Innovative Digital Regulatory Transformation:
The First Cloud-based Submission

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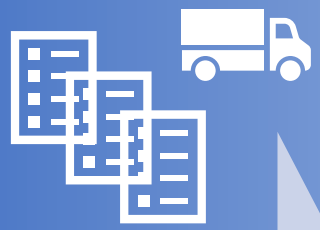
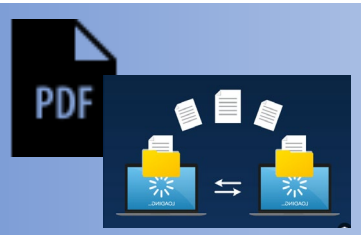
CMC Strategy Forum Latin America
20 August 2025

Regulatory Submissions: Then, Now and Next



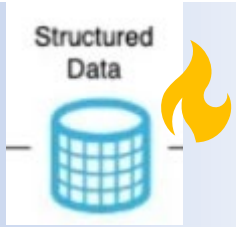
1990

Paper submissions



2000

E-paper submissions



2024

Standards & templates

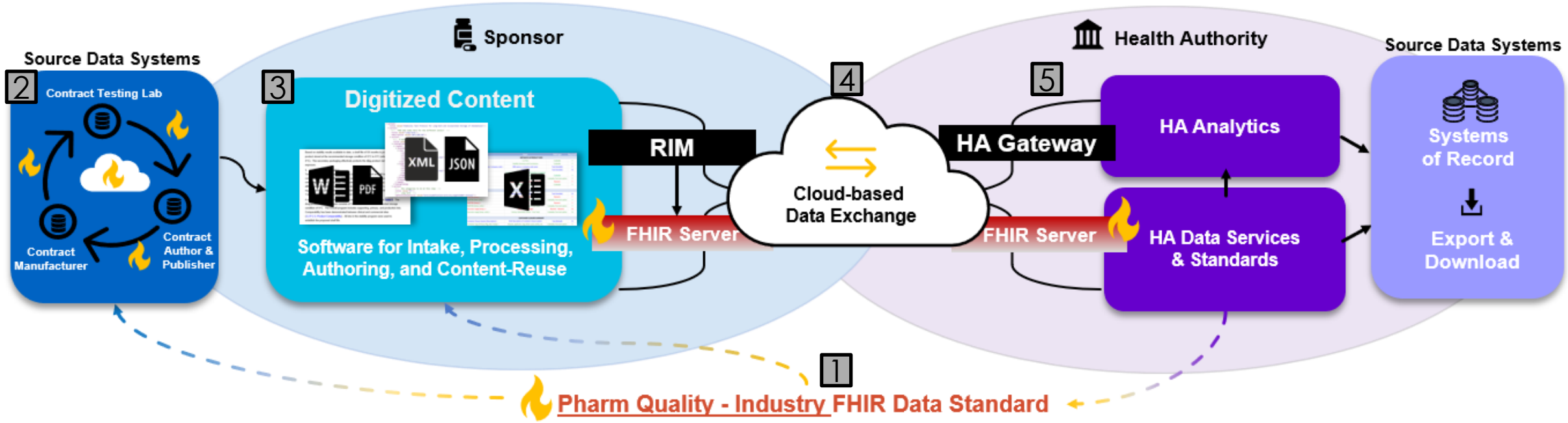
2026

automated submission preparation

Cloud based data exchange

ONE CLICK SUBMISSION

