Clinical Research and Pharmaceutical Product Development

Opportunities for innovation and realization of benefits of EHRs

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Objectives

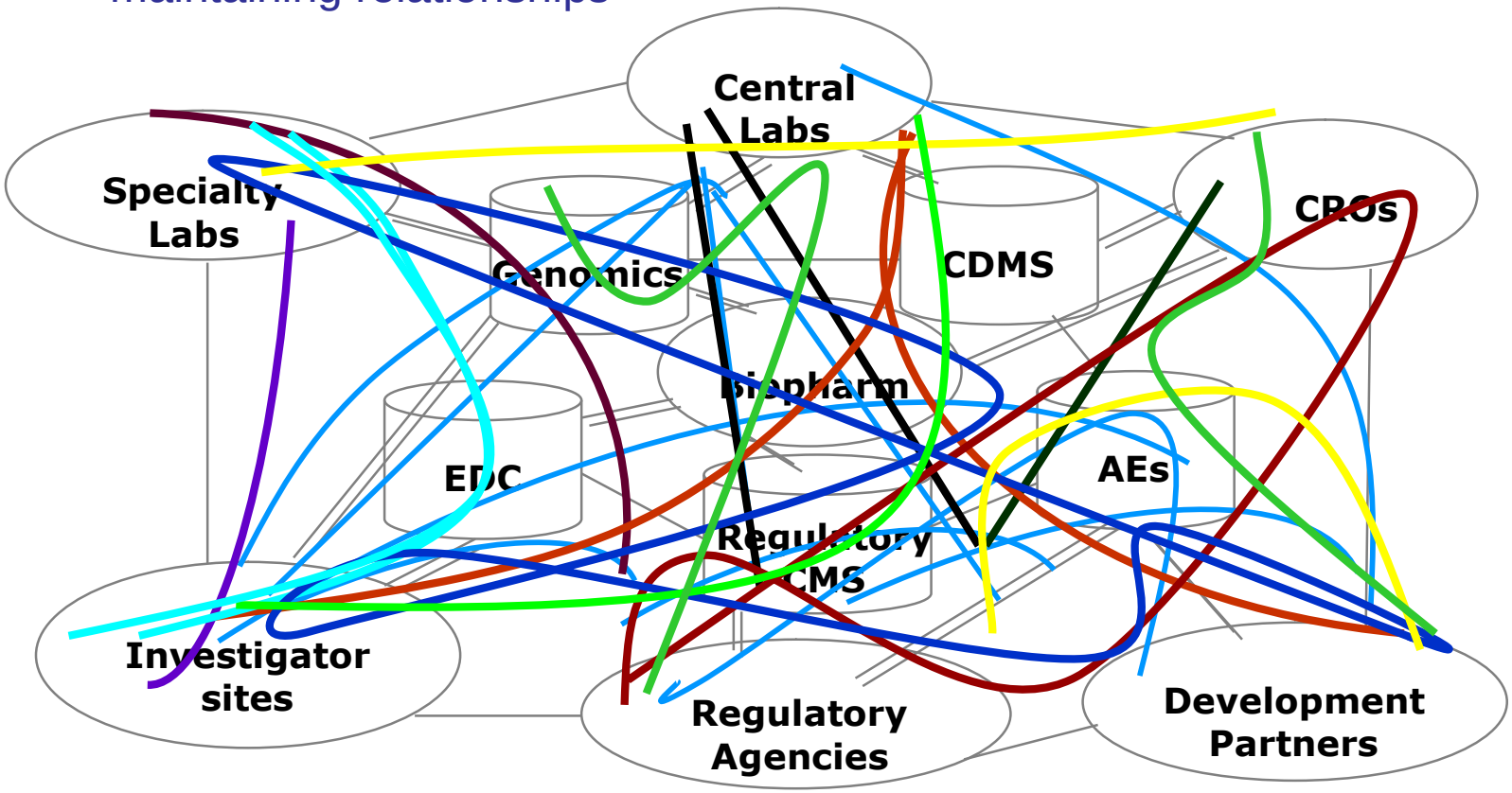
- Promote awareness re the role and effect of emerging health information interchange standards on the pharmaceutical industry
- Identify leadership opportunities for leveraging and advancing standards efforts for benefit of pharmaceutical product development

Standards are Central to taking Advantage of EHR

- Standards are means to desirable end for both Sponsors and Regulatory Authorities
  - **Goal**: Improved time to market for safe and effective treatments (increased patient safety and reduced costs)
  - **Strategy**: More efficient choreography of large number of data interchanges from many sources that occur over a long period of time in clinical research and regulatory evaluation
  - **Tactic**: Widespread adoption of standards enables efficient transfer data in a reliable, secure manner and in a way that specifies what data is being transferred and permits automated processing and **efficient reuse of data**

Efficient data transfers are extremely important

- Drug Development is an Increasing Complex Business System
  - Processes cross functional and organizational boundaries
  - Lots of stakeholders and users of information with varying agendas
  - Information exchanges play important role in connecting activities and maintaining relationships



Parallel worlds that overlap

- **Discovery research**: building blocks and pathways, molecular drug targets, molecular libraries, bioinformatics and computational biology, genomics, proteomics, metabolomics, structural biology, nanomedicine
- **Clinical research/medical product development**: in vitro and animal studies; toxicogenomics and pharmacogenomics; clinical trials and registries; regulatory submissions, regulatory review and approval
- **Clinical practice:** patient care, health care operations

