TAKING KNOWLEDGE MANAGEMENT INTO THE CLOUD: USING STRUCTURED DATA IN A CLOUD-BASED ECOSYSTEM TO ENABLE REUSABILITY, AGILITY, AND INTEROPERABILITY

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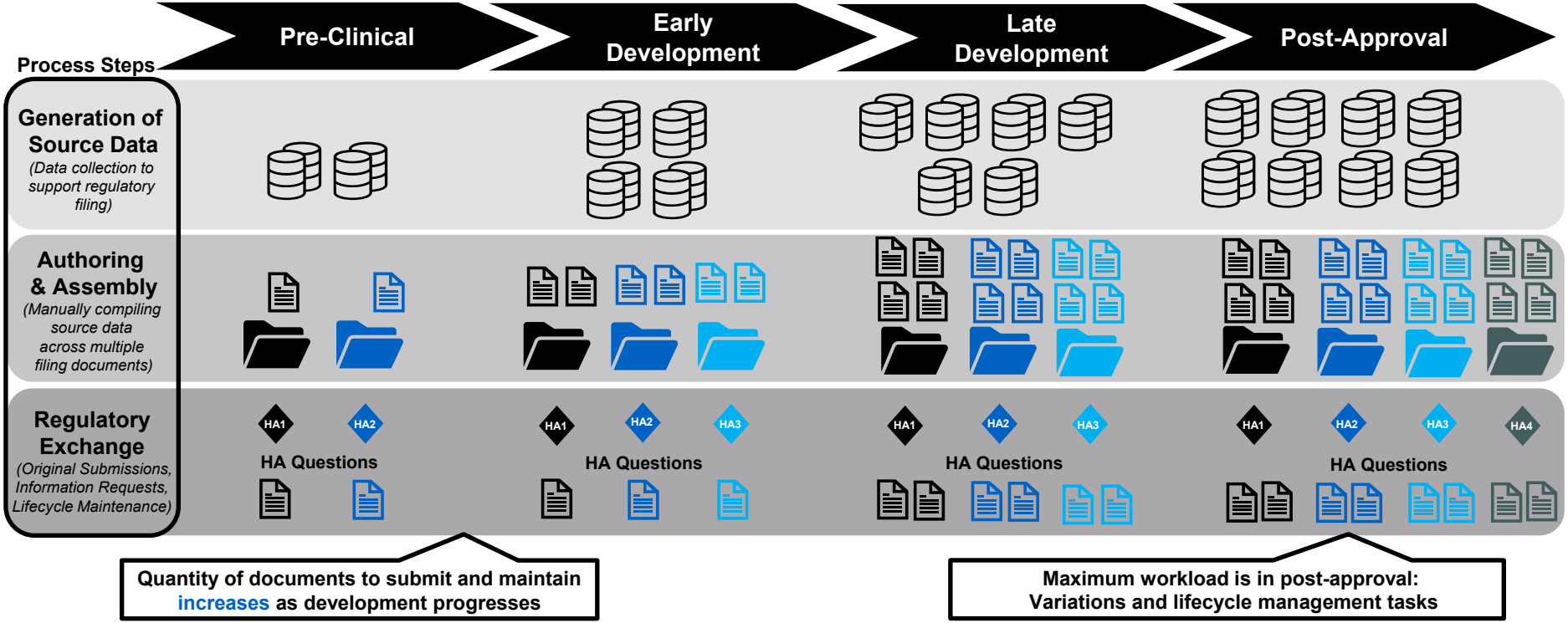
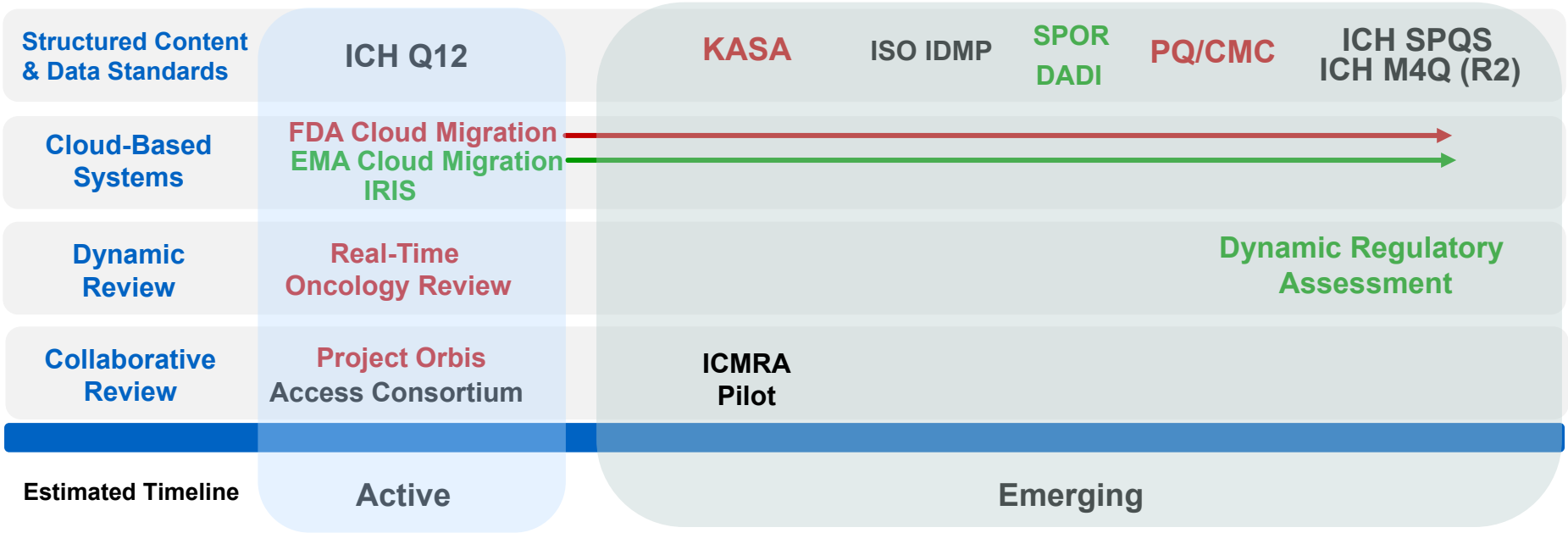
CURRENT REGULATORY CMC AUTHORING PROCESS