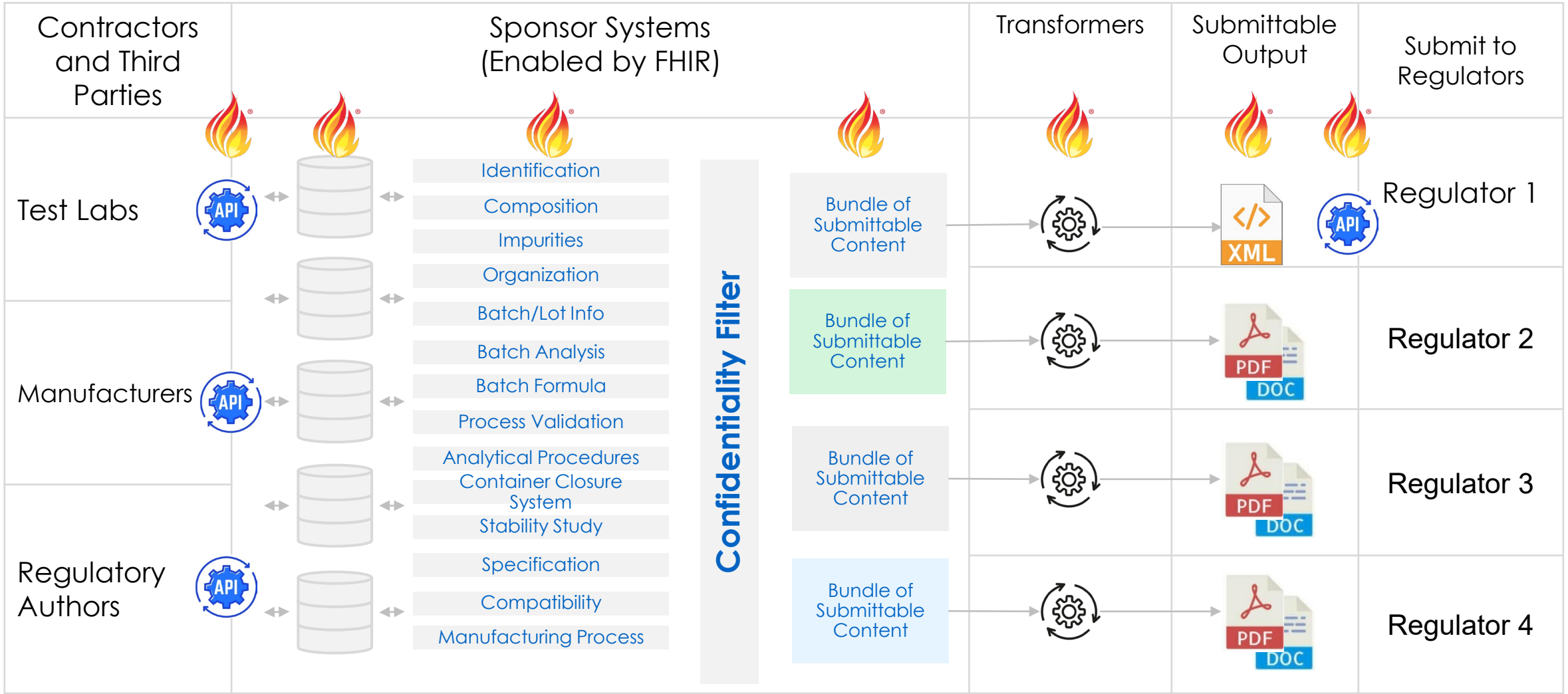
Future State Vision for Regulatory Exchange



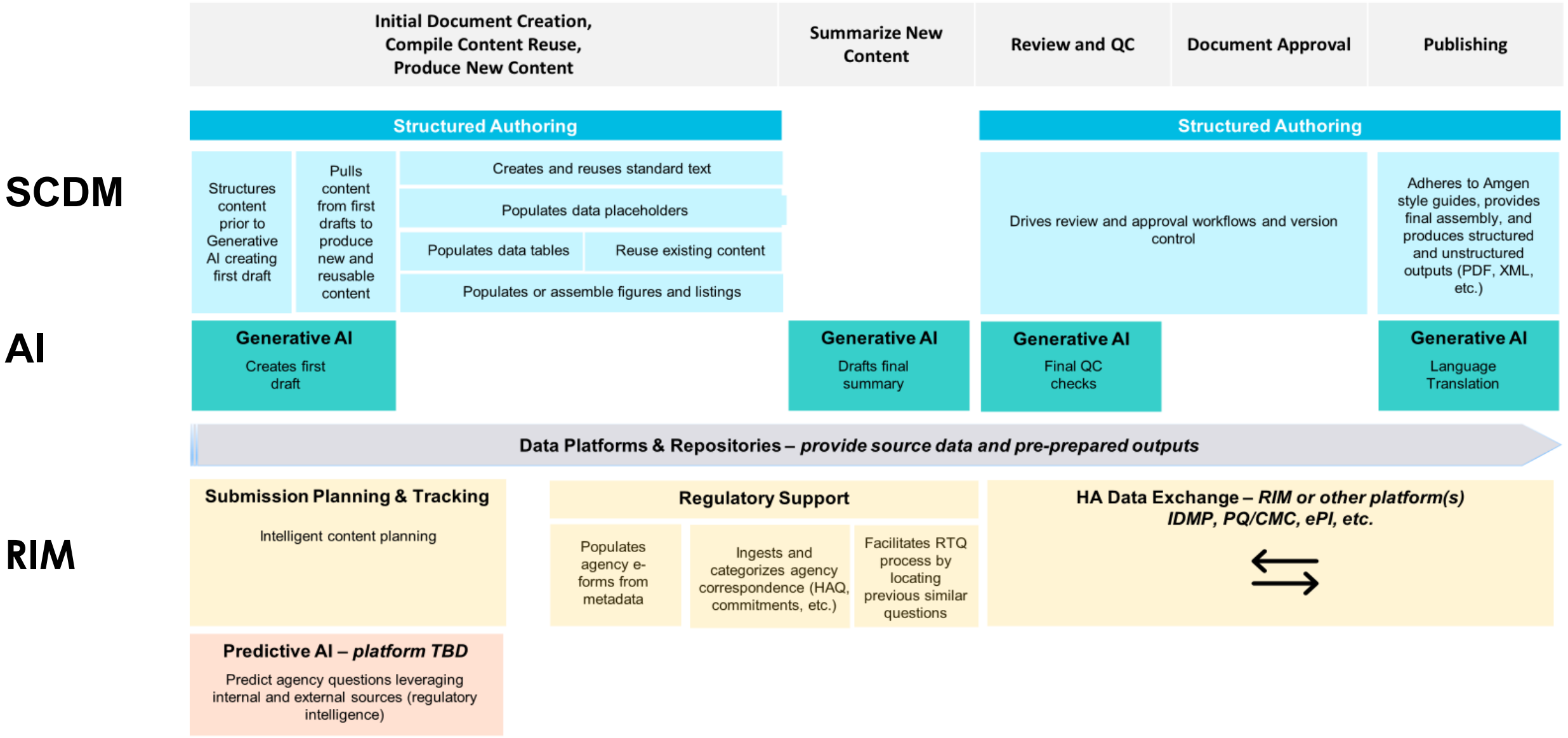
1. Health authority and industry FHIR standards are used to standardize data at the source
2. Sponsor Source data systems are connected through structured, standardized data
3. Digital content management systems render data in the required format
4. A cloud-based data exchange system connects the sponsor and regulator environments
5. Regulators receive structured, standardized data that can be used in analytics software