Information flows cross boundaries between these worlds

The Heart of the Matter

Interoperability:

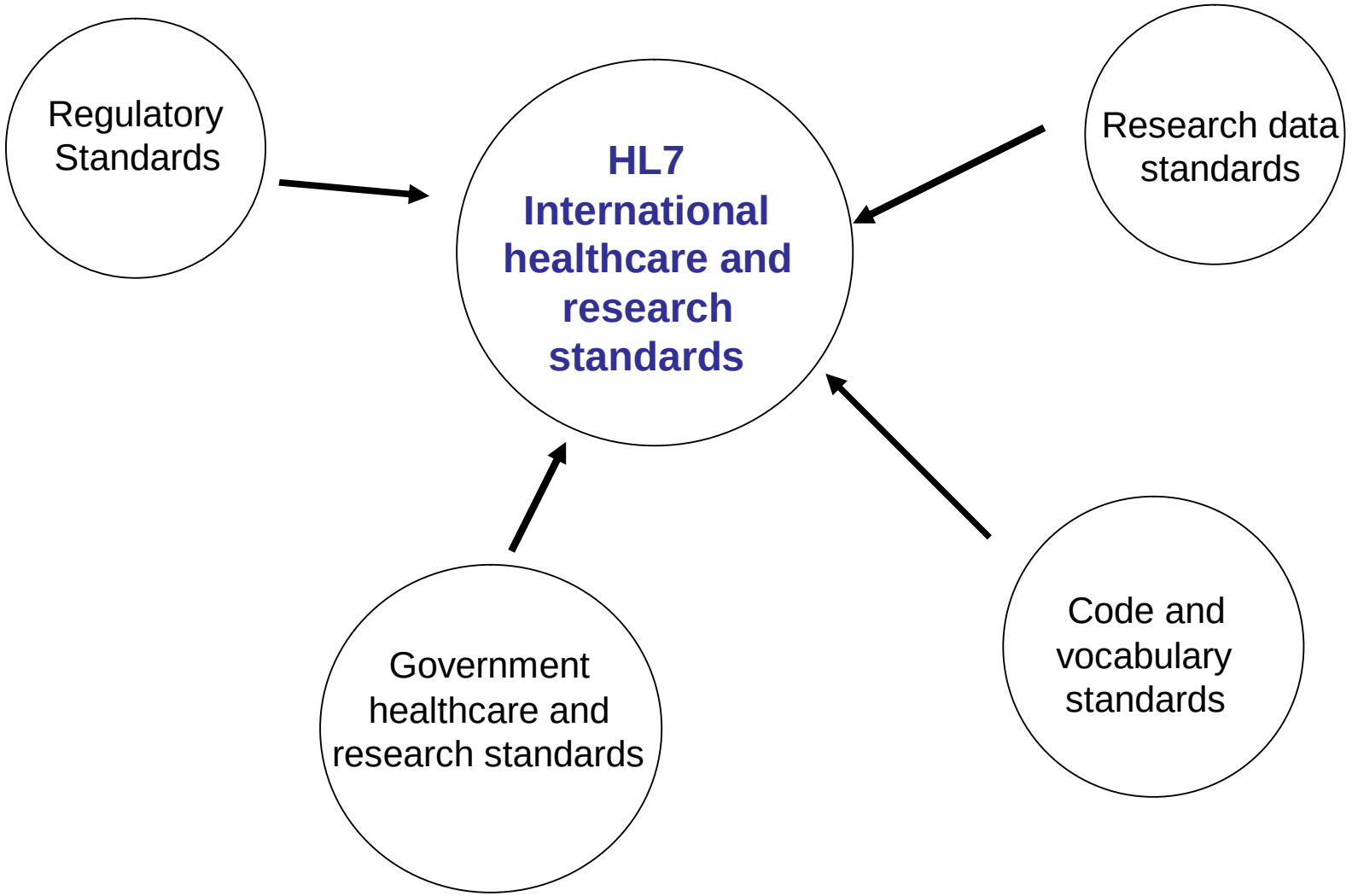
ability of two or more systems or components to exchange **information and to** use **the information that has been exchanged.**

Source: IEEE Standard Computer Dictionary: A Compilation of IEEE Standard Computer Glossaries, IEEE, 1990.

Interoperability

- Interoperability within a complex business space requires **a composite view** across all of the independent business processes and a **shared set of concepts, attributes, and relationships** between concepts that can be used to represent and execute business processes.

