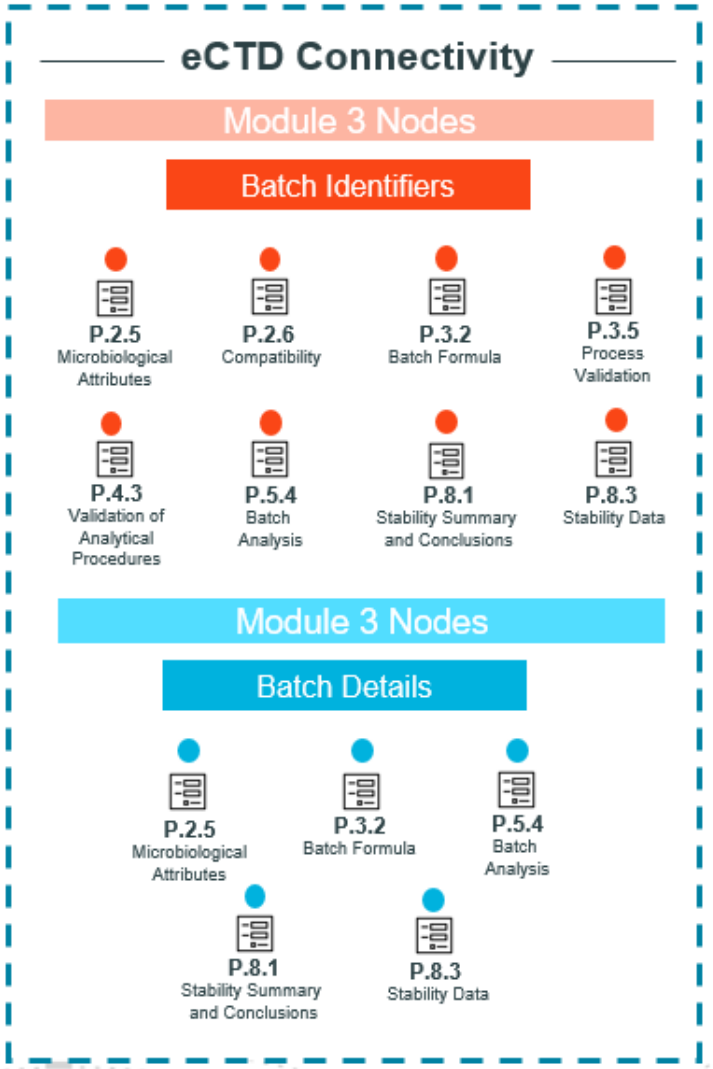
***the Model is adaptable to updates made under ICH M4Q (R2)**

The CMC Content Model organizes CMC information into Core Content Blocks and Sub-Content Blocks



Content Model Brings Modularity and Structure to Module 3 Data Exchange





ILLUSTRATIVE

Technical Application of the CMC Content Model

HL7 FHIR is a standard for exchanging information electronically across healthcare applications

SPOR, PQ/CMC, and several other emerging standards and projects (DADI, ePI) are being built in FHIR

HTML

Impurity
Classification: Degradation Product
Method: Chromatography
Level: 0.05%
Level: 0.1 mg per 1 day
Specified: true

Substance
Identifier: example-unii-nacl

Name: Sodium Chloride

Property
Type: Mutagenicity/Genotoxicity - Text: Mutagenicity/Genotoxicity extra info free text
Value: true

Property
Type: ICH M7 Class
Value: Class 1

Property
Type: (Q)SAR Assessment Summary
Value: QSAR Assessment Summary: details here

Information Source: UK Pharmacopeia

Structure

Representation

Document
Identifier: STRUCT-001
Type: Substance Structure
url: https://example.org/docStore/struct-001

