



SI08

Making Define-XML Work for You: Considerations in Supporting a Full Schema Implementation

March 2023

Agenda

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Define-XML: Historical Perspective

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Document vs. Metadata Source

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Content and Process Implications

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Submission or Not, Doesn't Need to Be the Question

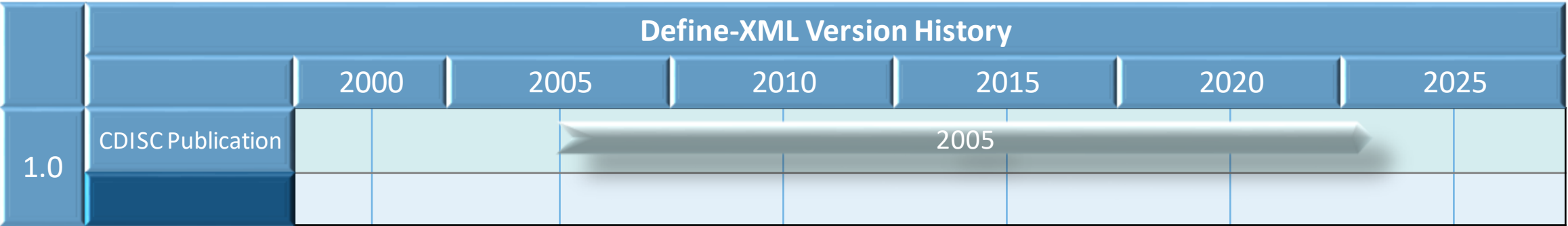
05

Questions

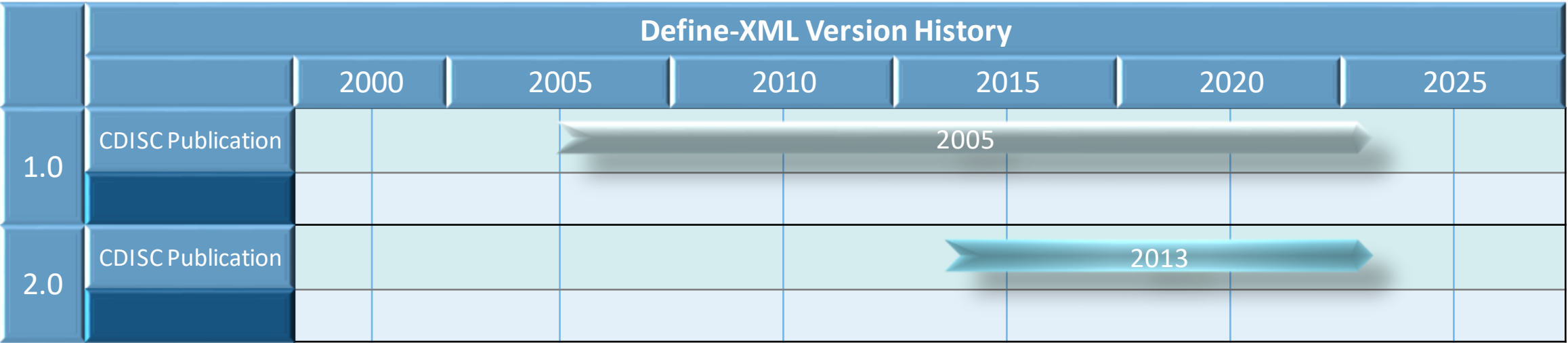
Define-XML

Historical Perspective

Define-XML: Historical Perspective

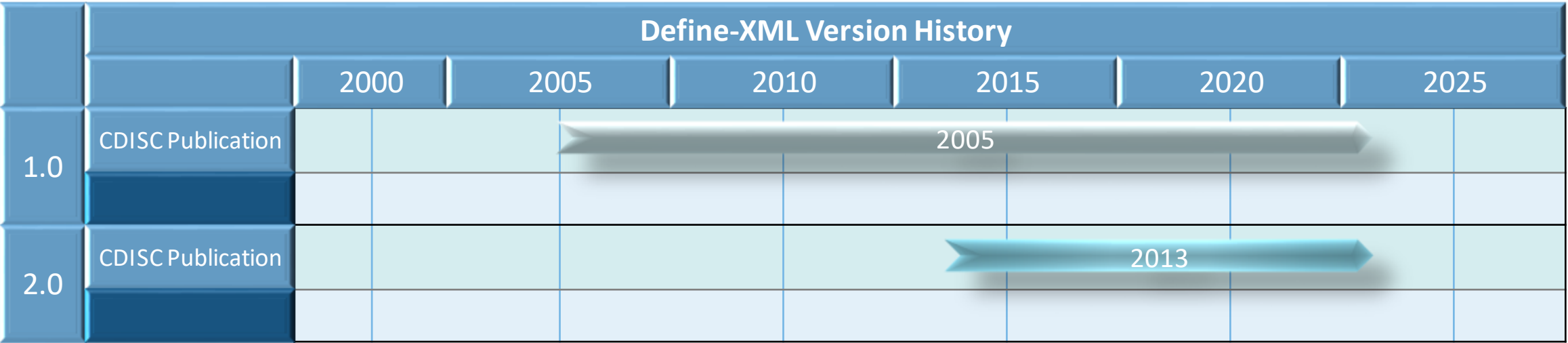


Define-XML: Historical Perspective



- Eight years before 2.0 released

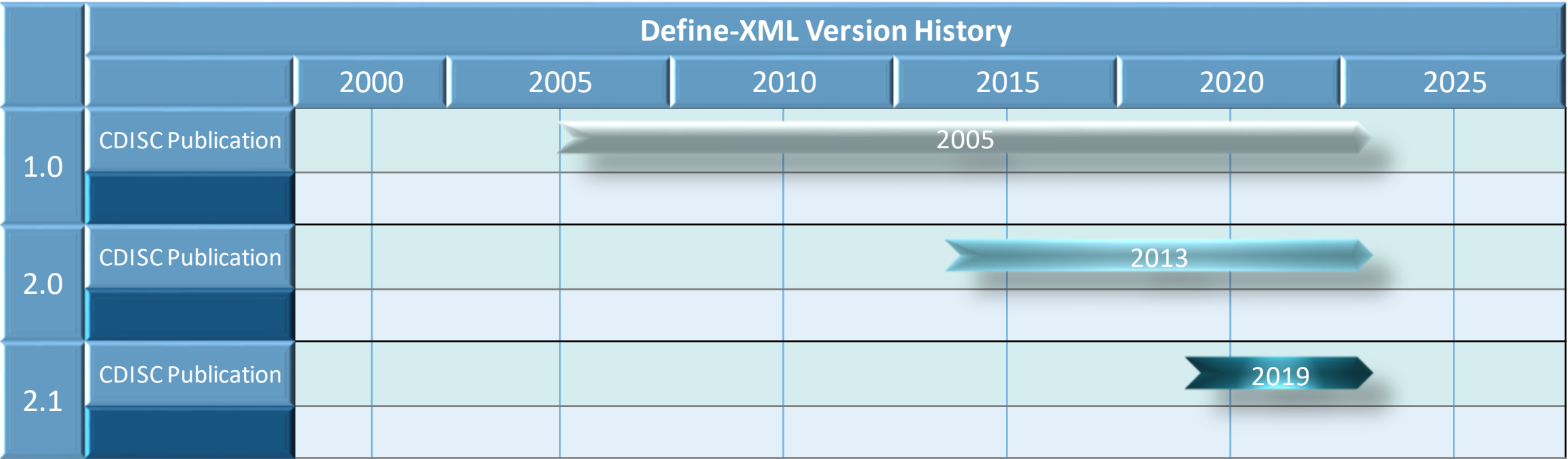
Define-XML: Historical Perspective



Version 2.0 enhanced usefulness of machine-readable metadata

- Direct link to CDISC Controlled Terminology (C-Codes)
- Improved VLM and ADaM support
- Improved traceability and comment functionality