HL7 Has Become a Clearing House for Health Care and Life Sciences



Health Level Seven

- Founded in 1987, not-for-profit, ANSI accredited standards developing organization
- Primary concerns:
  - A comprehensive framework and related standards for the exchange, integration, sharing, and retrieval of electronic health information that supports clinical practice and the management, delivery and evaluation of health services.
  - Improving or enhancing information management during research and regulatory evaluation of the safety and efficacy of therapeutic products or procedures worldwide [Regulated Clinical Research Information Management (RCRIM) TC]

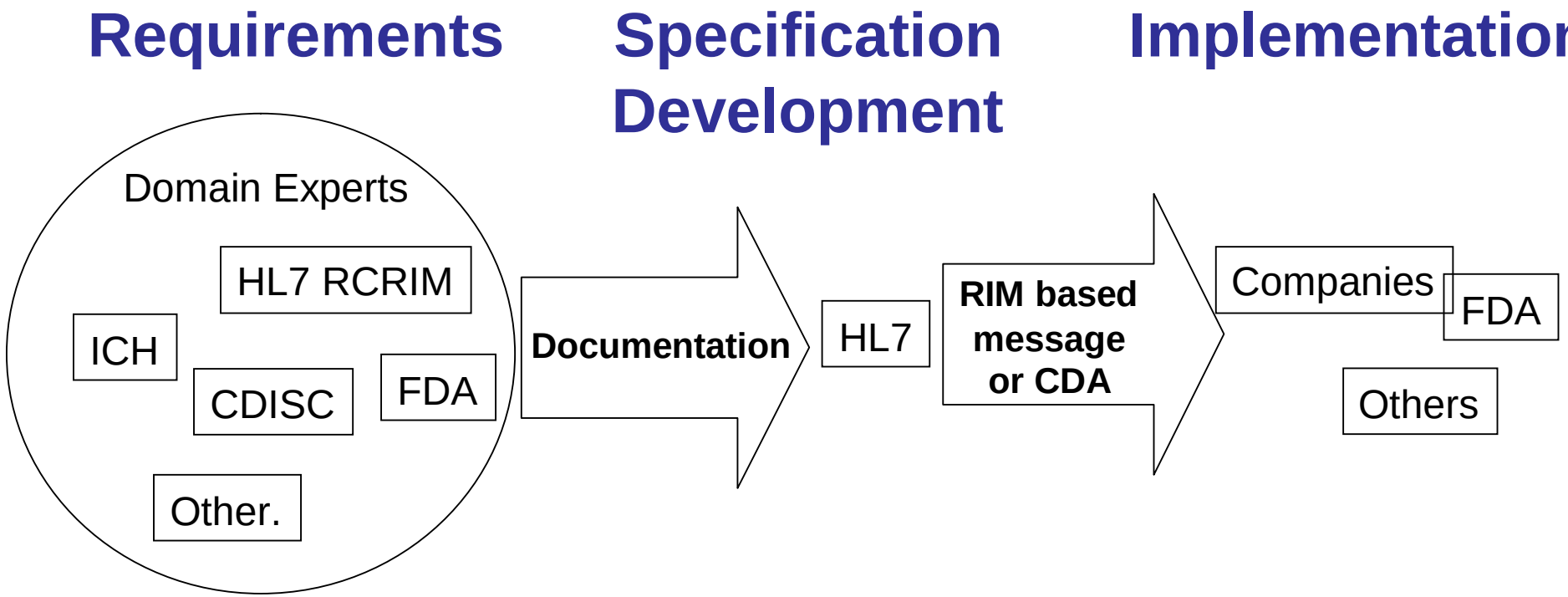
Health Level Seven

- How it works:
  - Accredited by the American National Standards Institute (ANSI)
  - Open, international membership
  - Defines messages, document structures, and terminology to support the systems and processes used in the collection, storage, distribution, integration and analysis of research and healthcare information.
- Most widely used HL7 specification is messaging standard that enables disparate healthcare applications to exchange key sets of clinical and administrative data.
- Structured document standard allows for the interchange of documents as well as individual data elements.

HL7: Governance

- Members of Health Level Seven (collectively called the working group) are organized into technical committees (TCs) and special interest groups (SIGs).
- TCs are directly responsible for the content of the Standards and the SIGs explore new areas that may need coverage in HL7's published standards.
- Well-defined set of operating procedures to ensure consensus, openness and balance of interest. Regularly scheduled open meetings and voting cycles.
- Anyone who is interested can participate and contribute at face-to-face meetings and in scheduled teleconferences but only registered voting members can vote during formal ballot cycles.