5000+ different events (authoring, review, verification) needed to assemble full CMC package (~200 documents)

SUMMARY OF EMERGING REGULATORY MODERNIZATION INITIATIVES



Key
Europe
USA
International

The external regulatory ecosystem is actively undergoing technological and operational transformation, with evolving expectations and requirements for industry.

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STRUCTURED CONTENT AND DATA MANAGEMENT (SCDM) FOR REGULATORY CONTENT AUTHORING

Structured Content and Data Management

SCM tracks content through the use of structured data elements or components

Structured Content can include:

- Sections
- Paragraphs
- Tables
- Data
- Figures

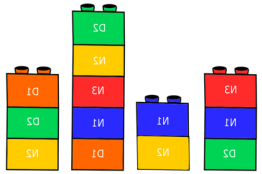
These structured components are made up of smaller blocks of content (data or narratives) that are combined and recombined to author regulatory filings

Content is organized at a component level, rather than the document level

Blocks of content are "component" structured in the appropriate arrangement in Module 3

The components are reusable and traceable: Components can be relinked, and data can be updated from the original component configuration

Knowledge map



While SCDM can be used to streamline document assembly, it also enables data to be "unlocked" from PDF format to simplify data management tasks and allow exchange of data in a usable, exportable format

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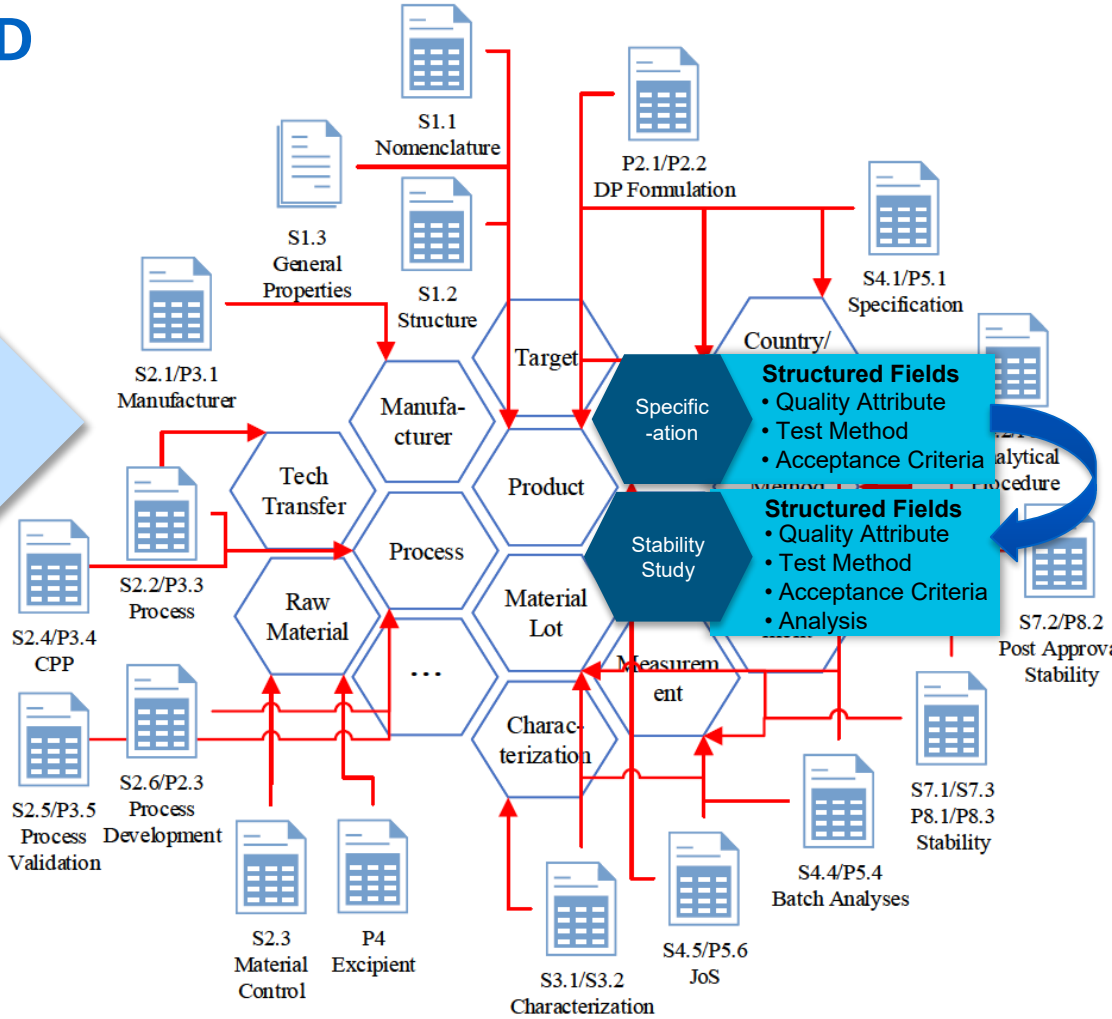
SPONSOR CMC UNIFIED DATA MODEL (UDM)

Key Points:

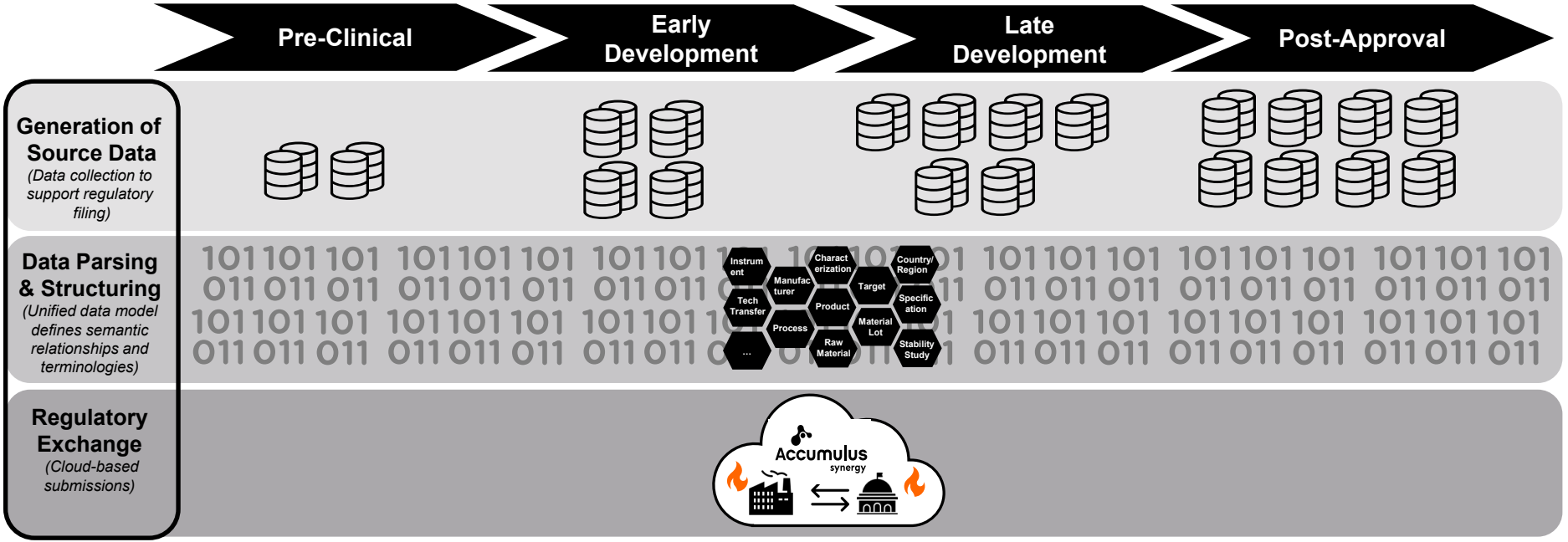
- Flexible data domains can be extended to promote reuse, lifecycling, and “smart” data management
- **Ideal Scenario:** Harmonized UDM structure and standardization across industry to facilitate consistent submission assembly and review