From Anderson, Algorri, Abernathy 2023

FHIR Data Pipeline – Pharmaceutical Quality (Industry)



Partnering Different Technologies to Digitalize RA Content



Structured/Standardized Data and Content Facilitates Automation

STATIC

Table 1. Formulation Buffer Batch Formula

Formula Ingredient	Reference to Standard	Target Concentration	Target Amount per XX kg Batch Size <Smallest batch>	Target Amount per XXX kg Batch Size <Largest batch>

* USP = United States Pharmacopeia; NF = United States National Formulary

2. X% Polysorbate 20/80 Solution

Polysorbate 20/80 is added during drug product formulation as a X% stock solution. The formulation ingredients and amounts for the X% polysorbate 20/80 solution are shown in the table below. The batch size for the polysorbate 20/80 solution is fixed at 1.0 kg.

AUTOMATION-READY

Table 1. Formulation Buffer Batch Formula

Formula Ingredient	Reference to Standard	Target Concentration	Target Amount per Batch size [Buffer].minimum Batch size [Buffer].range Units Batch Size	Target Amount per Batch size [Buffer].maximum Batch size [Buffer].range Units Batch Size
Excipient1.name	Excipient1.grade abbreviation	Strength [Excipient1] Strength.unit	Excipient1 quantity per batch [Buffer].minimum Quantity.unit	Excipient1 quantity per batch [Buffer].minimum Quantity unit.

2. Strength [Stock Solution Excipient] Stock Solution Strength [unit] Stock Solution Excipient.name Solution

Stock Solution Excipient.name is added during drug product formulation as a Strength [Stock Solution Excipient] Stock Solution Strength [unit] stock solution. The formulation ingredients and amounts for the Strength [Stock Solution Excipient] Stock Solution Strength [unit] Stock Solution Excipient.name solution are shown in the table below. The batch size for the Stock Solution Excipient.name solution is fixed at batch size [Stock Solution] Stock Solution batch size [Stock Solution].units.

ASSEMBLED

Illustrative

Table 1. Formulation Buffer Batch Formula

Formula Ingredient	Reference to Standard	Target Concentration	Amount per 50 kg Batch	Excipient batch quantity per <Enter Batch size [Buffer].maximum >
Proline (USP, PhEur, JP)		220 mM	1260 g	
Acetic acid, glacial (USP, PhEur, JP)		20 mM	59.8 g	
Sodium hydroxide, 10M solution (NF, PhEur, JP) a		qs	qs to target pH b	
Water for injection (USP, PhEur, JP)		qs	qs to target weight	

JP = Japanese Pharmacopeia; NF = United States National Formulary; PhEur = European Pharmacoepeia; qs = quantum suffict; USP = United States Pharmacopeia

2. 0.01 mg/mL Polysorbate 80 Solution

Polysorbate 80 is added during drug product formulation as a 0.01 mg/mL stock solution. The formulation ingredients and amounts for the 0.01 mg/mL Polysorbate 80 solution are shown in the table below. The batch size for the Polysorbate 80 solution is fixed at 1.5 kg.