How Standards Get Developed: HL7 Standards Development Process

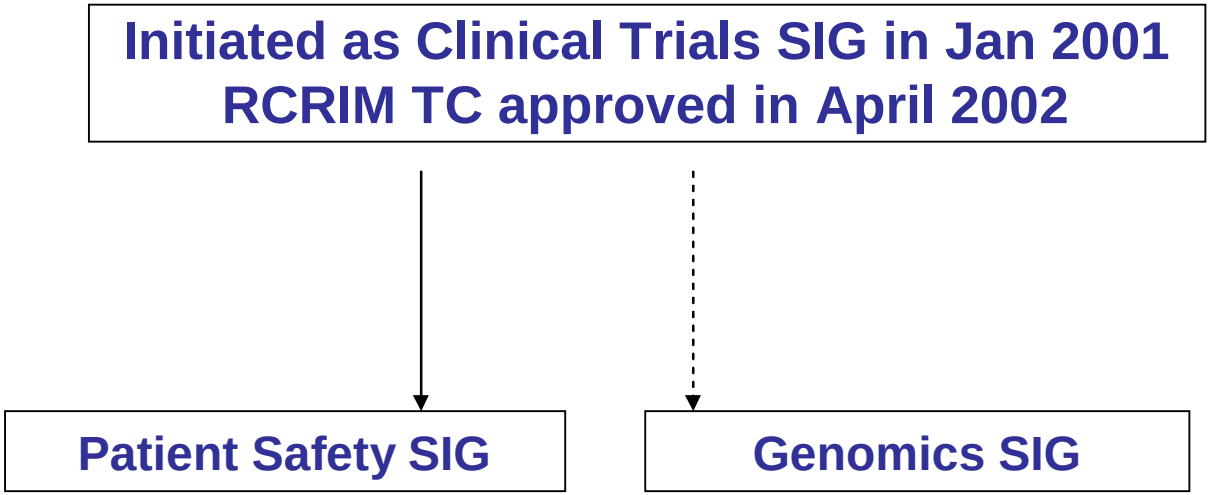


Source: R. Levin, EuroInterchange, May 2004

HL7: Regulated Clinical Research Information Management TC

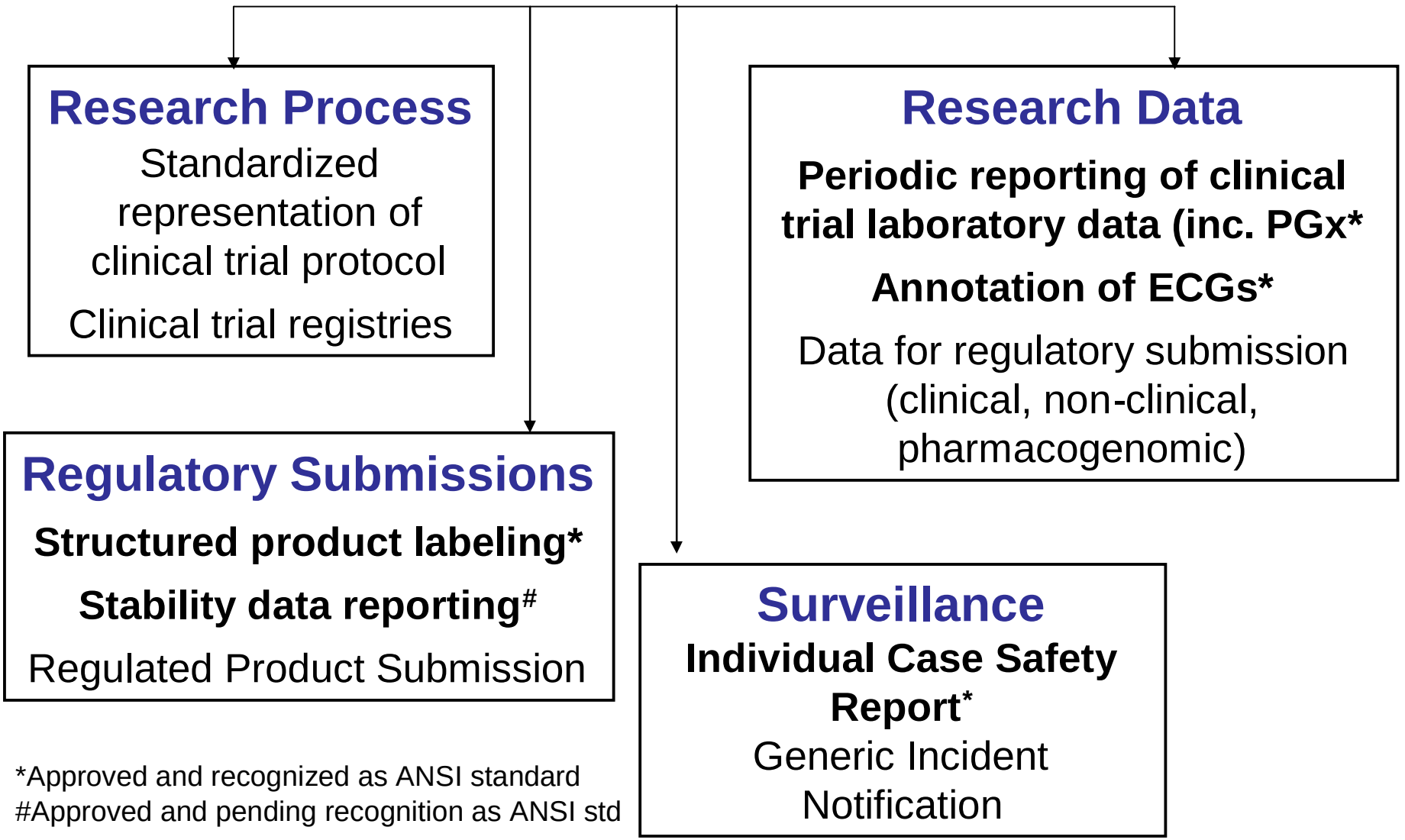
- Focus is standards that improve or enhance information management during research and regulatory evaluation of the safety and efficacy of therapeutic products or procedures worldwide.
- Participation from FDA and international regulatory agencies, other government agencies (e.g. CDC), PhRMA, CDISC, academic research organizations, biopharmaceutical companies, and vendors and service providers who operate in pharmaceutical market.
- Defines messages, document structures, and terminology to support the systems and processes used in the collection, storage, distribution, integration and analysis of clinical research and drug development information.
- Interchange structure specifications are developed to conform to **business requirements** and data and information needs of regulatory authorities and pharma industry AND common **information model, defined data types, controlled vocabularies** and **code lists.**

How Standards Get Developed: HL7 RCRIM TC



- Develops data interchange standards for clinical research and regulatory evaluation based on requirements (content specifications) of and input from industry and regulatory authorities
- Assures that other HL7 standards (healthcare standards) can be used in regulated clinical research
- Co-chaired by Randy Levin (FDA), Linda Quade (Lilly) and Barbara Tardiff (CDISC, Merck)