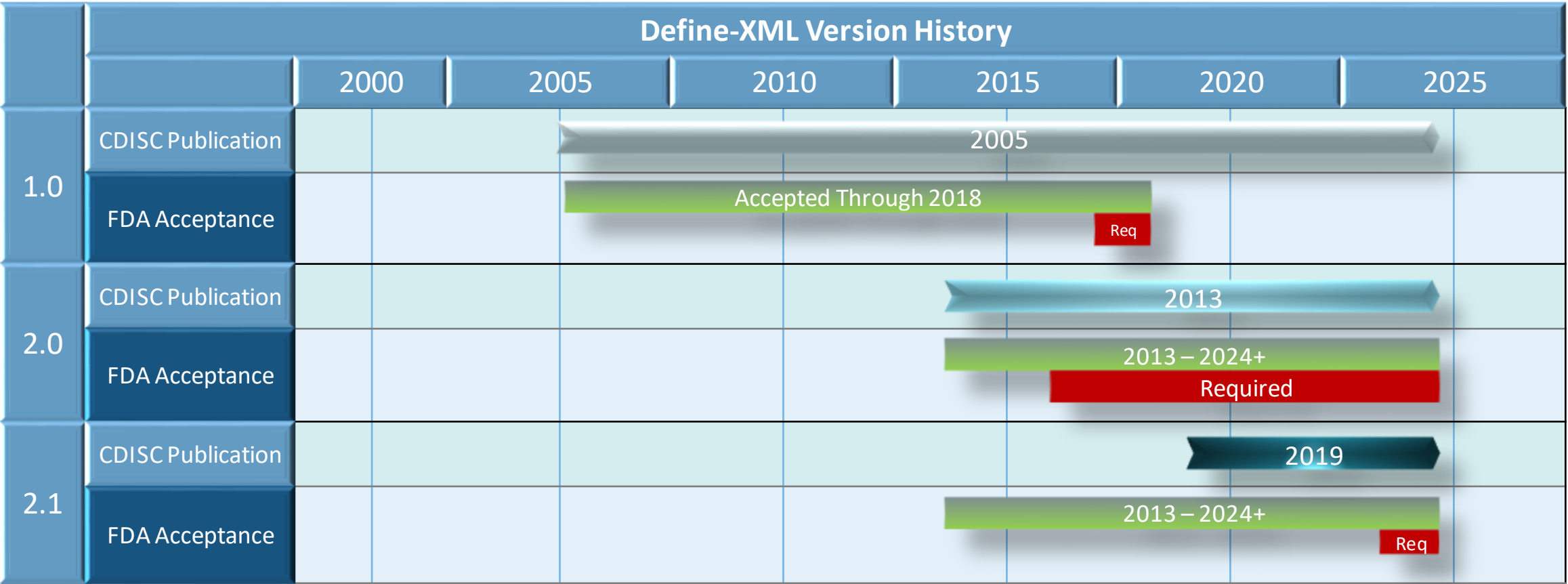
Define-XML: Historical Perspective



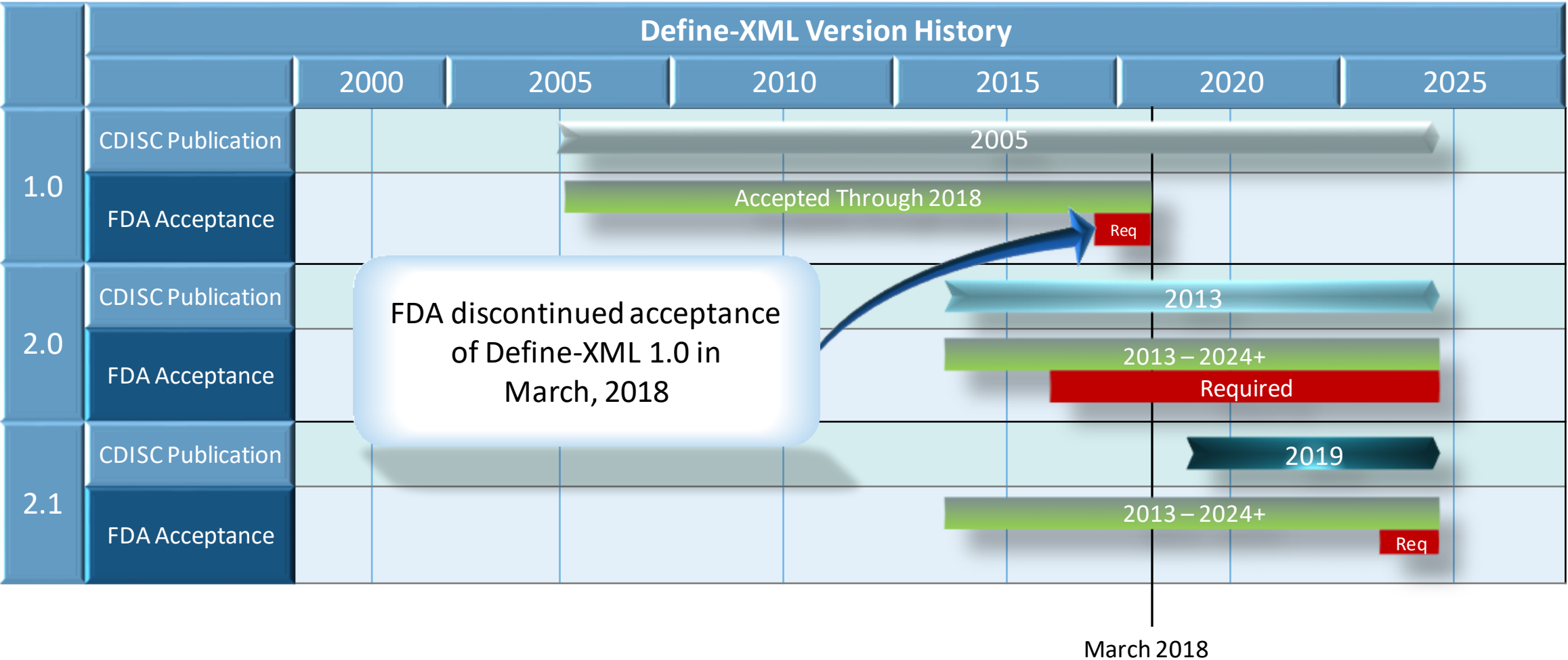
Version 2.1 added flexibility and granularity, even beyond what regulatory authorities were explicitly supporting