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

FUTURE STATE REGULATORY CMC AUTHORING PROCESS



Simplified, automation-ready, real-time data exchange can be enabled by a CMC unified data model and a cloud-based ecosystem

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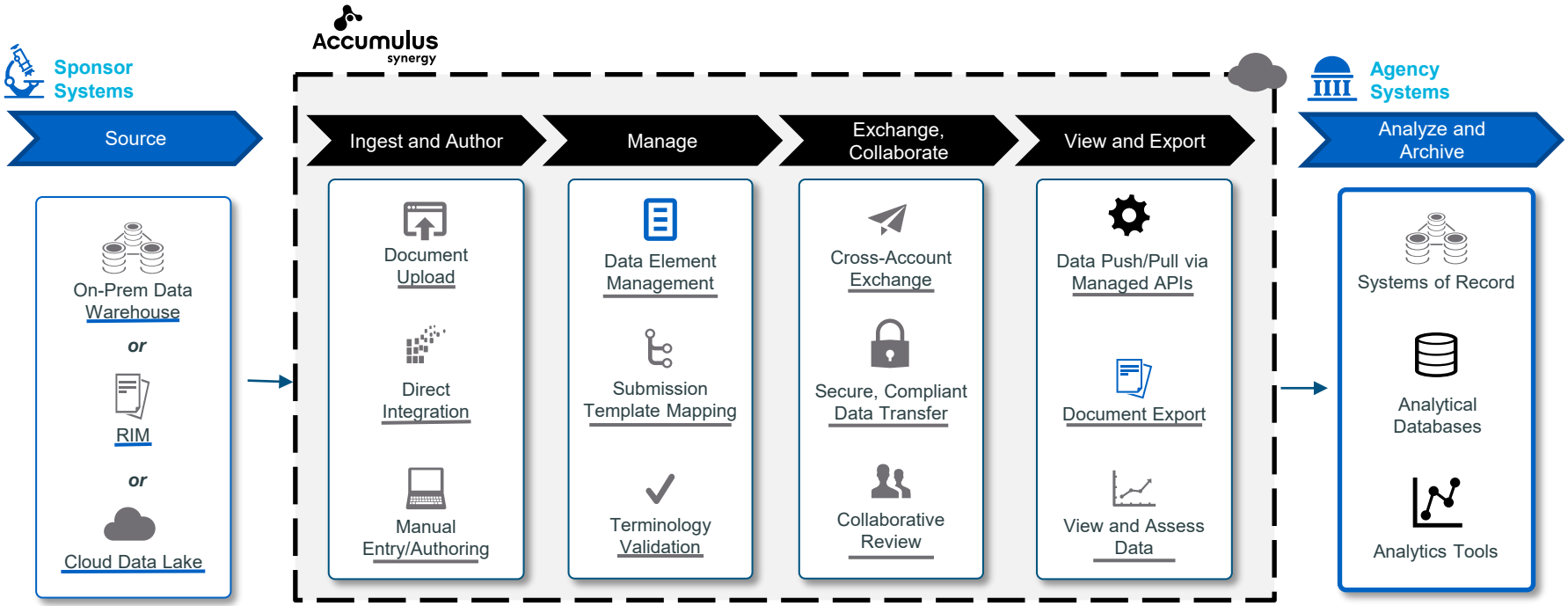
ACCUMULUS PLATFORM VISION

Accumulus is a non-profit organization developing a managed cloud-based platform for sponsors and regulators to securely exchange and collaborate on structured regulatory information