Standards Development and Adoption: RCRIM



*Approved and recognized as ANSI standard
#Approved and pending recognition as ANSI std

Value Proposition for Pharma

- Realizing the benefits of EHRs
- Important and fundamental groundwork:
  - Implementation of systems and processes that taking advantage of standards that are available and being used now
  - Contributing to standards under active development
  - Advancing opportunities for involvement and accelerating innovation

HL7 Standards that are Available and in Use

- Structured Product Label
  - Structured Product Labeling (SPL) specifies structure and semantics for the regulatory requirement and content of product labeling and has been approved as a Clinical Document Architecture (CDA) (based on HL7 RIM) at the membership level and is recognized as an ANSI standard.
  - FDA Electronic Labeling Rule has been implemented and provides for use of new technologies (e.g. SPL) as available. FDA Physician Labeling Rule will be released soon in final form and will require highlights supported by SPL.
  - Several vendors have or are developing application that support SPL. FDA has received several submissions in this fomat.

- Notifiable Condition Report
  - For public health/biosurveillance reporting
- Individual Case Safety Report (ICSR)
  - Passed membership level ballot. Submitted as ANSI standard.
  - Meets requirements of ICH E2B. Electronic replacement for Medwatch

HL7 Standards that are Available and in Use

- Periodic Reporting of Clinical Trial Laboratory Data
  - Based on CDISC LAB Model V1.0; fully balloted Version 3 RIM message and recognized as ANSI standard; **Release 2 incorporating PGx data and other extensions scheduled for ballot this year**
  - Oracle incorporating standard into technology
  - A number of pilots underway this year (inc. Merck)

- Annotation of ECGs (Annotated ECG waveform standard)
  - Fully balloted Version 3 RIM message and recognized as ANSI standard; Implementation Guide approved.
  - FDA has now received thousands of submissions in this format

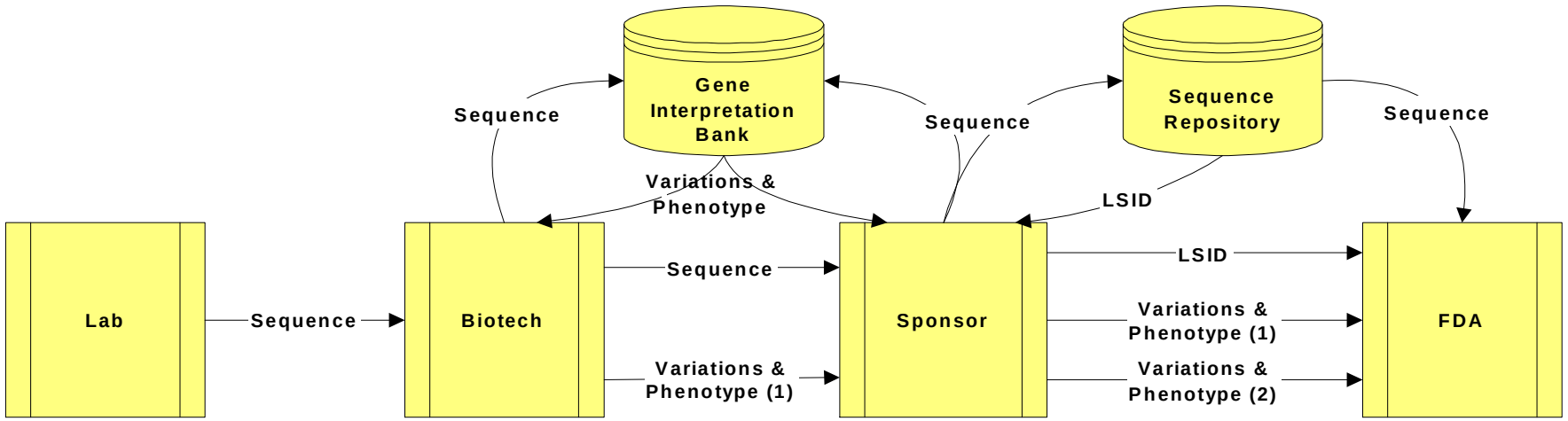
- eStability data
  - Drug Stability Report (for submitting product stability data to the FDA) is being balloted as HL7 Version 3 message.

PGx Extension of CT Lab Message

- Pharmacogenomics message modeled as an extension of the RCRIM LAB message
- Uses HL7 model of genomics science common element and family history model

Key Assumptions

- Pharmacogenomic model must be end-to-end
  - Collection to submission
  - Add and drop off data as it moves downstream



Pharmacogenomic Use Cases

Lab and Sponsor

- Lab provides all data
  - Sequence based analysis
  - Alleles and phenotype only
  - Includes Pharmacokinetic data
- CYP2D6 drug metabolism study

Lab, Biotech and Sponsor

- Lab
  - Collects specimen
  - Extracts DNA
  - Reports results
- Biotech perform gene expression analysis
  - Microarray analysis of 4 disease marker genes

Pharmacogenomic Use Cases

DNA Banking

- Lab
  - Collects specimen
  - Extracts DNA
  - Freezes DNA

FDA Submission

- SDTM Pharmacogenomic domain reports
  - Sequence LSID
  - Gene
  - Alleles
  - Phenotype
- Pharmacogenomics message carries
  - Sequence values