- Multiple versions of standards and terminology, multiple origins

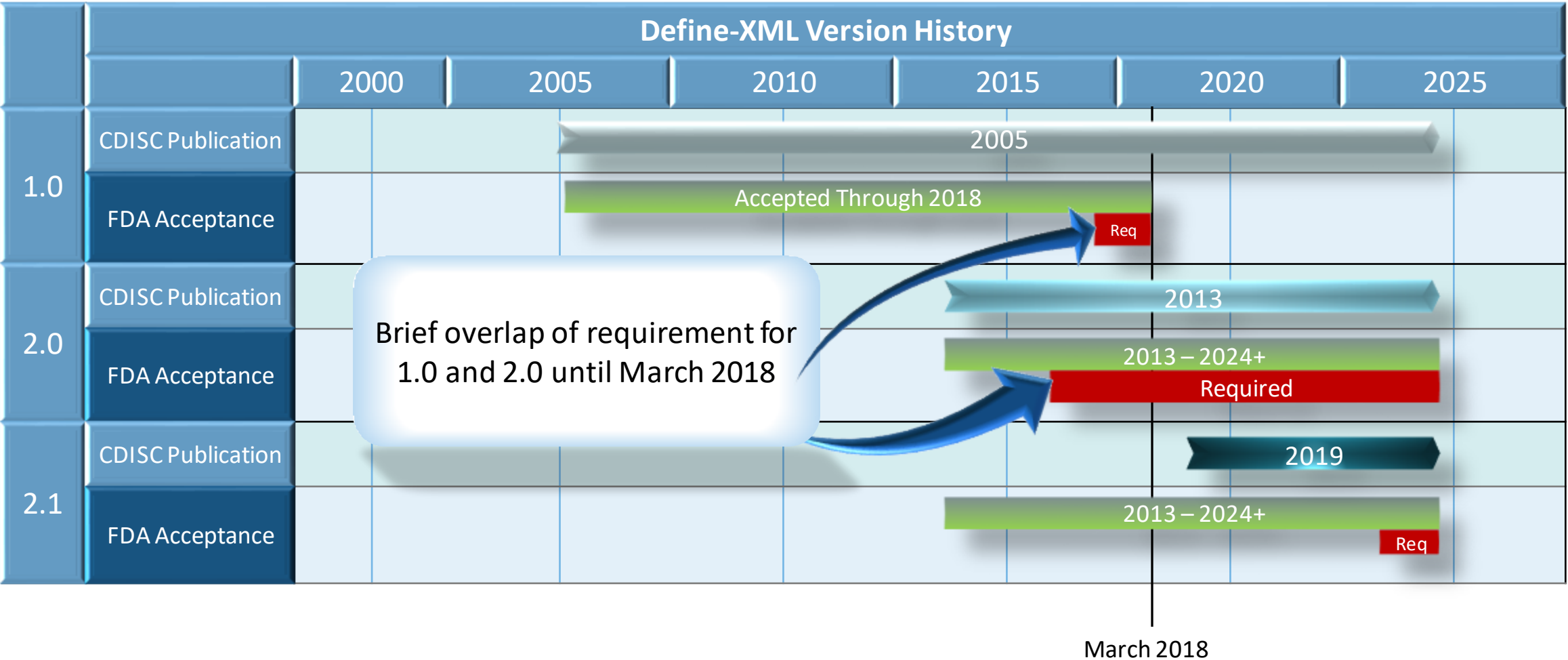
Define-XML: Historical Perspective



Define-XML: Historical Perspective



Define-XML: Historical Perspective

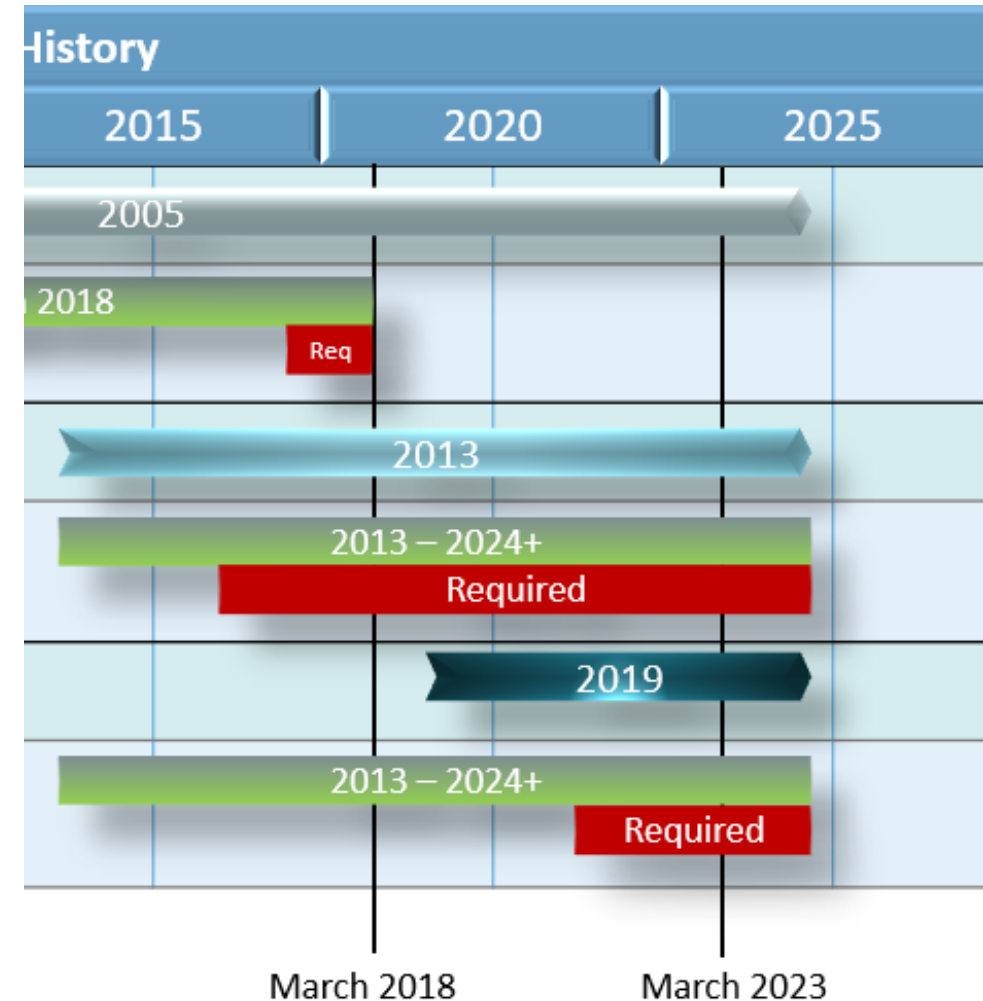


Define-XML

Document vs. Metadata Source

Define-XML – Document vs. Metadata Source

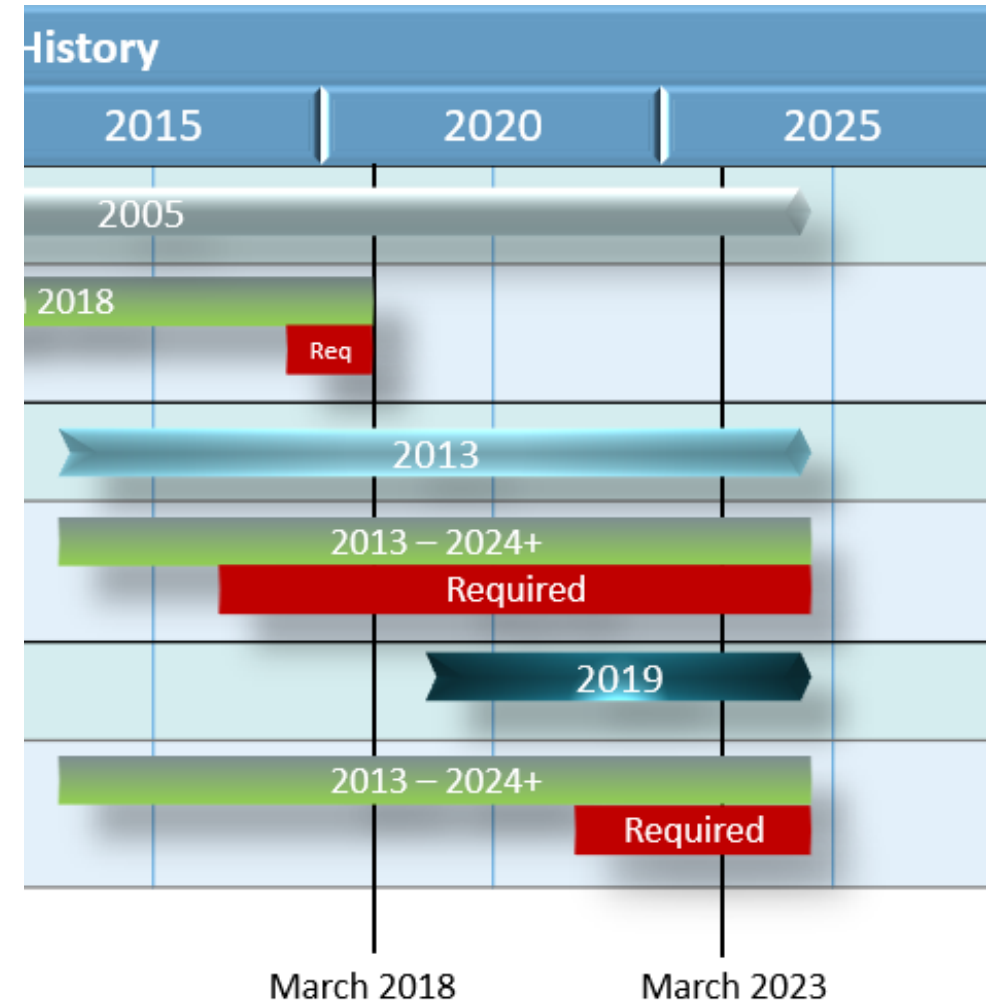
- For much of Define-XML's history, it has been more document than metadata source



Define-XML – Document vs. Metadata Source

- For much of Define-XML's history, it has been more document than metadata source
- A critical “bad habit” from this legacy:

Define-XML generated just-in-time for submission

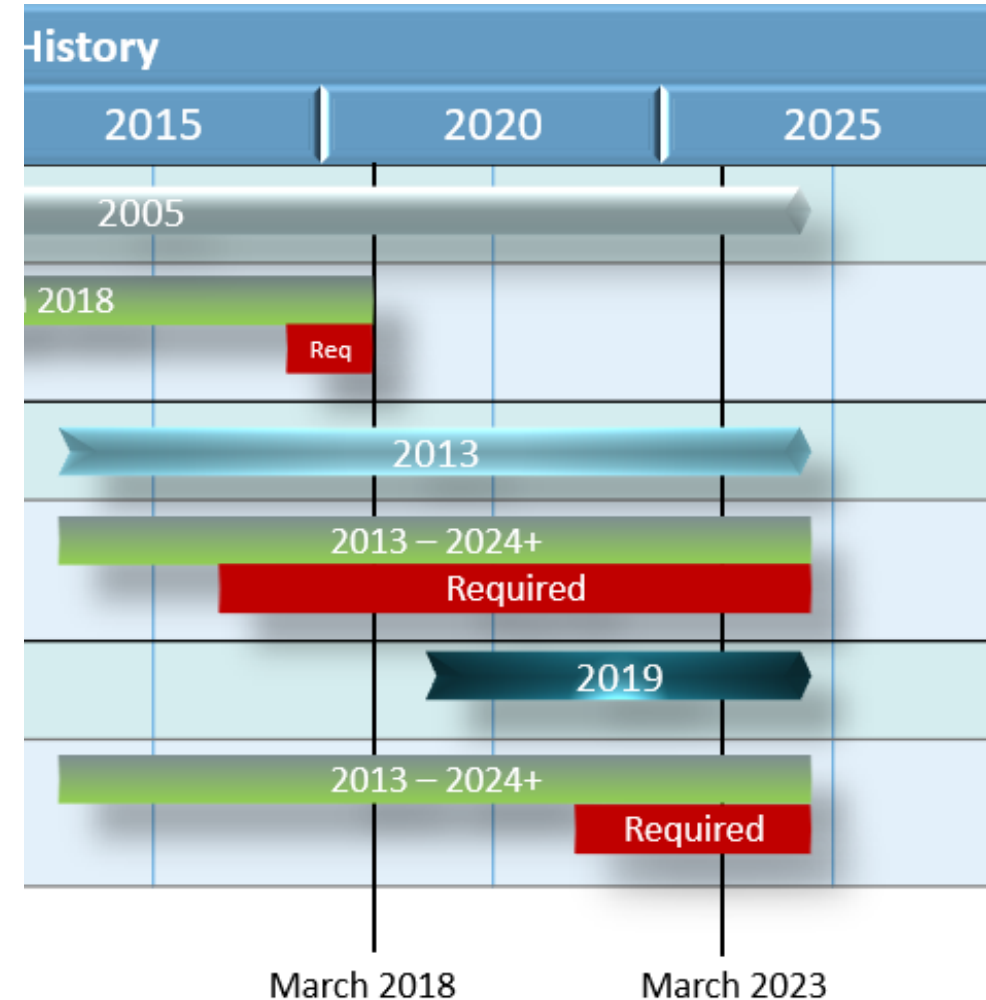


Define-XML – Document vs. Metadata Source

- For much of Define-XML's history, it has been more document than metadata source
- A critical “bad habit” from this legacy:

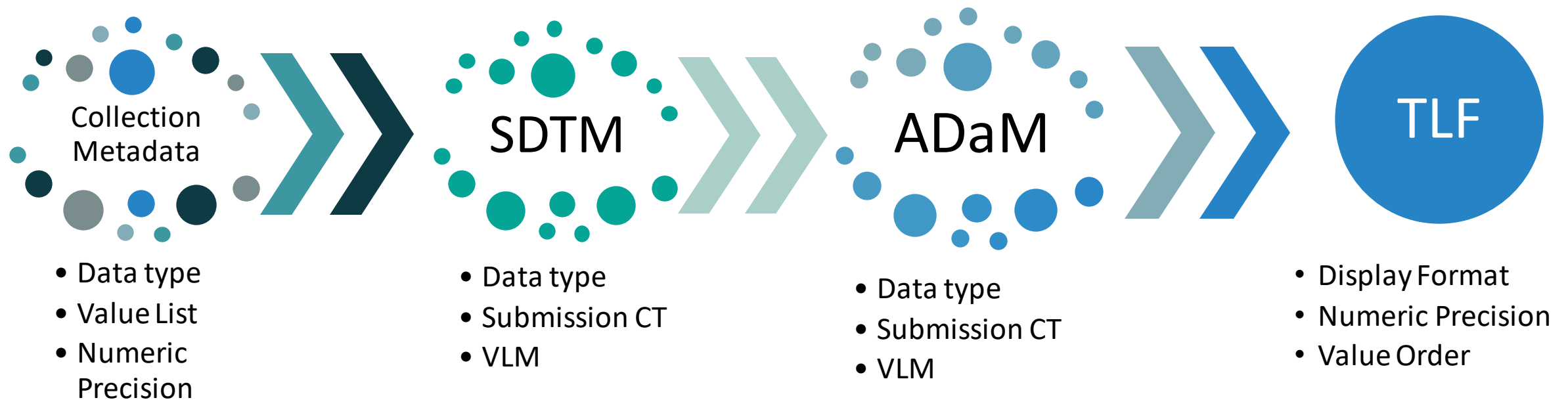
Define-XML generated just-in-time for submission