Unstructured Content

- Difficult to keep updated
- Time consuming to format
- Limited scalability & reusability

Structured Content

- Independent from submission
- Human & machine readable
- Individual building block

Structured Content Authoring

- Automated authoring
- Reuse across documents
- Reduce DV requirements

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Automation Facilitates Digitalization and Flexible Outputs

Current Filing Templates → **Convert and Transform** → **Automation-Ready Templates**

Only unstructured Word/PDF documents are used

Stability studies are conducted at the recommended storage condition to support the shelf life and were performed per ICH Harmonized Tripartite Guide, *Stability Testing of Biotechnological/Biological Products* (Q5C) and *Stability Testing of New Drug Substances and Products* (Q1A). Stability studies at elevated temperatures are also conducted to assess the effect of these conditions on product quality. In addition, experimental drug product studies including ICH and clinical photostability, temperature cycling, and transportation were performed.

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 2°C to 8°C (referred to as 5°C). Storage for a single period of up to X months is proposed for the drug product stored at a maximum of XX°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: 100 mg (10 mL) and 500 mg (50 mL) single-use vials containing 10 mg/mL <<INN>>. The 2 presentations are considered to be equivalent, differing only in fill volume and container size. The results from the 100 mg and 500 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 5°C. The overall program includes supporting, primary, and production lots. Comparability has been demonstrated between clinical (Amgen Thousand Oaks [ATO])

Automation-ready Templates are Compatible with Structured Data Formats

Amgen commits to continue the ongoing stability studies described in 3.2.S.7.1 (Stability Summary and Conclusions) until completion.

For future production of drug substance, a minimum of {{Stability lots [DS, post-approval].quantity}} lot(s) of {{Name.nonproprietary}} drug substance will be added to the postapproval- stability program annually, stored at the recommended condition of {{Storage condition [DS, recommended].temp}}°C ({{storage condition [DS, recommended].temp range max}}- {{storage condition [DS, recommended].temp range min}}°C), and tested according to the protocol provided in Table 1. If drug substance is not manufactured during a given year, a stability study is not required for that year.

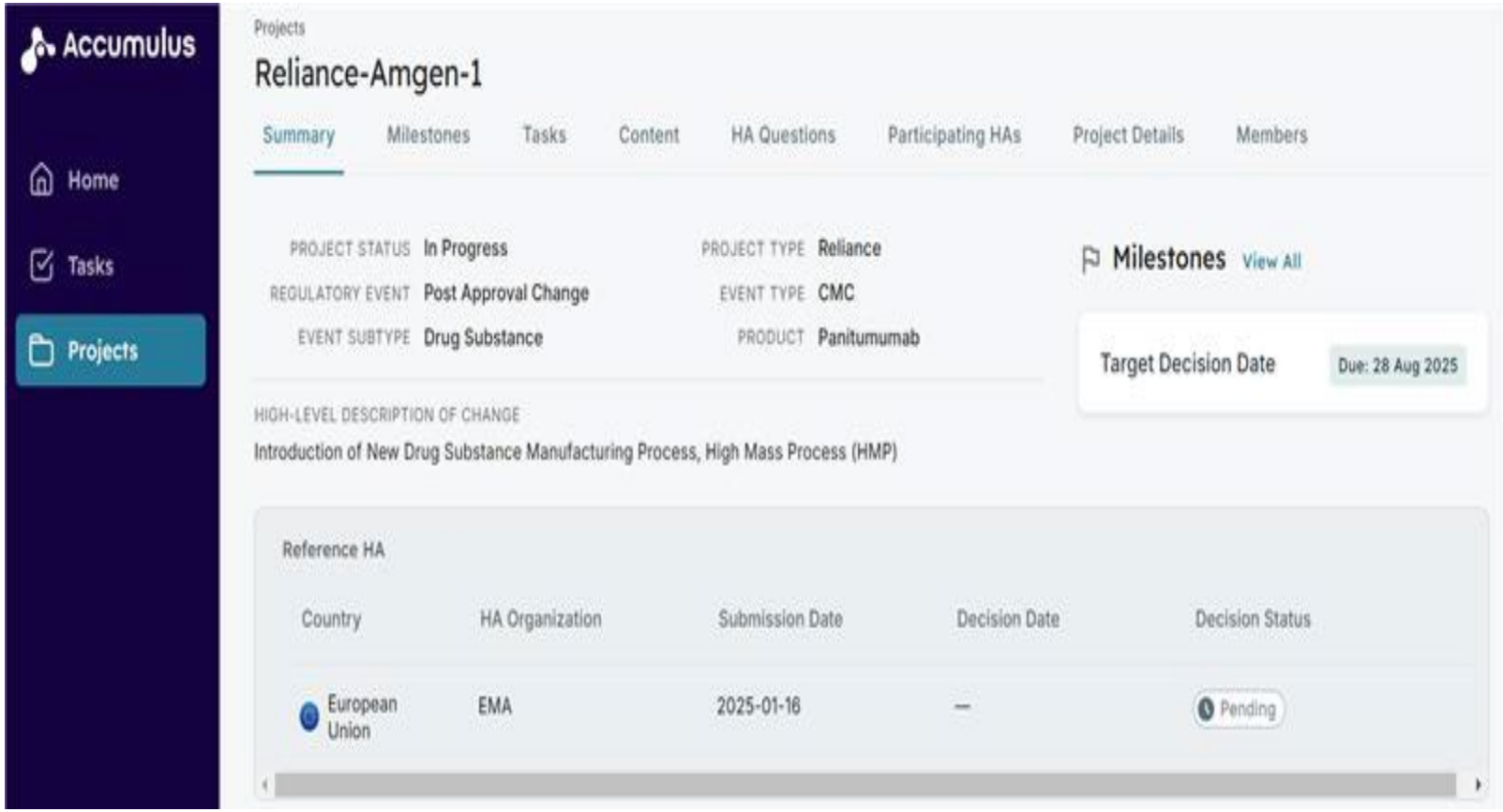
	A	B	C	D	E	F	G	H	I
1	Table 1. Post-approval Test Schedule for Product.Name Drug Substance Stored at the Recommended Storage Condition (°C)								
2									
3	Time Point (months)								
4									
5									
6									