Periodic Reporting of CT Lab Data

- Key Additions to Base Model
  - Consent to Genotype
  - Genetic Extraction
  - Genetic Specimen
  - Genetic Test

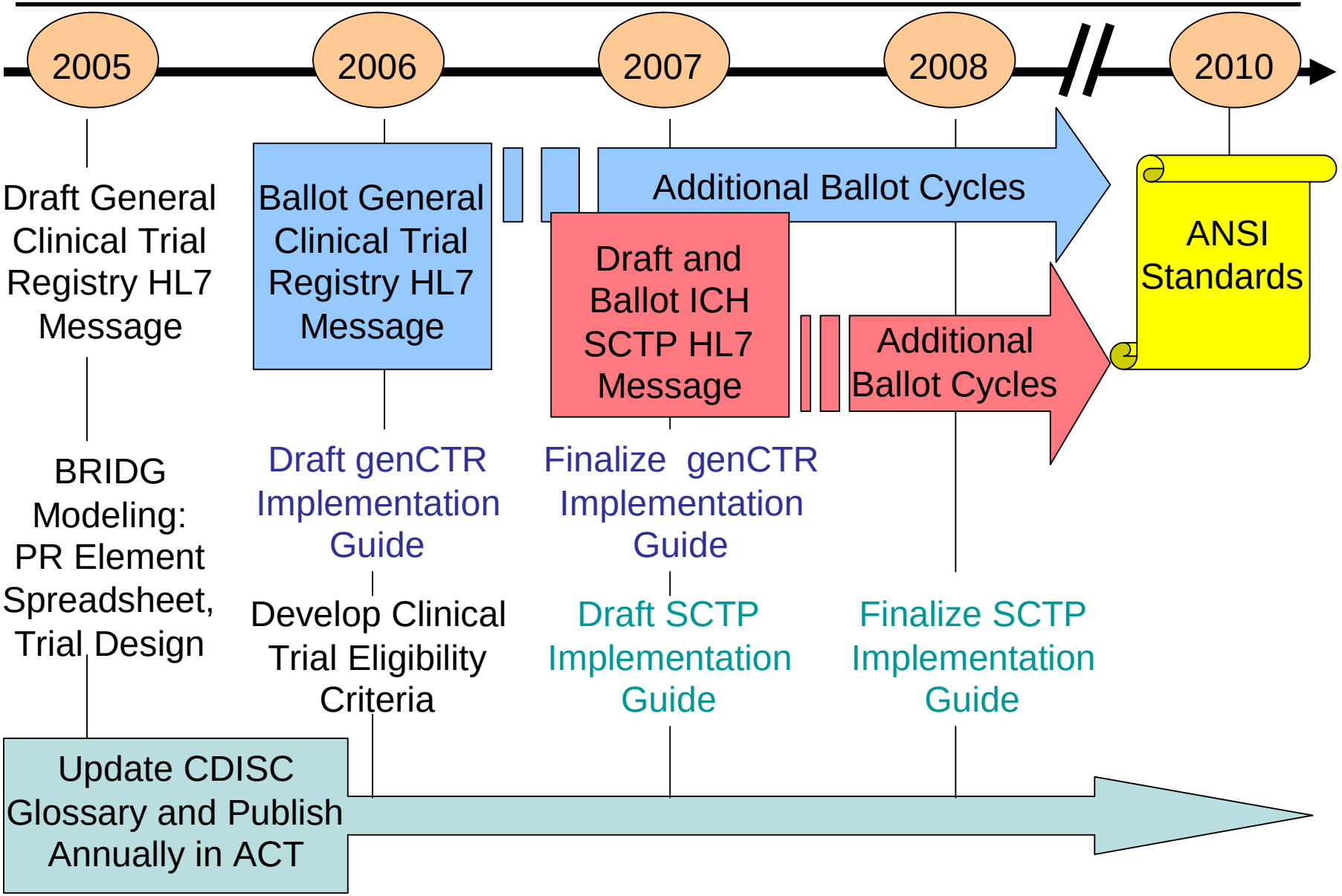
HL7 Standards that are Under Development

- Structured Clinical Trial Protocol (SCTP)
  - Release 1 (subset of elements) balloted as an HL7 Clinical Document Architecture (CDA) at the committee level in May 2004
  - Protocol Representation (PR) Group working on defining standard elements and semantics for the content of clinical trial protocols, with the goal of creating a machine-readable electronic protocol representation. Full SCTP will be developed through incremental releases of specification.
  - Messages for two related use cases under development.
- Clinical trial registries
  - Project to develop requirements and interchange standards approved September 2004
- eDCI (electronic definition of Data Collection Instrument)
  - Undertaking to create an HL7 V3 message to convey the definition of an Data Collection Instrument between applications.
  - Being developed under auspices of NCI as early adopter

External Clinical Trial Registry Message Specification

- Goal:
  - Develop HL7 message specification for submission of trial information to external clinical trial registries, e.g., ClinicalTrials.gov, EudraCT, PDQ, WHO
- Assumptions:
  - Focus on Registries, not Results Databases
  - Message should be generic and comprehensive
  - Additional Use Cases:
    - ***Internal project management tools for trial/protocol tracking***
    - ***Regulatory submission***
- Status:
  - Gathering requirements
    - ***PR Elements Spreadsheet***
    - ***WHO requirements***
    - ***Clinicaltrials.gov, EudraCT, PDQ specificiations***
    - ***SDTM Trial Summary dataset***