PROJECTED INITIAL USE CASES FOR ACCUMULUS SYNERGY

Initial focus areas for product development are:

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)

Expected progression of features will be concurrent with expansion of user base (both Health Authorities and Biopharma Companies)

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The Vision for Data Exchange

We will bring safe and effective medicines to patients faster and more efficiently by reimagining regulatory information exchange

To achieve our mission, we will focus on delivering a cloud platform that allows for exchange of structured data in alignment with changing regulatory needs. The platform will allow customers to:

- **Store validated regulatory data in a common format**
- **Automatically map terminology across jurisdictions**
- **Construct templated filings from common data**
- **Exchange structured filings with global regulators**
- **Flexibly import/export data through key integrations**

Cross-Functional Application and Scalability

CMC | **Clinical** | **Pre-clinical** | **Safety**

ACCUMULUS IS BUILDING A NOVEL CMC INTERNATIONAL STANDARD TO TRANSFORM NARRATIVE-BASED SUBMISSIONS TO A STRUCTURED, DATA-DRIVEN FORMAT

ILLUSTRATIVE

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 & FDA SOPP 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

Cloud-Based 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

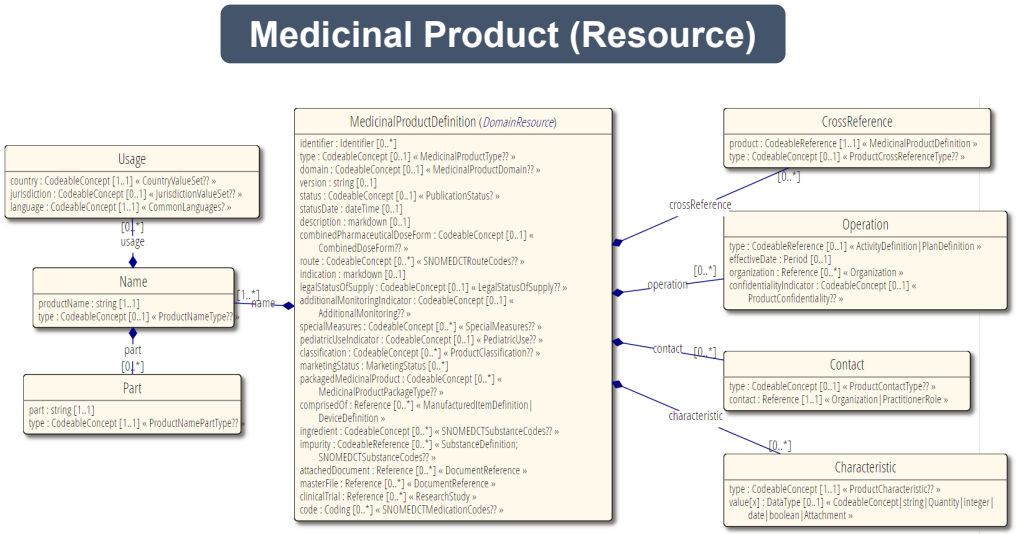
Secondary Packaging Component Add Row

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 International Standard project establishes a data model and information architecture to support the transition from the present state to the future state.

Accumulus Synergy is working with multiple collaborators and stakeholders to develop the international CMC standard via HL7 FHIR processes, targeting **Implementation Guide publication in 2024**

FHIR AS AN ENABLER FOR STRUCTURED DATA



http://hl7.org/fhir/index.html

- **FHIR – Fast Healthcare Interoperability Resources**
- Healthcare data exchange standard with accompanying application program interface (API)
- Accepted formats include XML, JSON, HTTP, REST, UML
- Capability to manage structured and semi-structured data, as well as file attachments
- Compatible with external controlled terminology lists for codable elements
- Standardized templates with customization options

FHIR is increasingly being adopted to support Regulatory Affairs activities to enhance data interoperability, searchability, accessibility, and standardization

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FHIR-BASED STRUCTURED DATA TRANSFORMATION

Current State

3.2.P.7 Container Closure System

The drug product tablets are packed in white, high density polyethylene (HDPE) plastic bottles, or in blister packs with aluminum lidding.

Each bottle is capped with a white, child-resistant closure containing a pulp liner and aluminum foil induction seal

Tablets are also packaged as unit-dose in a base film consisting of rigid blister film laminated to a barrier film. A configuration scheme of the tablets is presented in Table 1.