- No opportunity for value-added processes



Define-XML – Document vs. Metadata Source

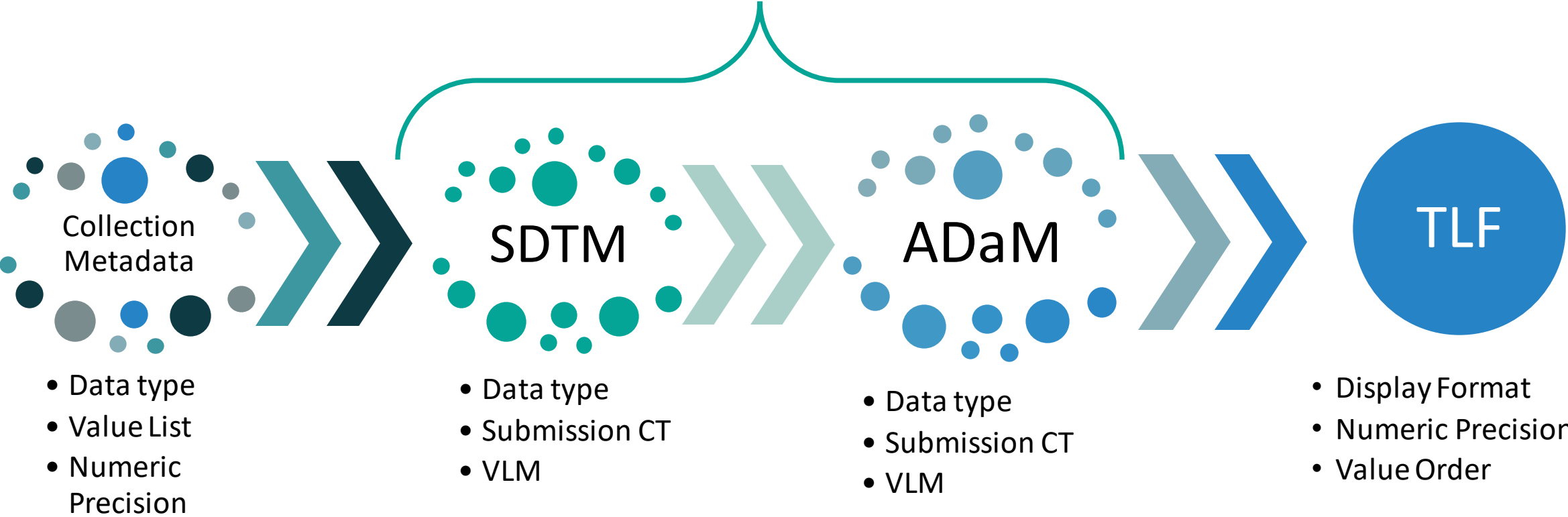
End-to-End Metadata Traceability



Define-XML – Document vs. Metadata Source

End-to-End Metadata Traceability

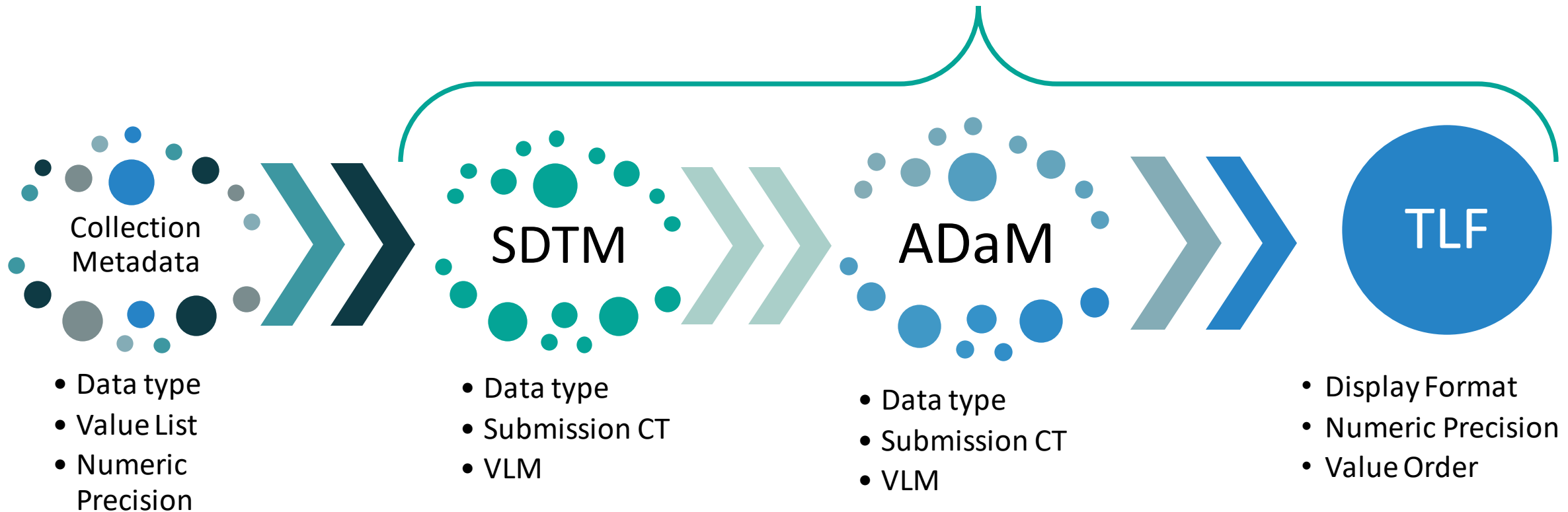
Directly Facilitated by Define-XML



Define-XML – Document vs. Metadata Source

End-to-End Metadata Traceability

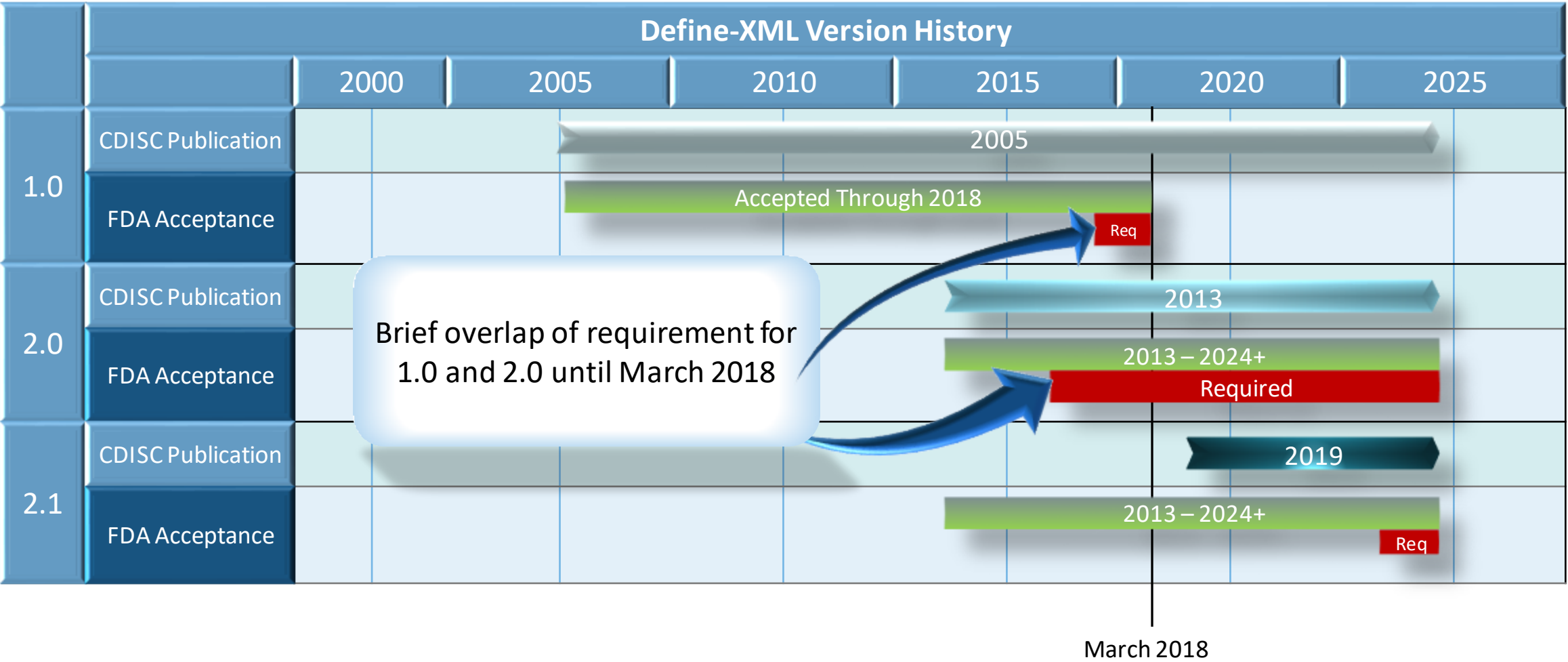
Directly Facilitated by Define-XML if leveraging ARM



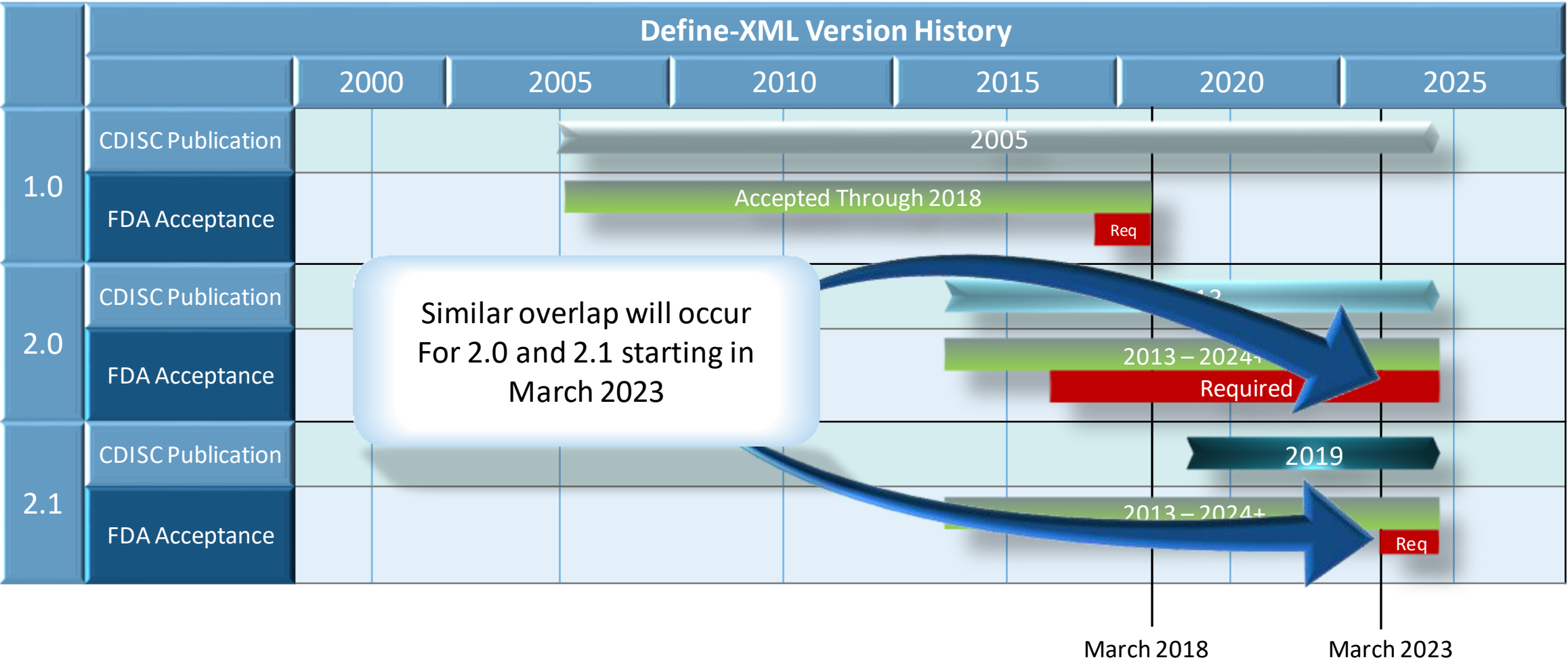
Define-XML

Content and Process Implications

Define-XML: Content and Process Implications



Define-XML: Content and Process Implications



Define-XML: Content and Process Implications

- Per FDA **Providing Regulatory Submissions In Electronic Format — Standardized Study Data Guidance for Industry (June, 2021)**
 - Section II: REQUIREMENT TO SUBMIT ELECTRONIC STANDARDIZED STUDY DATA
 - E: When Will Electronic Submission of Standardized Study Data Be Required?

*The requirement to submit using a particular standard is dependent on its support by FDA as listed in the Catalog at the time of study start. FDA recognizes that standards development organizations may release version updates to standards in the interval between the start of a study and the submission of study data to the Agency. The Catalog may list more than one version of a supported standard (e.g., PDF versions 1.4 - 1.7, SDTM versions 1.2 and 1.3, Define versions 1.0 and 2.0, and MedDRA versions 8 or later). Sponsors or applicants are encouraged to use the latest version listed in the Catalog. However, when there are **multiple versions** of a standard listed, **sponsors or applicants can select the version to use for their study.***