Protocol Representation Timeline



HL7 Standards that are Under Development

- Generic Incident Notification (GIN)
  - To support generic reporting for process improvement and organizational learning
- Regulated Product Submission
  - Project to define a message that is general enough to used broadly for submissions across all regulated products and includes information (metadata) that allows regulators to support structured review

Regulated Product Submission Message

- Scope
  - Animal and Human products including but not limited to food additives, human therapeutics, veterinary products, and medical devices
    - ***Same message structure for all product types***
    - ***Different controlled lists for each product type***
  - Worldwide use
- Out of Scope
  - Submission content
- Planned for a later release
  - Inclusion of information about the submission (e.g. information currently collected on application forms)
  - Two-way communications.

- Regulators may review content received as HL7 V3 message or as eCTD in the same fashion

Regulated Product Submission Message: Phase 1

- Transmission of electronic submissions for a regulated products.
- Tagging of submissions for effective review, including, but not limited to allowing creation of a table of contents.
- Provides an electronic submission standard to regulated products where no submission standards exist.
- Basic requirements: re-use of documents and document components; management of submission lifecycle, submission of form data (different for each regulated product)
- Allows applicants to re-use documents that were already submitted. In the case of human therapeutics, standard will allow applicants to move from an IND to a marketing application seamlessly.

Regulated Product Submission: Work to date

- 16 unique lifecycle scenarios documented (business process use cases)
- Business rules that encompass the requirements
- Simple model of a regulated submission
  - Entities, relationships, cardinality, attributes documented
- Simple model of an application type
  - Entities, relationships, cardinality, attributes documentation in progress
- Controlled lists for human therapeutics

Parallels with EHRs

- Have been able to leverage healthcare standards
  - Document lifecycle is almost exactly like document lifecycle of the medical record message.
  - Story boards, application roles, trigger events, and interactions are, for the most part, already documented.
  - Sequencing addendums are built in to the Laboratory DMIM
  - Two way communication with reasons and codes are already in the medical record message.
  - Defining how to manage documents, with ids and URLs, are already apart of the medical record document message

Regulated Product Submission Use Cases (1)

- A procedure document was submitted for the first time.
  - The model must allow original documents to be submitted
- A synthesis document that was previously submitted has been updated. Reviewers need to be aware that the older document was been replaced with a newer document.
  - The model must have the ability to replace previously submitted documents
- A sample case report form was submitted as an original. In the next submission, additional pages to that sample case report will be submitted.
  - The model must have the ability to add pages to a submitted document
- A document was submitted about an investigator. The investigator is no longer involved with the study. Regulators should not review any documents related to this investigator.
  - The model must have the ability to inform reviewers to disregard previously submitted documents

Regulated Product Submission Use Cases (2)

- A document was submitted about an investigator. The investigator is no longer involved with the study. In a previous submission, documents related to the investigator were disregarded. The investigator is involved in the study again. Regulators need to be aware of that any previous documents about the investigator that they were asked to disregard to review. In addition, lifecycle needs to restart and continue with these previously disregarded documents
  - The model must have the ability to restart and continue lifecycle on disregarded documents
- A sample case report form has been submitted. In a later submission, additional pages to the sample case report form has been submitted. Both the original sample case report form and the additional pages have been consolidated into one document.
  - The model must have the ability to allow one document to replace multiple documents

Regulated Product Submission Use Cases (3)

- The same document was submitted twice by accident as original. In a later submission both documents will be updated with only one document.
  - The model must have the ability to allow one document to replace multiple documents
- An original document has two separate appendices/attachments. Together the original document and the appendices/attachments make a single document (see slide 13, 14 and 15).The appendices has been updated.
  - The model should allow sub documents to have their own life cycle
- A summary document was submitted. In a future submission that document was broken up into several document with more granularity.
  - The model must have the ability to allow one document to be replaced by multiple documents while continuing all of the documents lifecycle.