DRAFT

XML

```
▼<impurity>
  ▼<extension url="http://example.org/fhir/extension/impurityClassification">
    ▼<valueCoding>
        <system value="http://example.org/fda/impurity-classification"/>
        <code value="C176816"/>
        <display value="Degradation Product"/>
      </valueCoding>
    </extension>
  ▼<extension url="http://example.org/fhir/extension/impurityMethod">
    ▼<valueCoding>
        <system value="http://example.org/fda/impurity-method"/>
        <code value="123456"/>
        <display value="Chromatography"/>
      </valueCoding>
    </extension>
  ▼<extension url="http://example.org/fhir/extension/impurityLevel">
    ▼<valueQuantity>
        <value value="0.05"/>
        <unit value="%"/>
      </valueQuantity>
    </extension>
```

DRAFT

Accumulus is working with multiple collaborators and stakeholders to develop the CMC Content Model into an **implementable, publicly available Common CMC Standard** via HL7 FHIR processes

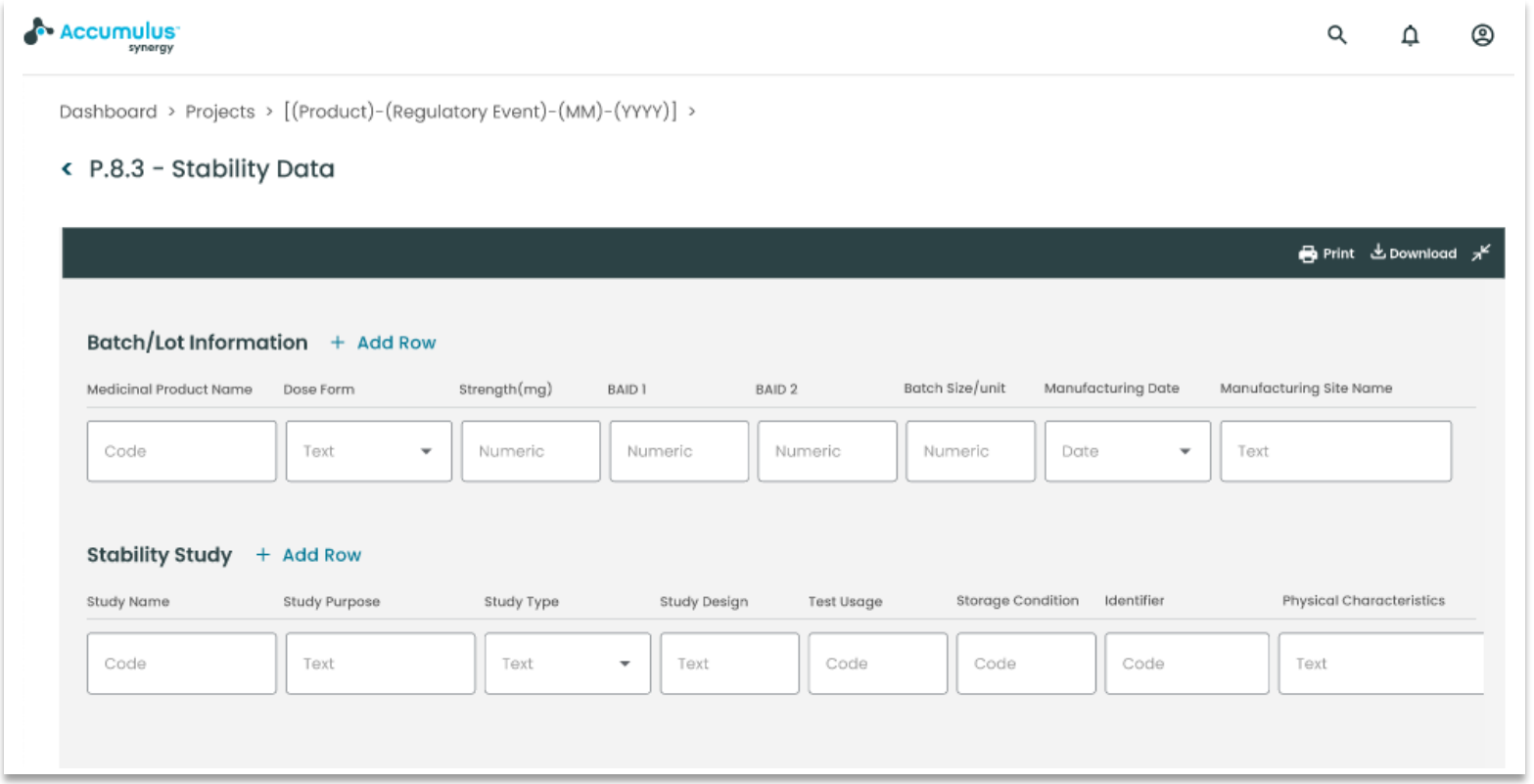
Data is Brought into the System, Assessed to Ensure Quality, and Submitted for Agency Review