STABILITY LOT INFORMATION		
Summary Info		
Stability lot [DS/DP].Description =	Description of stability lot information;Drug product used in stability testing was taken from several sources:	Text (Default
Batch size [DS/DP].range =	Value - Value (range)	Numeric - Numeric
Batch size [DS/DP].range units =	Kilograms, grams, pounds, etc.	Codeable
Primary stability lots.quantity =	Number of primary lots	Numeric
Supporting stability lots.quantity =	Number of supporting lots	Numeric
Commercial stability samples.Description =	Brief description of commercial stability samples, if present	Text (Variable)
validation stability lots.quantity =	Number of validation lots	Numeric
Detailed Data Table		
Batch Number [DS/DP, packaged/internal/external/bulk/filled] =	DP batch number for packaged product, bulk materia	Text (Variable)
Batch [DS/DP, copack].date =	dd/mm/yyyy	Date
Strength =	[Quantity]	Numeric
Strength.unit =	milligrams, grams, etc.	Codeable
Site [DS/DP].name =	Manufacturer name and acronym	Text (Variable)
Batch size [DS/DP].units =	[Quantity]	Numeric
Batch Size [DS/DP, filled units] =	Kilograms, grams, pounds, etc.	Codeable
Stability Program [DS/DP] =	Long-term, forced degradation, etc.	Codeable
Batch.utilization =	Clinical, Nonclinical, Primary, Validation, Supporting	Codeable
Latest Stability Time Point =	[Time]	Numeric
Latest Stability Time Point. units =	Days, Months, Years, Other (Free Text)	Codeable
Batch.process variant =	CP 1.1, CP 1.2, etc.	Text (Variable)

```
<action>
  <title value="Stability Test Protocol for Long-term and Accelerated
  <action>
    <!-- TODO add codes here for the different levels? -->
    <title value="Long-Term"/>
    <description value="30°C/65% RH"/>
    <action>
      <!-- 0 months -->
      <title value="Initial"/>
      <timingTiming>
        <repeat>
          <boundsRange>
            <low>
              <value value="0"/>
              <unit value="months"/>
              <system value="http://unitsofmeasure.org"/>
              <code value="mo"/>
            </low>
            <high>
              <value value="0"/>
              <unit value="months"/>
              <system value="http://unitsofmeasure.org"/>
              <code value="mo"/>
            </high>
          </boundsRange>
          <frequency value="1"/>
        </repeat>
      </timingTiming>
      <action>
        <!-- the categories to do at this step -->
        <title value="XY"/>
        <!-- Long term -->
        <definitionCanonical value="ActivityDefinition/activityLongTerm30XY-Initial"/>
```

- **Auto-generation of text and tables**
- **Reuse of data components across templates**
- **Virtual replication of filing content to support regional filings**

Amgen's Vectibix Pilot: Leading the Way in Cloud-based Exchange



82%
COUNTRY ENGAGEMENT

70%
NRA PARTICIPATION

- **52 of 63 Vectibix licensed countries participating in PAC Reliance -** enhancing efficiency, collaboration, and accelerating patient access
- **26 out of 37 National Regulatory Authorities participating in PAC Reliance**
- **Of those 26 NRAs, 24 are are using Accumulus** to access the Vectibix PAC dossier, the EMA Assessment Report, and other regulator questions and Amgen responses **in real time**.