Define-XML: Content and Process Implications

- Impact of overlaps

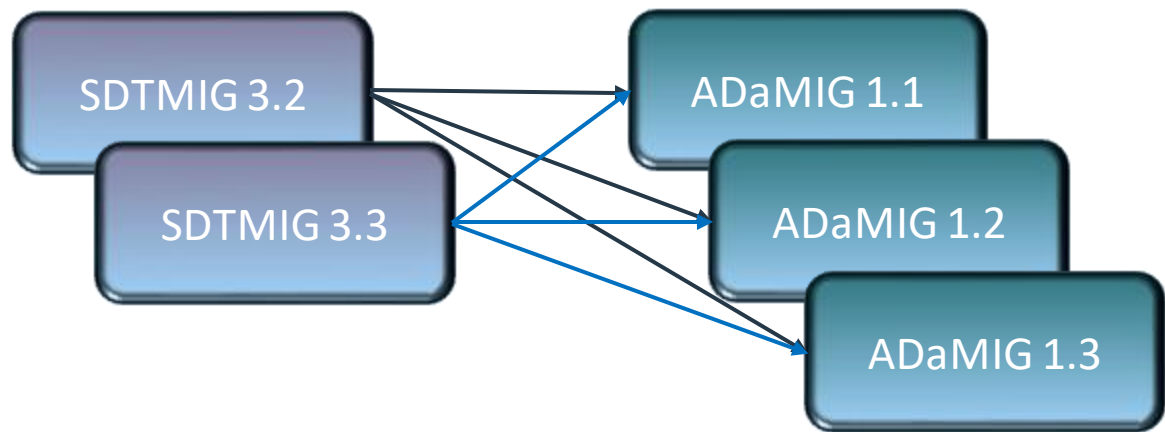


- To start, the FDA's currently accepted versions of SDTM and ADaM

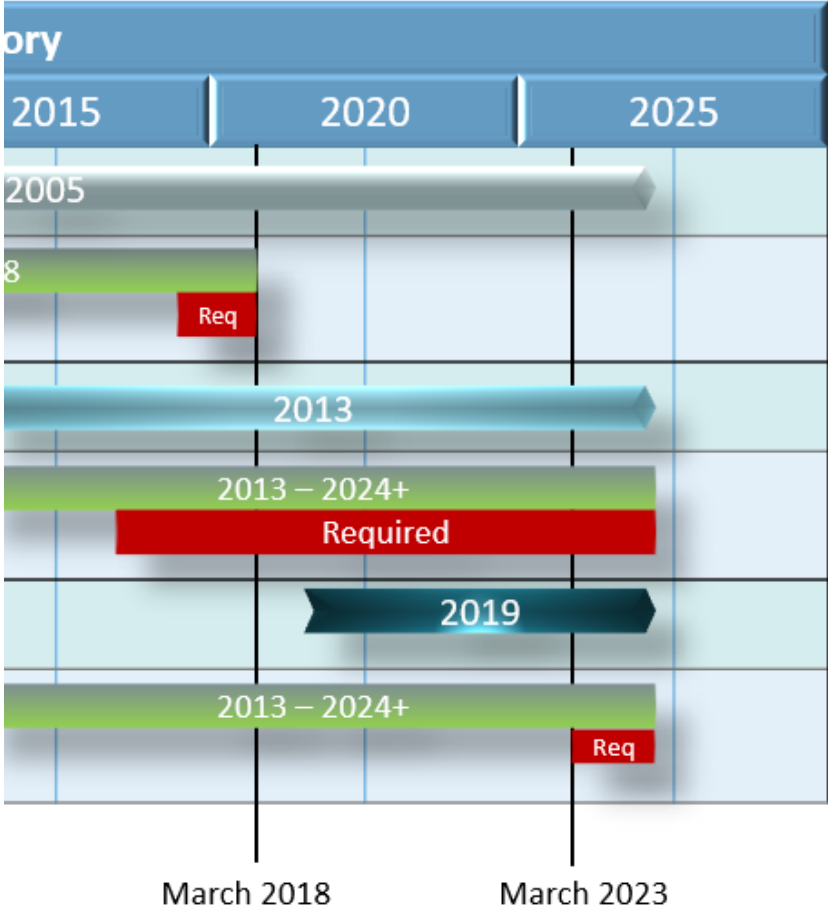


Define-XML: Content and Process Implications

- Impact of overlaps

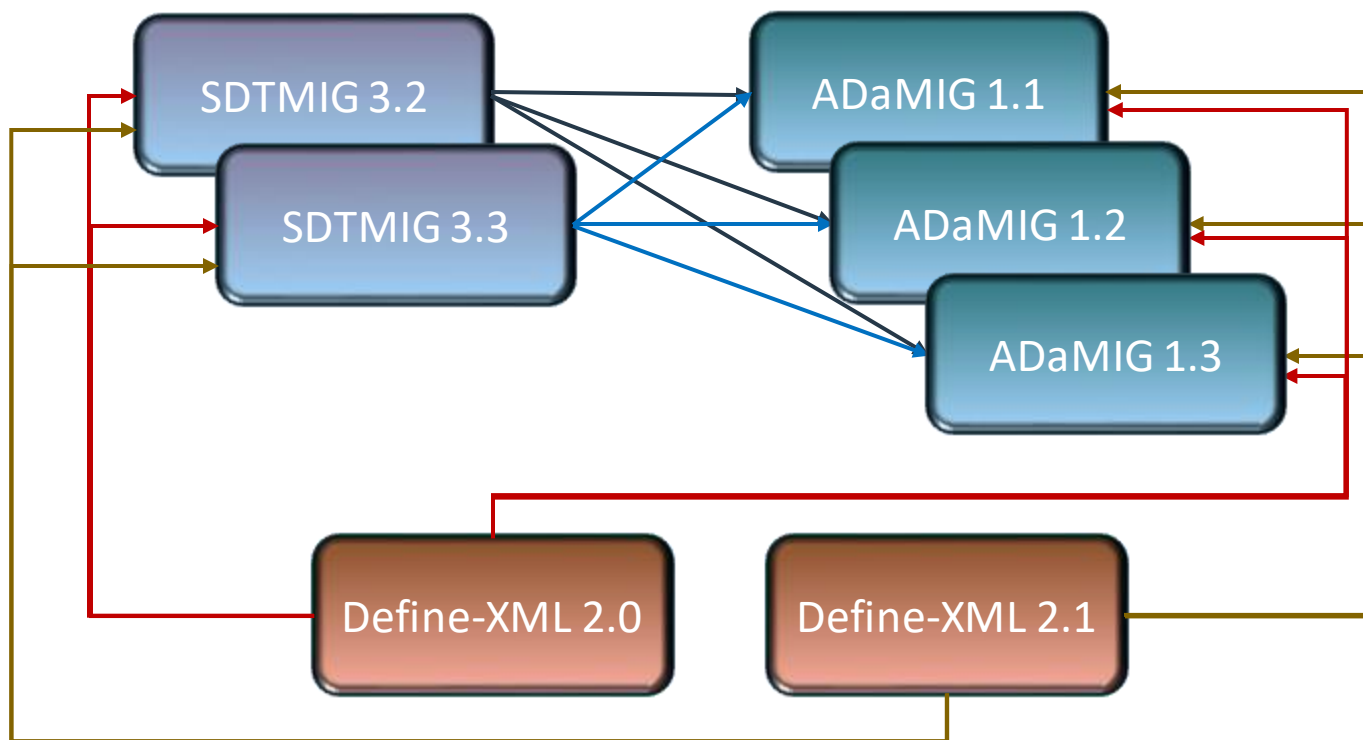


- Possible combinations today

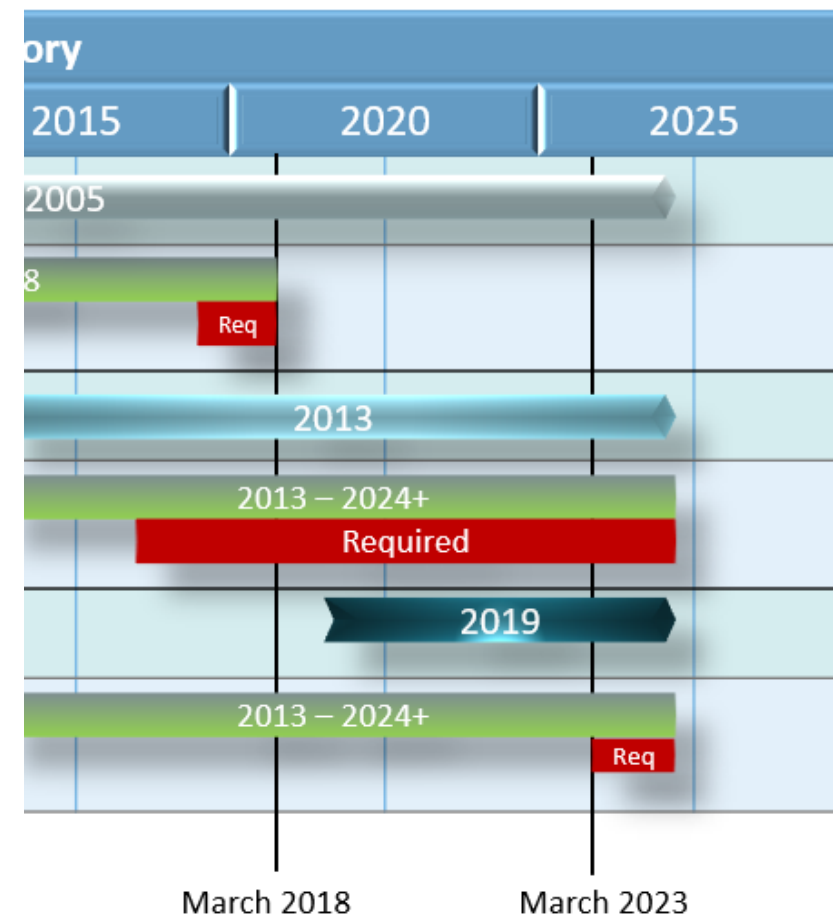


Define-XML: Content and Process Implications

- Impact of overlaps

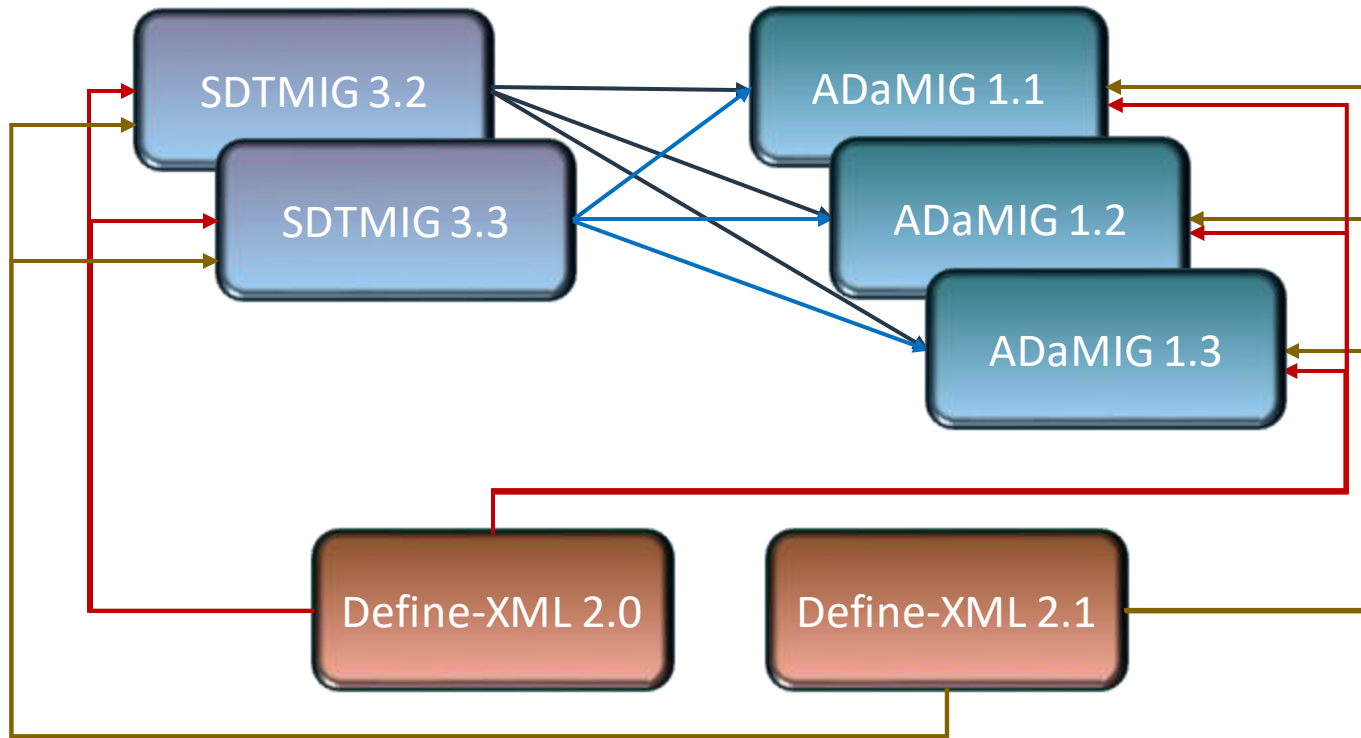


- When you add in Define-XML, which is version independent of the standards....