Table 1: Configuration Scheme

Strength	Package Type	Supplier	Count
45 mg	white, high density polyethylene (HDPE) plastic bottles with child-resistant closure containing a pulp liner and alumnium foil induction seal	Container Co. of America (all components)	28 tablets
	Unit-dose blister strips consisting of a rigid blister film laminated to a barrier film; the package contains 2 blister strips of fourteen tablets	Foil – Reynolds Wrap USA Film - Plastics of America	28 tablets
350 mg	white, high density polyethylene (HDPE) plastic bottles with child-resistant closure containing a pulp liner and alumnium foil induction seal	Container Co. of America (all components)	28 tablets
	Unit-dose blister strips consisting of a rigid blister film laminated to a barrier film; the package contains 2 blister strips of fourteen tablets	Foil – Reynolds Wrap USA Film - Plastics of America	28 tablets

Proposed Future State

Package : *Section 10 - Container Closure System*
Description: Any textual comments that describe the sum of container closure system (CCS) components that together contain and protect the dosage form or drug substance.

Packaging
Type: Box
Material: Cardboard
Shelf Life: 2 a

DRAFT

Manufacturer
Organization : *Section 4.1 - Manufacturer*
Identifier: 3008816891
Name: A+ Secure Packaging, LLC
Address: 339 Mason Rd, La Vergne, Tennessee, 37086, USA

Property
Type: Functional
Value: false

Property
Type: Quality Standard
Value: USP

Packaging (part)
Type: Tape
Material: Plastic

Manufacturer
Organization : *Section 4.1 - Manufacturer*
Identifier: 3008816891
Name: A+ Secure Packaging, LLC
Address: 339 Mason Rd, La Vergne, Tennessee, 37086, USA

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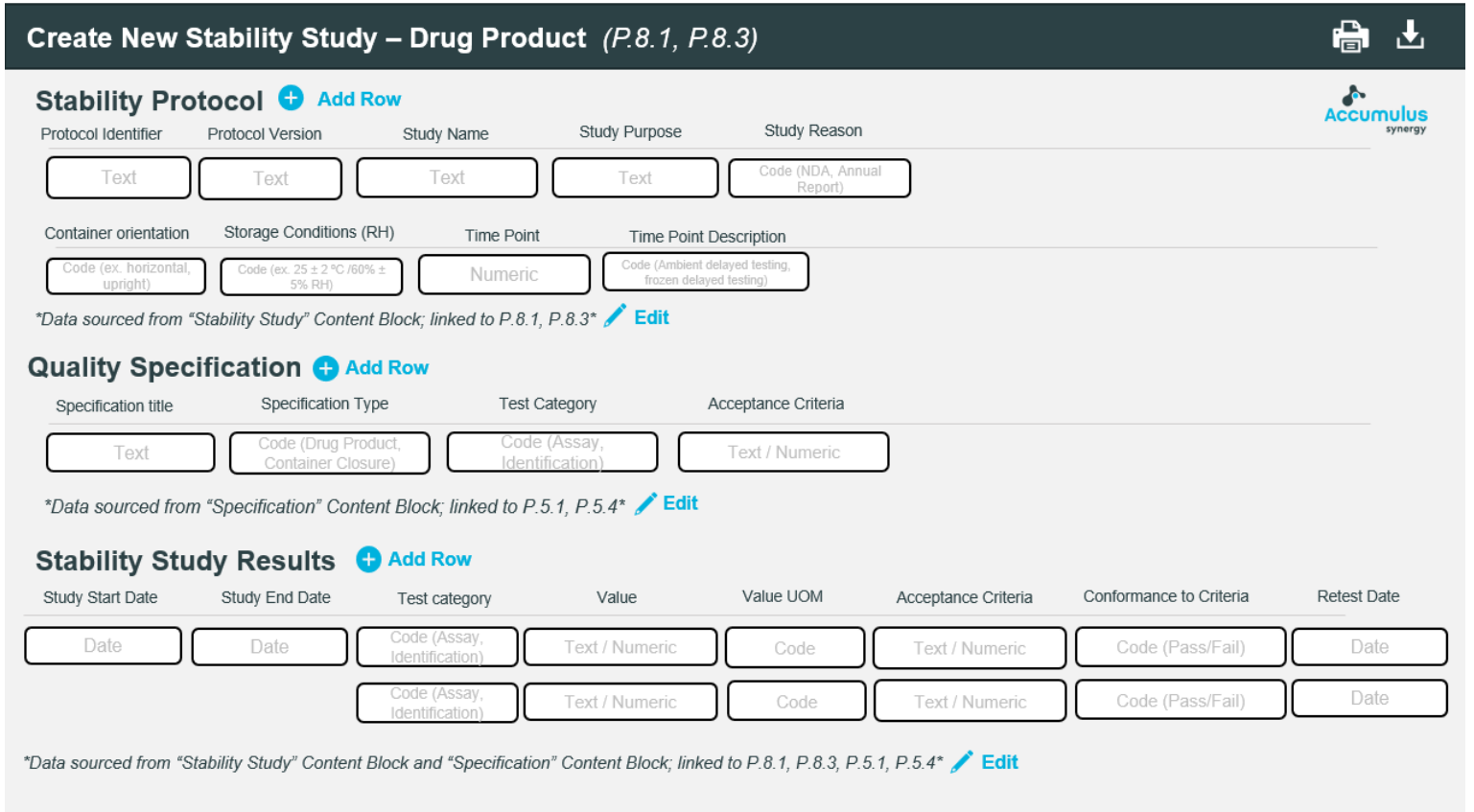
SAMPLE STABILITY STUDY VIEW FOR DRUG PRODUCT