Amgen's PAC Reliance – Cloud Collaboration Pilot

Target

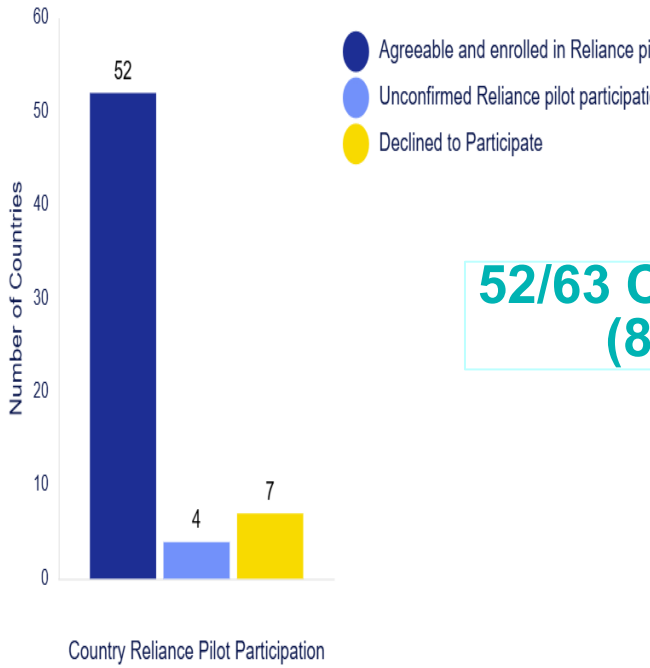
63 countries

where Vectibix is licensed

Target Countries

Algeria, Argentina, Australia, Bahrain, Bosnia and Herzegovina, Brazil, Canada, Chile, Colombia, Costa Rica, Ecuador, Egypt, Guatemala, Israel, Jordan, Kuwait, Lebanon, Malaysia, Mexico, Montenegro, Morocco, Oman, Panama, Peru, Philippines, Qatar, Saudia Arabia, Serbia, Singapore, South Africa, Taiwan, Thailand, Turkey, UAE, UK, Ukraine and EU (27 countries: Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden.)

Country Reliance Pilot Participation

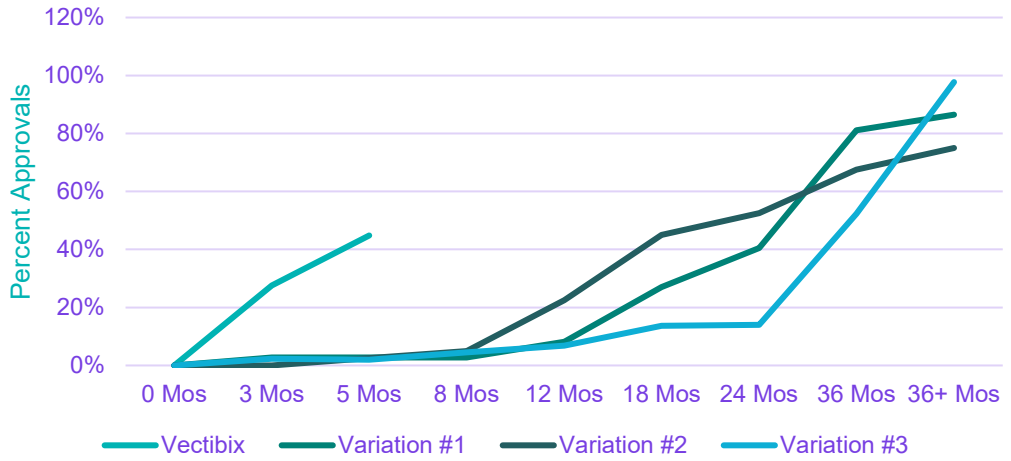


52/63 Countries (83%)