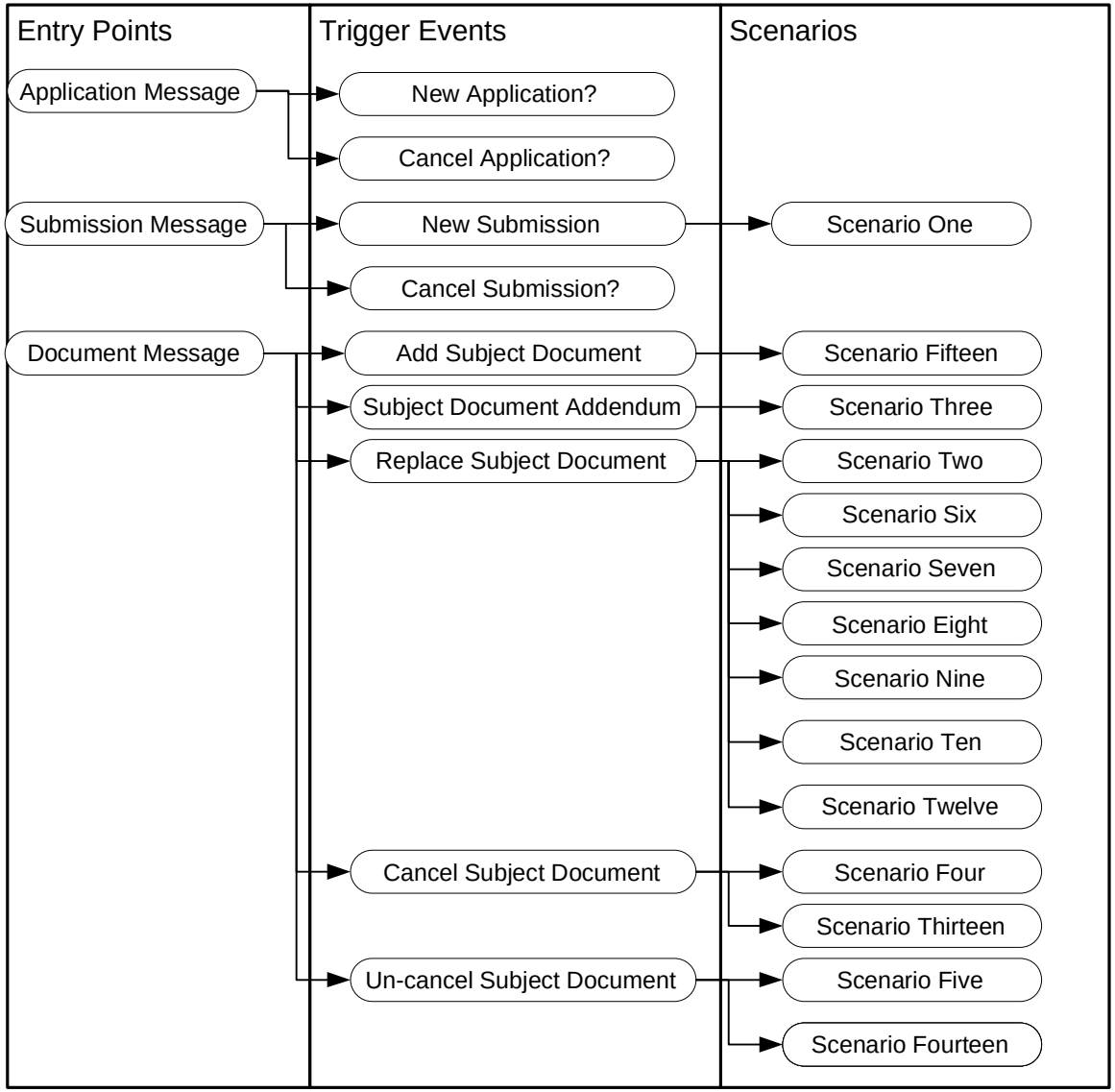
Regulated Product Submission Use Cases (4)

- Drug-substance (non-granular) was submitted as an original document. In a latter submission more granular documents were submitted to fully replace the drug-substance document.
  - The model must allow multiple documents to replace one document
- A legacy study report (non-granular) was submitted as an original document. A protocol and synopsis document was submitted. Although the protocol and synopsis documents do not fully replace the legacy study report, these documents do update section of the legacy study report.
  - The model must have the ability to update sections of one document
- A summary of safety was submitted as a summary document and as a clinical document. In the clinical section the safety document was replaced with a much larger document.
  - The model must have the ability to replace one document in one section and not replace the other document in another section

Regulated Product Submission Use Cases (5)

- Several manufacturer documents were submitted. The manufacturer has lost the contract.
  - The model must have the ability to inactivate sections as it relates to keywords.
- Several manufacturer documents were submitted. The manufacturer has lost the contract and was marked as inactive. Then this manufacture won the contract.
  - The model must have the ability to activate sections as it relates to keywords.
- Several documents were submitted for a study in one application. That study applies to another application. Whenever a change for the study is made in the first application, that data should be reflected in the second application.
  - The model must have the ability to link logical documents between applications
- Several documents were submitted for a manufacturer in one application. That manufacturer applies to another application. Although the same manufacture applies to both applications, some documents only apply to one application.
  - The model must have the ability to have the same logical documents in more than one application with different lifecycles

Entry Points and Trigger Events



Opportunities for Advancing the Pace of Innovation

- ICH: Requirements for information exchanges with regulatory authorities

- CDISC: Requirements for information content and organization to support the business of research
  - Industry Advisory Board
  - Team participation:

- HL7: Technical specifications for information interchange messages and structured documents
  - TC and Project team participation: RCRIM, Patient Safety, Clinical Genomics

Opportunities for Advancing the Pace of Innovation

- Leveraging existing standards to promote interoperability
  - Implementation of SPL
  - Implementation of Periodic Reporting of Clinical Trial Lab Data
  - Use of CDISC SDTM and ODM to facilitate transfers of clinical trial data with regulatory authorities and partners and archival of data

- Become more effective in participation in standards organization
  - Collaborate, represent expertise and perspectives and communicate across company and industry in standards development and adoption process
  - Contribute resources to facilitate development of standards needed
  - Propose domains or use cases for standards development
  - Be an “early adopter”

Essential Elements for Success

- Multi-national Industry and government involvement
- Public relations and education
- Leveraging lessons learned and accomplishments from other electronic submission and interchanges experience
- Messages that are general/flexible enough to handle spectrum of related use cases; then constrain to meet needs of individual use case (e.g event notification).