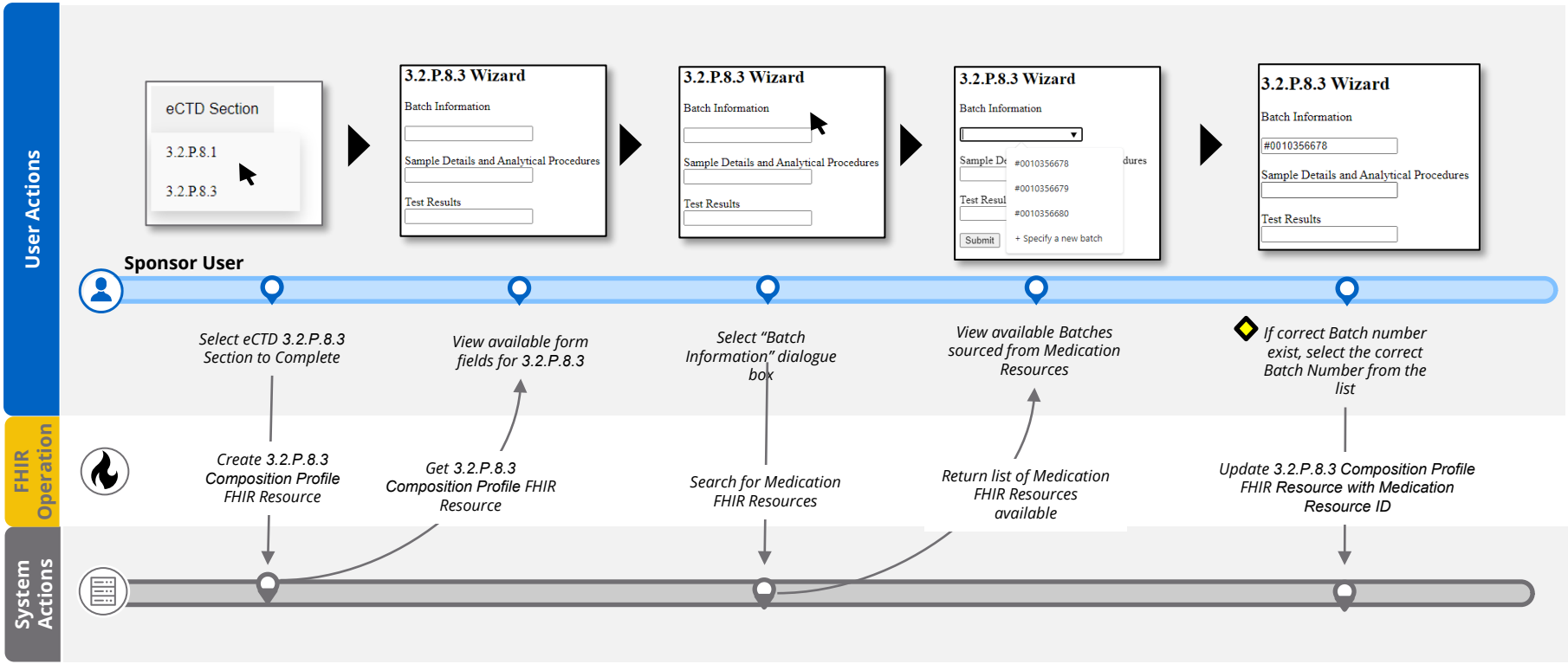
(ECTD SECTIONS P.8.1, P.8.3)