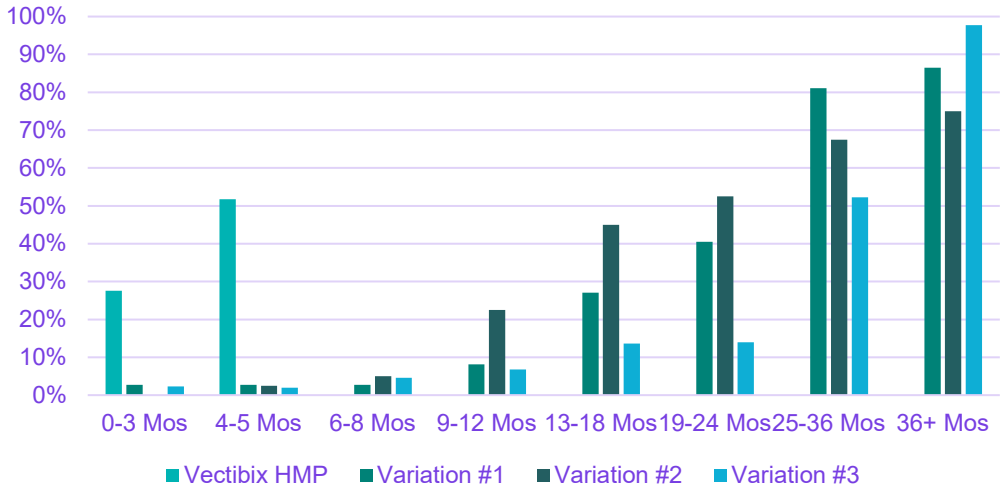
Country Reliance Pilot Participation Detail

Number of Countries Participating in Reliance Pilot	52
Countries Agreeable and enrolled in Reliance Pilot	Argentina, Australia, Brazil, Canada, Colombia, Ecuador, Egypt, Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Guatemala, Israel, Jordan, Malaysia, Mexico, Montenegro, Oman, Panama, Peru, Saudi Arabia, Serbia, Singapore, South Africa, Taiwan, Thailand, Turkey, UK, Ukraine
Countries Unconfirmed Reliance Pilot participation	Algeria, Chile, Costa Rica, Philippines
Countries Declined to Participate in Reliance Pilot	Bahrain, Bosnia and Herzegovina, Kuwait, Lebanon, Morocco, Qatar, UAE

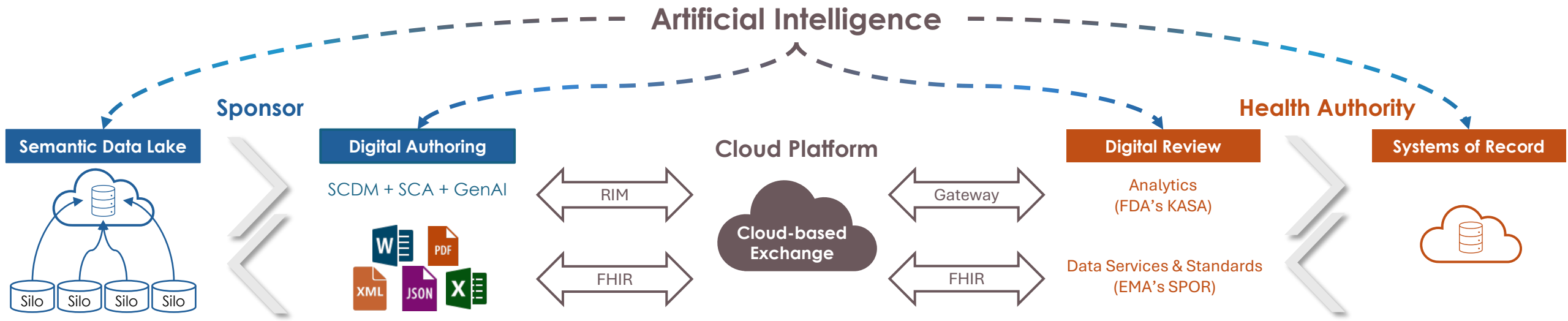
Approvals over Time



Percentage of Approvals After First Submission



Practical Application of Regulatory Exchange



Foundational End-to-End Data Standards (PQ-CMC, ISO IDMP, HL7 FHIR Pharm Quality - Industry)

Benefits of Digitalization

- Time Efficiency & Optimization
- Manual Error Reduction
- Increased Manufacturing Capacity
- Reduced Medicinal Waste
- Real-time Collaboration
- Accelerated Approvals
- Global Patient Access

Figure from "The Future of Regulatory Filings: Digitalization," Ahluwalia et al., 2025, doi: 10.1186/s41120-025-00113-7

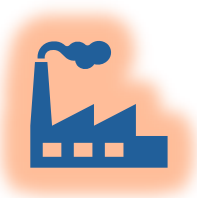
Cloud-based Digital Regulatory Filings: Benefits Realization

Time Efficiency & Optimization

- Single global submission eliminates regional variations
- Accumulus usage is 75% more efficient than conventional pathways
- Reduced number of RFIs
- Eliminated repeat questions

Manual Error Reduction

- Digital tools improve filing compliance
- Reduction in variation of registered details
- Improves internal compliance to registered regulatory details



Increased Manufacturing Capacity

- $10 to $100 Million benefit/Major Post Approval Change in available manufacturing capacity

Reduced Medicinal Waste

- Reduced inventory scrap due to accelerated approvals and transition to optimized product SKU