Define-XML: Content and Process Implications

- Impact of overlaps:



Proliferation of relationships

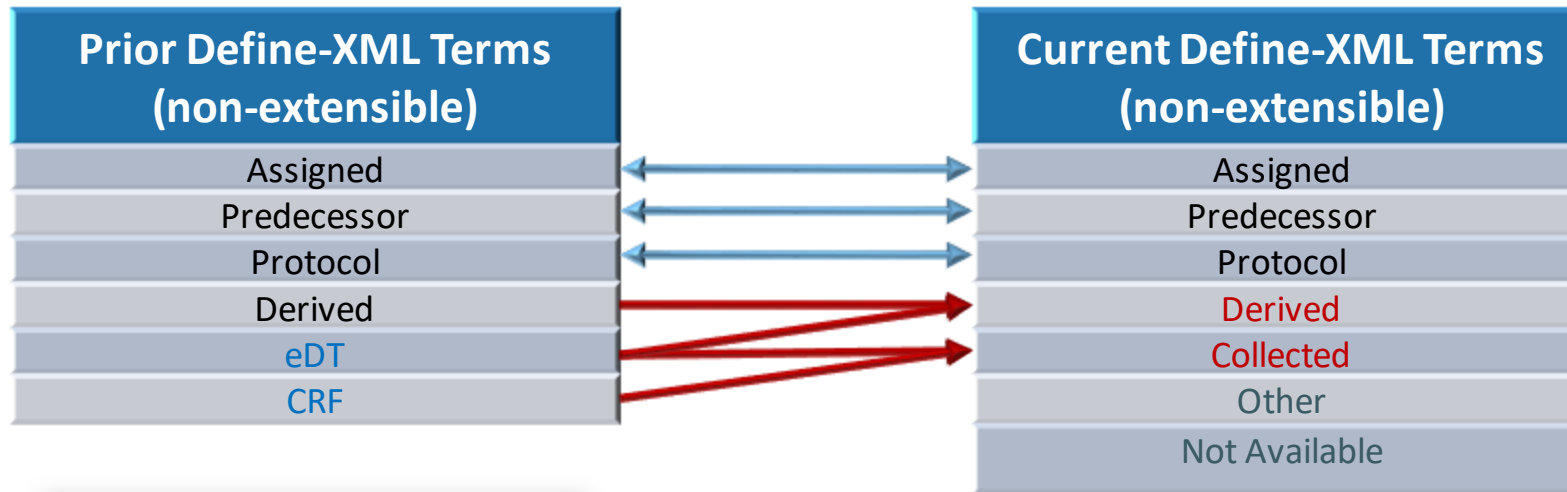
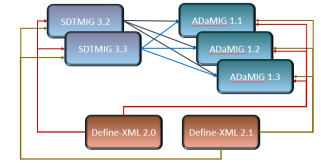
- Expansion of governance/curation content
- Increased complexity of tools/solutions

What about ...



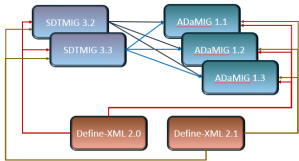
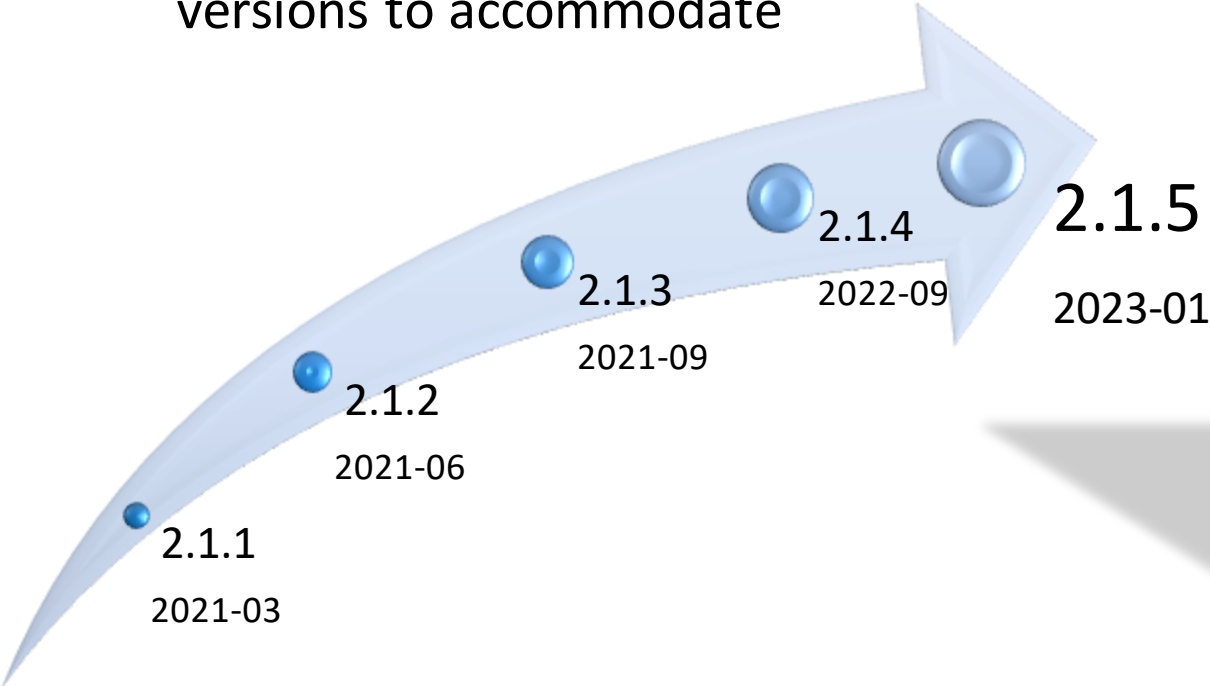
Define-XML: Content and Process Implications

- Challenges for standards governance
 - Shifts in terminology, not backward compatible
 - Origin requires multiple attributes if establishing default values in support of both Define-XML v2.0 and v2.1



Define-XML: Content and Process Implications

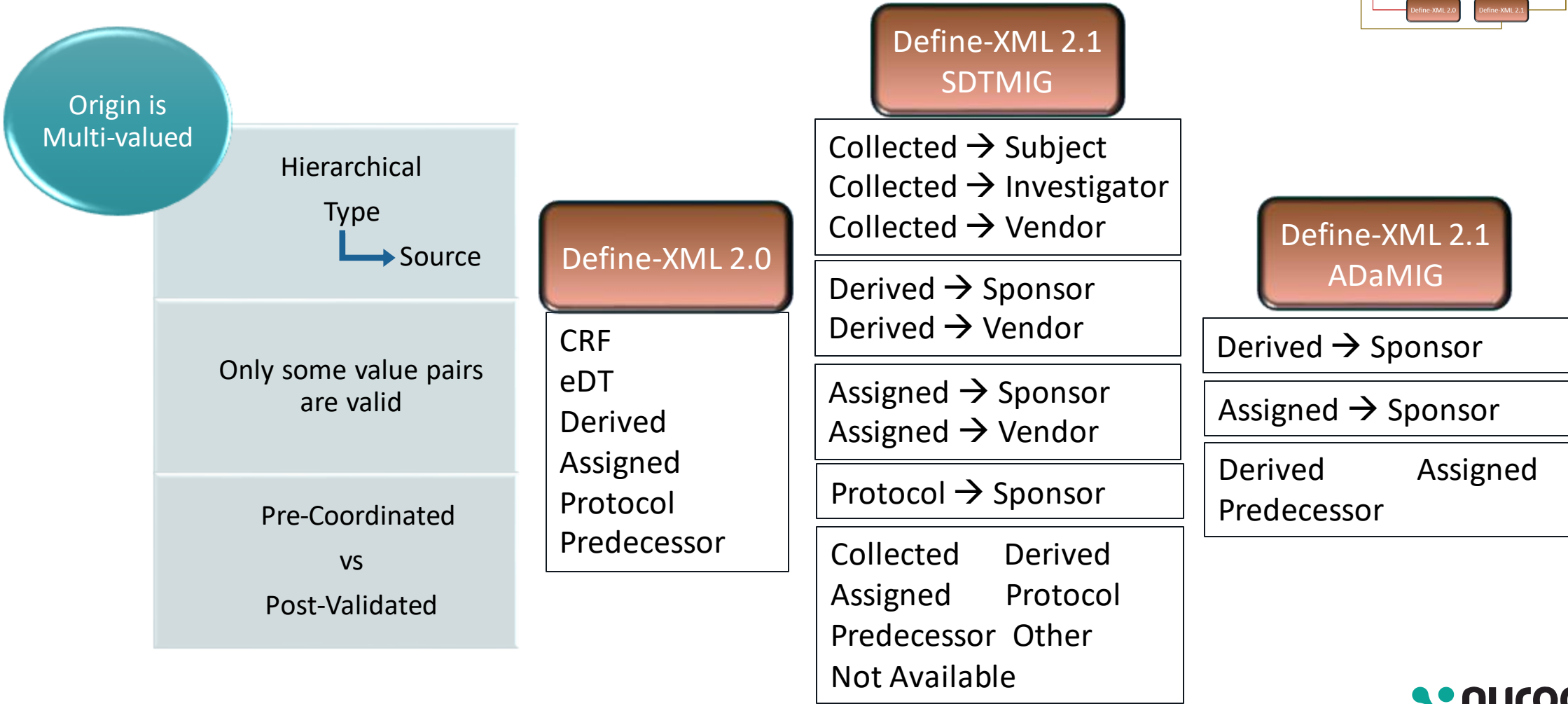
- Challenges for standards governance
 - Indicative of broader change, where Enumerations (CT) have been added to the Define-XML schema
 - CDISC has released several minor versions to accommodate



Define-XML Entities with Schema Enumerations	Impact
def:Standard@Name	Full support will require alignment to terminology references that can change over time
def:Standard@Type	
def:Standard@Status	
def:Standard/@PublishingSet	
ItemGroupDef/@def:Class	
def:Origin/@Type	
def:Origin/@Source	
def:PDFPageRef/@Type	