ILLUSTRATIVE



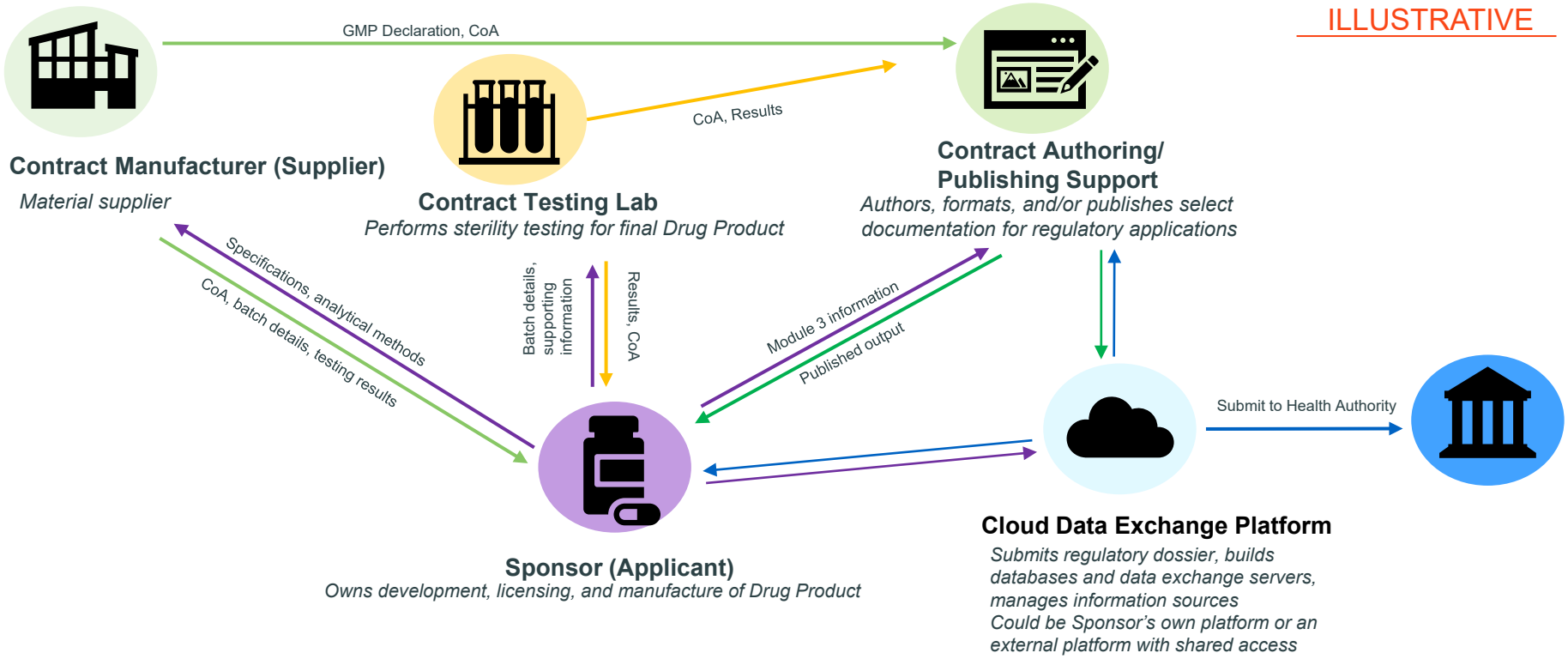
THE PLATFORM'S UI CAN BRIDGE CTD REGULATORY REQUIREMENTS WITH SEAMLESS FHIR EXCHANGE CAPABILITIES

ILLUSTRATIVE



EXAMPLE SCENARIO BUILDING – SPONSOR WORKFLOW

ILLUSTRATIVE



NEXT STEPS

Continuing Activities Towards Advancing CMC Regulatory Innovation

- Maintain and expand engagement with Global Health Authorities
- Maturation of the International CMC Standard via HL7 FHIR

Anticipated Accumulus Platform Development Milestones, 2023 – 2025:

- **Feature Previews** – *Limited scope highlight of select features*
- **Product Previews** – *Mock submission workflows enabled*
- **Pilot Studies** – *Real data submission in pilot environment*
- **Platform Launch** – *Real data submission via the platform*

Accumulus synergy

Sponsors

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

Health Authorities

Conducted dozens of meetings across eleven different health authorities

Thank you!

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