Illustrative

Sponsor

- ***Manual Entry***
- or
- ***Excel Upload***
- or
- ***Direct Integration***

Import data

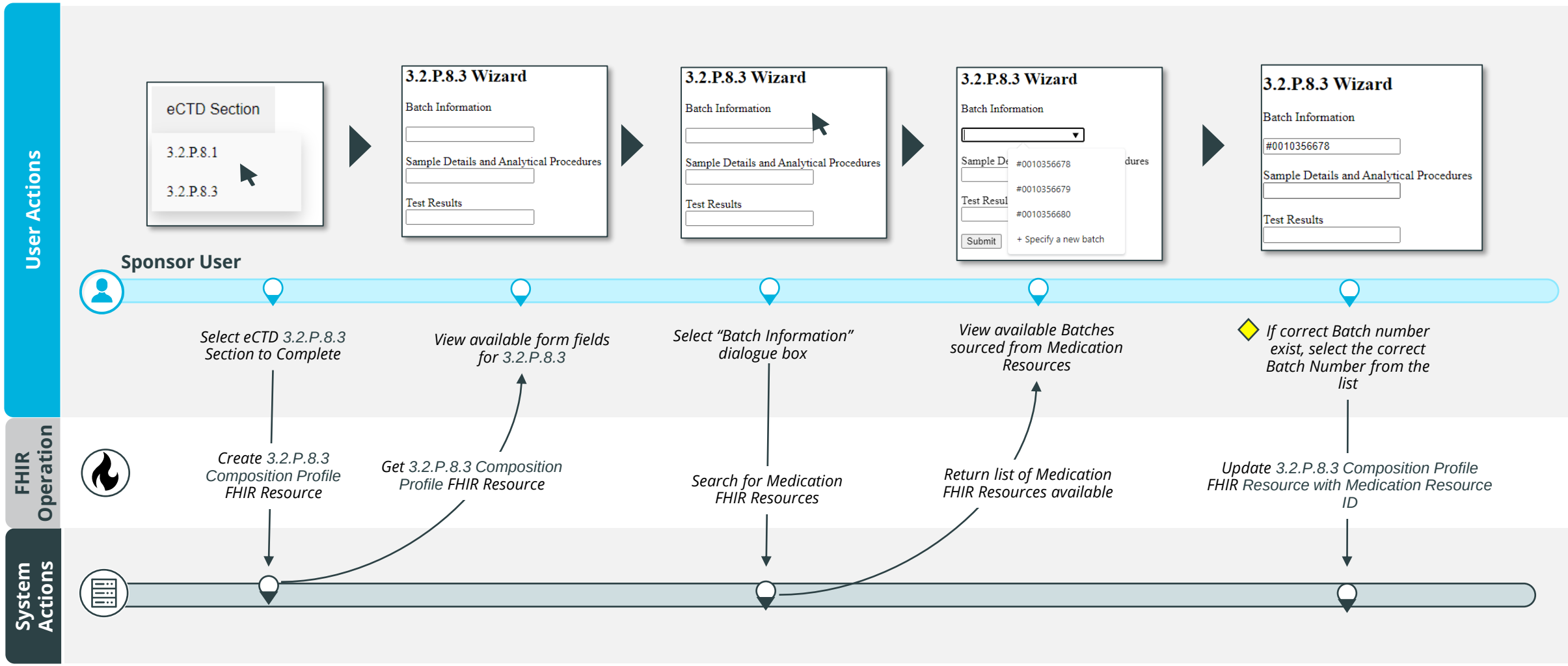


HA

Export shared data in alignment with regulatory requirements

- *Excel Export*
- *Integrate with systems of record*

Content model can be used to bring the **eCTD structure** and data requirements to the platform's **UI** and **FHIR** exchange capabilities



Illustrative

DataX Supports Visualization of Data, Narrative, and Graphical Content in a “Single Pane of Glass”

www.accumulus.org

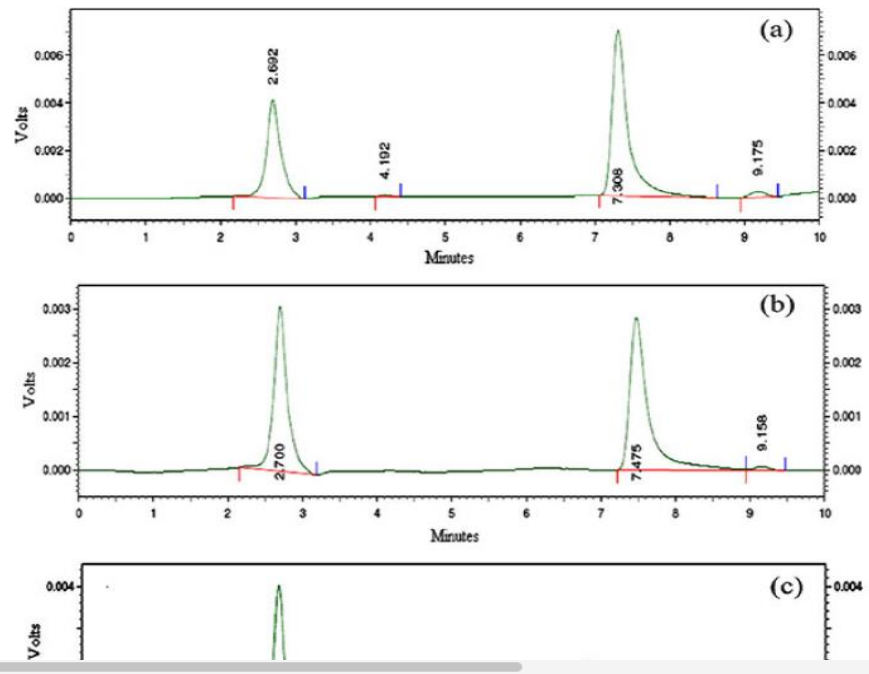
Accumulus synergy

View Only Mode

[(Product)-(Regulatory Event)-(MM)-(YYYY)]

Print Download

Figure 2. Chromatogram of degradation products of bromazepam obtained during the kinetic study of acid hydrolysis after 30 (a), 60 (b), 90 (c), 120 (d), and 150 (e) minutes.



Documentss Download all

DATA

P.8.3 - Stability Data

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PREVIEW

NARRATIVE

Quality Overall Summary

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GRAPHIC

Fig 2. HPLC Chromatograms

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PREVIEW

Next Steps and Acknowledgements

Continuing Activities Towards Advancing CMC Regulatory Innovation

- Maintain and expand engagement with Global Health Authorities
- Maturation of the CMC Content Model into a Common CMC Standard via HL7 FHIR

Estimated Accumulus Platform Development Milestones, 2022 – 2024:

- **Feature Previews** – *Limited scope highlight of select features*
- **Product Previews** – *Mock submission workflows enabled*
- **Pilot Studies** – *Real data submission*

Accumulus synergy

Sponsors

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

Health Authorities

Conducted dozens of meetings across eleven different health authorities

Thank you!