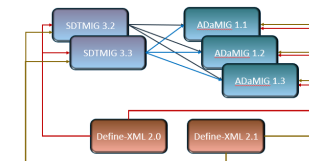
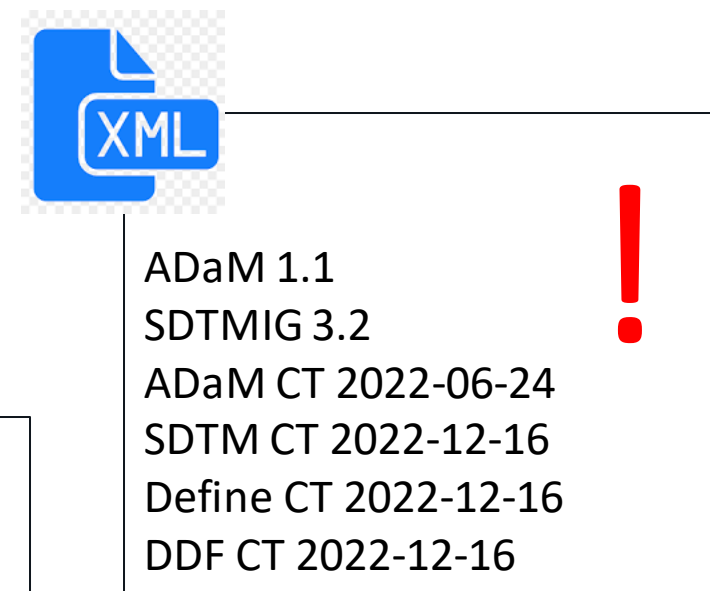
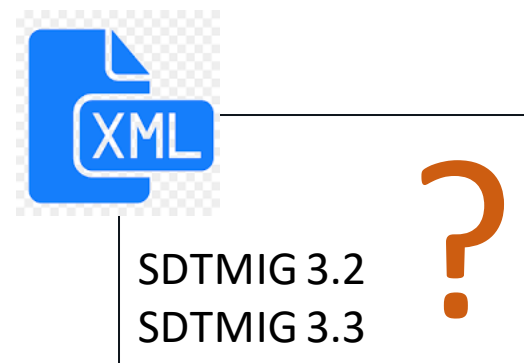
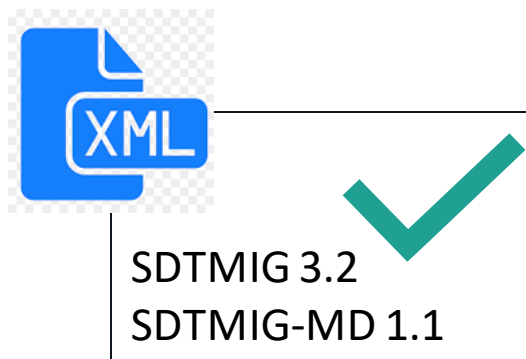
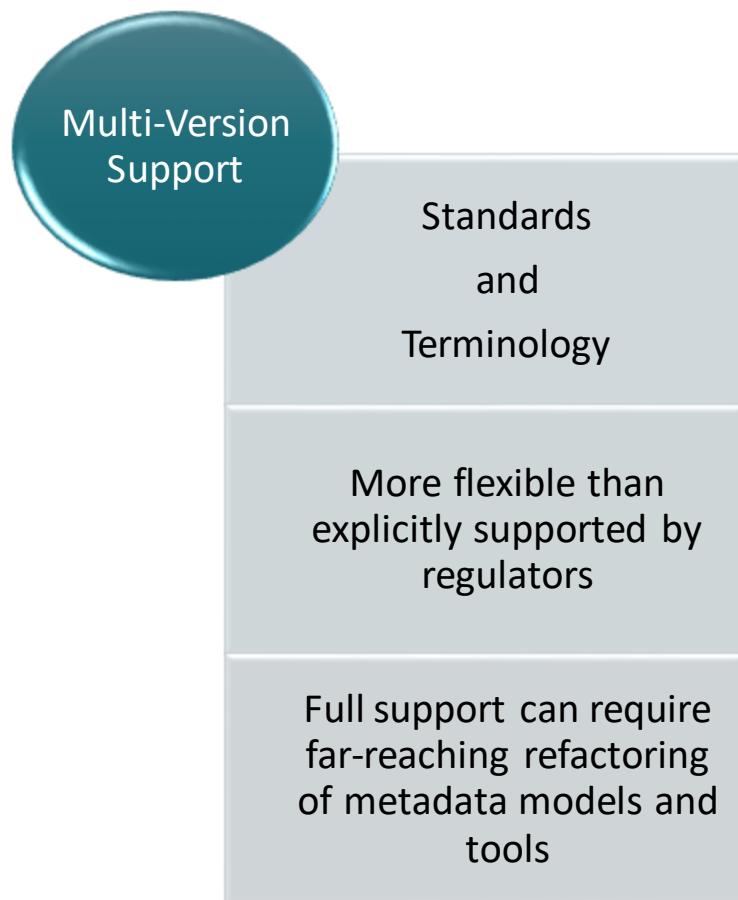
Define-XML: Content and Process Implications

- Other Considerations



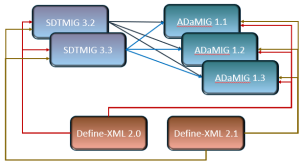
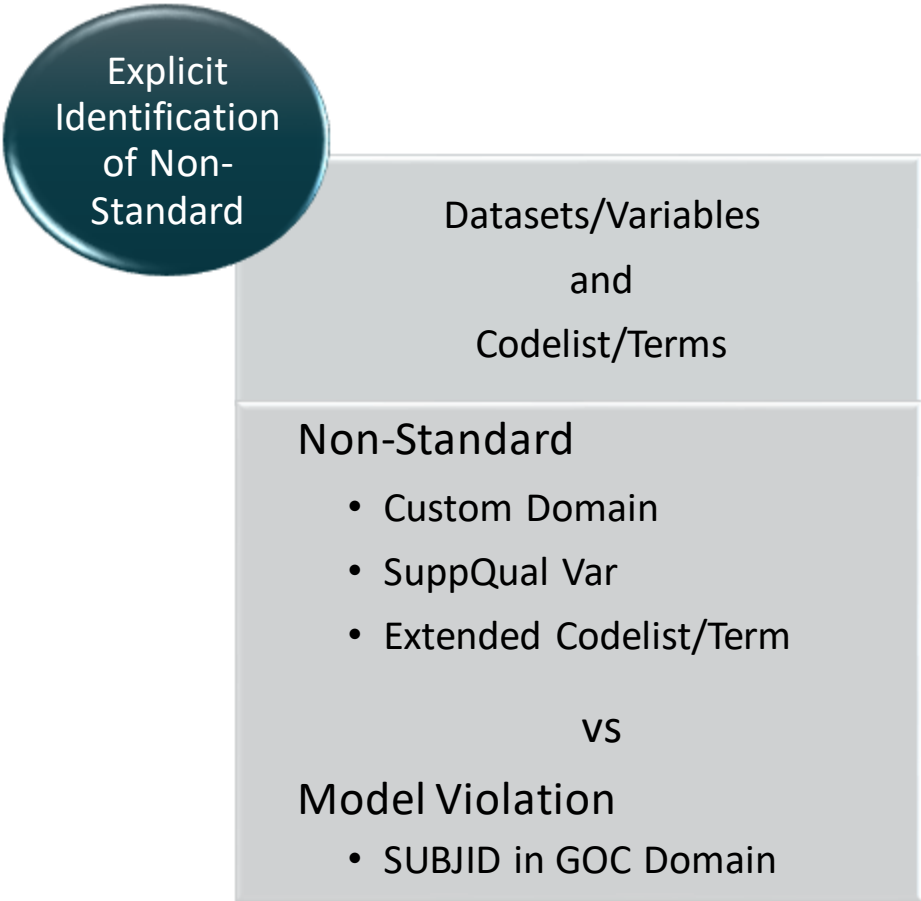
Define-XML: Content and Process Implications