Real-time Collaboration

- Simplifies document management and exchange
- Promotes submission and approval of a single global dossier
- Facilitates cross-agency communication
- Provides for more efficient information exchange

Accelerated Approvals

- Global life-cycle management approval timelines reduced from > 4 years to < 1 year and in most instances < 6 months

Global Patient Access

- Accelerated access to optimized product
- Facilitates changes that would perhaps not be made due to long review and approval lag times

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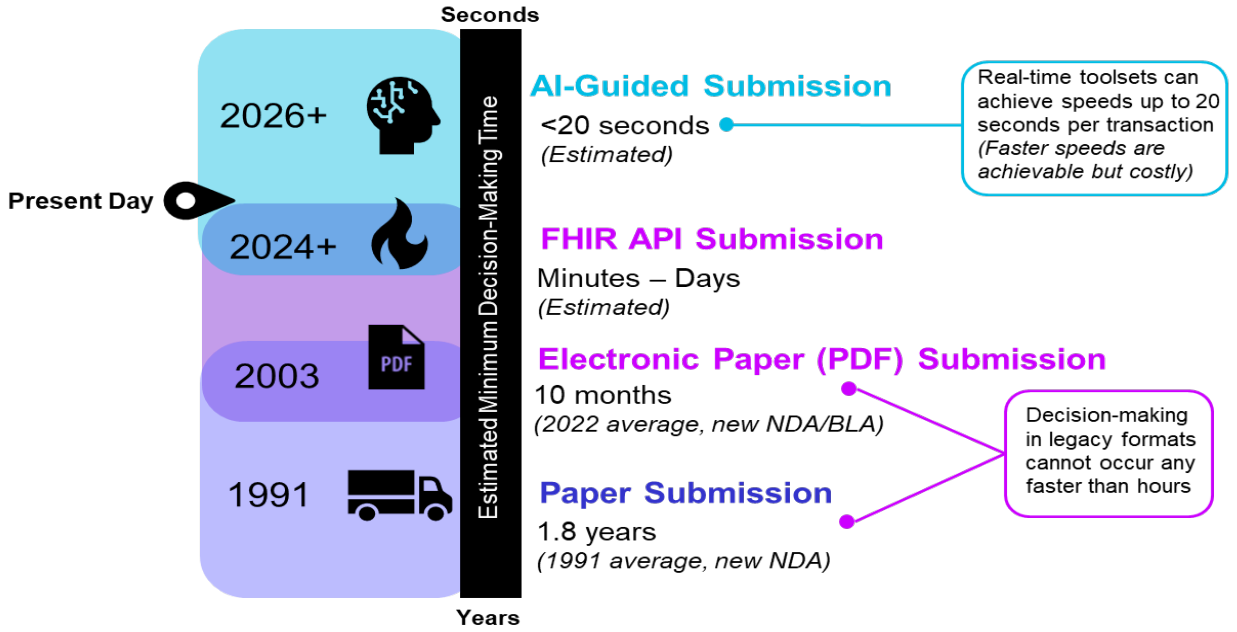
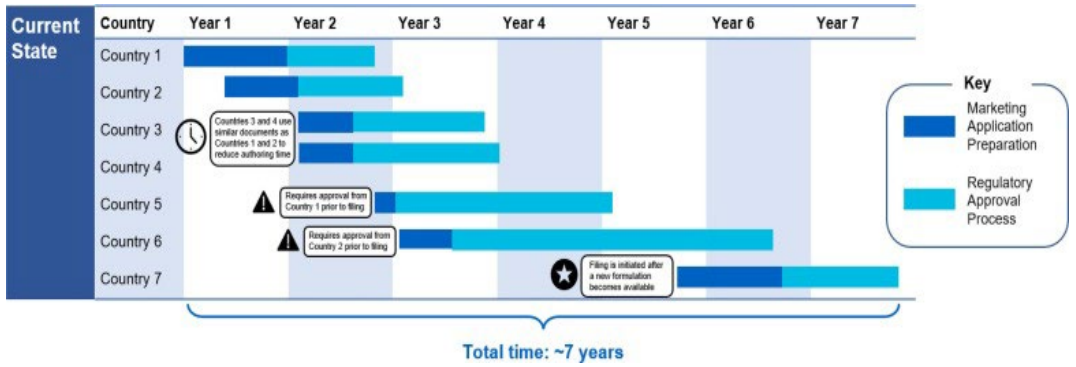
The Art of the Possible in the Regulatory Ecosystem is Here

1. Accelerate document generation timelines (i.e., hours rather than weeks/months)

2. Enable real-time data exchange (i.e., seconds/subseconds)

3. Replace staggered submission wave model with simultaneous global submission model





From Anderson, Algorri, Abernathy 2023