- Other Considerations



Define-XML: Content and Process Implications

- Other Considerations

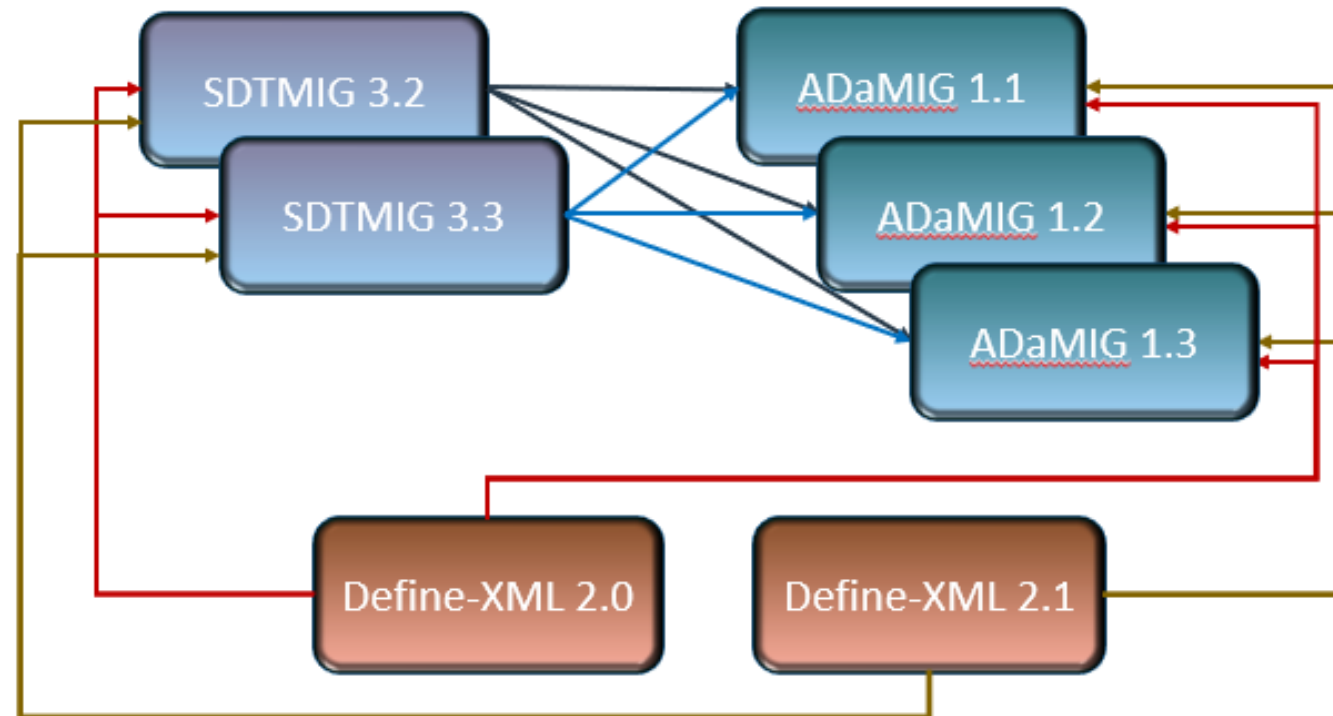


Define-XML

Submission or Not, Doesn't Need to Be the Question

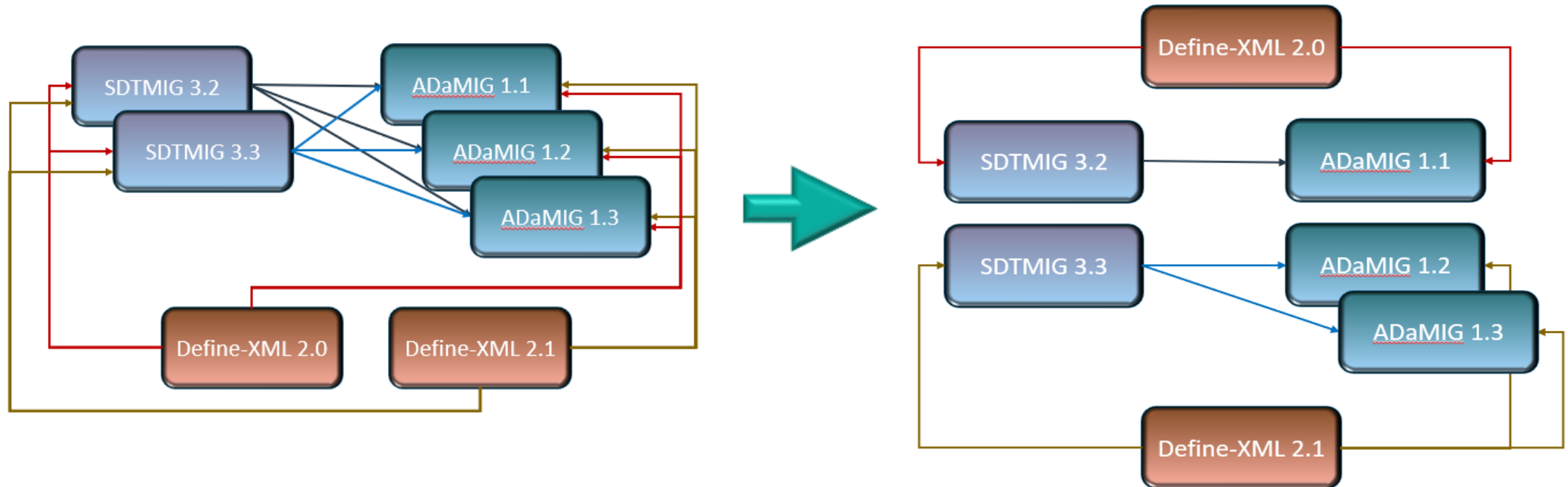
Define-XML: Submission or Not

- What to do?



Define-XML: Submission or Not

- Consider minimizing cross-standard impacts by minimizing backward compatibility
 - Align SDTMIG 3.2, ADaM 1.1 and Define-XML 2.0
 - Align SDTMIG 3.3, ADaM 1.2, ADaM 1.3, and Define-XML 2.1



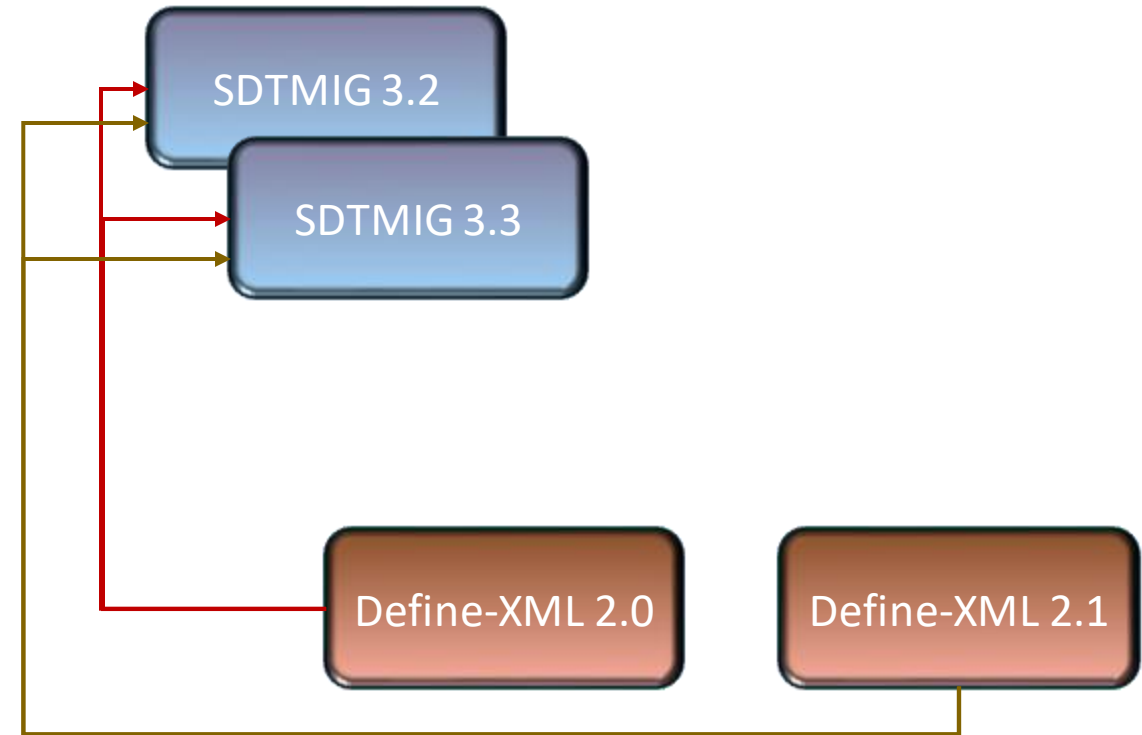
Define-XML: Submission or Not

- Consider minimizing cross-standard impacts by minimizing backward compatibility
 - Align SDTMIG 3.2, ADaM 1.1 and Define-XML 2.0
 - Align SDTMIG 3.3, ADaM 1.2, ADaM 1.3, and Define-XML 2.1
- Reduces the interdependencies and minimizes (ideally eliminates) any impact to existing standards
- Cap the ever-growing scope of standards to be curated

Out with the old, in with the new

Define-XML: Submission or Not

- Regardless of approach, however, processes and tooling will need to accommodate multiple versions as long as there is a need to support them
- Given the study-start anchor, this can be for years to come
- Taking just SDTMIG/Define-XML, the minimum is.....



Define-XML: Submission or Not

- Define-XML 2.1 introduces granularity and traceability
- Based on recent public review of the updates to the ODM model, more to come
- If your organization is building out this content regardless of Define-XML version, is there a way to represent new attributes in an old Define-XML?

Define-XML: Submission or Not

Yes

Sort Of

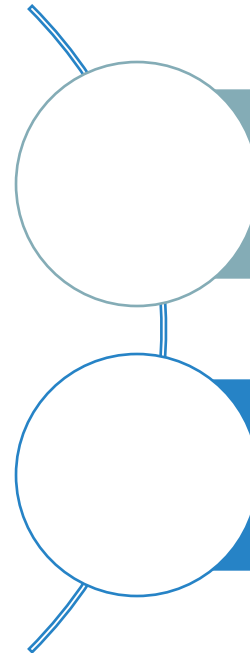
Kind Of

Maybe

Well...

Non-Standard in Define-XML 2.0

- Take the non-standard attribute as an example
- Can represent in Define-XML 2.0 through...



Custom Extension

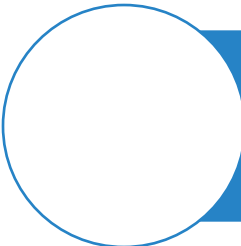
Existing Syntax

Custom Extension

- Flexible
 - Can add almost anything anywhere
- Requires XML SME
 - In a robust implementation, should be a formally defined extension
- Main Drawback: not suitable for submission
 - Custom extensions are to be stripped out of submission Define-XML
 - While it may support internal processes, but complicates submission preparation

Existing Syntax

- Limited Options
 - Requires you to beg, borrow, and steal from existing syntax
 - Can only use where pre-defined (e.g., can't add Alias to an ItemDef)
- Is acceptable for submission
 - “Drawing in the lines” results in no validation issues
 - May be value-added if conveying useful information
- **Main Drawback: Unarguably a *Duct-Tape Solution***



Existing Syntax

- In Define-XML 2.0, the ItemGroupDef element has the following:

Attributes	
OID	Purpose
Name	def:Structure
Repeating	def:Class
IsReferenceData	def:ArchiveLocationID
SASDatasetName	def:CommentOID
Domain	

Child Elements
Description
ItemRef
Alias
def:leaf

Existing Syntax

- In Define-XML 2.0, the ItemGroupDef element has the following:

Attribute

def:CommentOID

- Unstructured
- Can use delimiters to capture multiple attributes in a single string

Child Element

Alias

- Limited to a two-part value
 - Context
 - Name
- Unlimited number

- Alias can be used for
 - Datasets (ItemGroupDef element)
 - Codelists (Codelist element)
 - Terms in a Codelist (CodelistItem and EnumeratedItem elements)
- Comments can be used for
 - Where Clauses
 - Datasets
 - Variables

Existing Syntax – Alias Use Case

```
<!-- Dataset Definition (CV) -->
  <ItemGroupDef OID="IG.CV"
    Domain="CV"
    ...
    <ItemRef ItemOID="CV.DOMAIN" .../>
    <def:leaf ID="LF.CV" xlink:href="cv.xpt">
      <def:title>cv.xpt</def:title>
    </def:leaf>
    <Alias Context="IsNonStandard"
      Name="Yes"/>
  </ItemGroupDef>
```

Existing Syntax – Alias Use Case

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<!-- Dataset Definition (CV) -->  
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      <def:title>cv.xpt</def:title>  
    </def:leaf>  
    <Alias Context="def:IsNonStandard"  
      Name="Yes"/>  
  </ItemGroupDef>
```

- Whether a custom extension or leveraging the existing schema
 - Enables a more version-agnostic use of Define-XML metadata in internal processes and tools
 - Supports a more robust representation of content
 - Can be value-added both internally and externally

- Value added: Extended content can be surfaced up to reviewers with updated style sheets

Define-XML 2.0
Original Style Sheet

Datasets

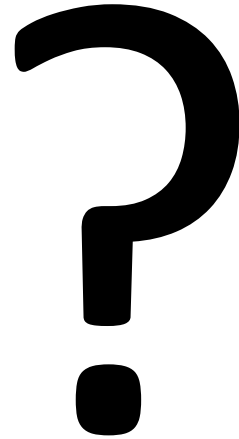
Dataset	Description	Class	Structure	Purpose	Keys	Documentation	Location
TA	Trial Arms	TRIAL DESIGN	One record per planned Element per Arm	Tabulation	STUDYID, ARMCD, TAETORD		ta.xpt 

- Value added: Extended content can be surfaced up to reviewers with updated style sheets (can require SME)

Define-XML 2.0
Augmented Style Sheet

Datasets

Dataset	Description	Class	Structure	Purpose	Keys	Documentation	Location
TS [SDTMIG 3.1.2]	Trial Summary	TRIAL DESIGN	One record per trial summary parameter value	Tabulation	STUDYID, TSPARMCD, TSSEQ		ts.xpt 



Contact: Carlo Radovsky
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