Harmonizing CDISC Submission Models and Pharmacovigilance

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Current State

- SDTM developed with raw/observed data in mind
- ADaM designed for analysis datasets (includes derived data)
- Some company-specific work has been done to put derived data into SDTM
- Question: How do we create a single model (THE CDISC model) for submitting all data to FDA?
  - Raw and derived and metadata
  - What are the full requirements for such a single model?
  - What would it take to make this approach reasonable for pharma industry business process and FDA review process?

CDISC Project

Objective

- To assess the data structure/architecture, resources and interoperability needed to transform data from legacy data sets (observed, derived and analysis data) into the CDISC SDTM and/or ADaM formats.
- CDISC will perform case studies which demonstrate the effective transformation of legacy data into CDISC SDTM domains and ADaM datasets and their associated metadata.
- A case study/test(or series of studies/tests) would allow CDISC to understand how SDTM might be used for submission of derived data and the specific needs for separate ADaM datasets/programs.
- CDISC wants to repetitively test and learn the very best application of its interoperable standards to meet the industry regulatory data submission requirements.

CDISC Project

- CDISC and PhRMA are building a stronger relationship to solve these problems
- Streamlining and standardizing the data flow for pharma business and submission to FDA will require multiple steps / endeavors

Disclaimer

- The views in this presentation are not necessarily the views/policies of :
  - the CDISC Board
  - Eli Lilly and Company
  - SAS Institute, Inc.
  - Ed Helton, Dave Christiansen, Wayne Kubick, and FDA

    but they should be.

CDISC Goals-Simply Stated (circa 2001)

A future conversation on data interchange:

- anyone: How do you want me to send the data?
- everyone: We are using CDISC version x.y
- anyone: I can do that

PS Data = raw, derived, meta

PPS Anything said about submission of data to the FDA could apply to how CROs 'submit' data to Sponsors

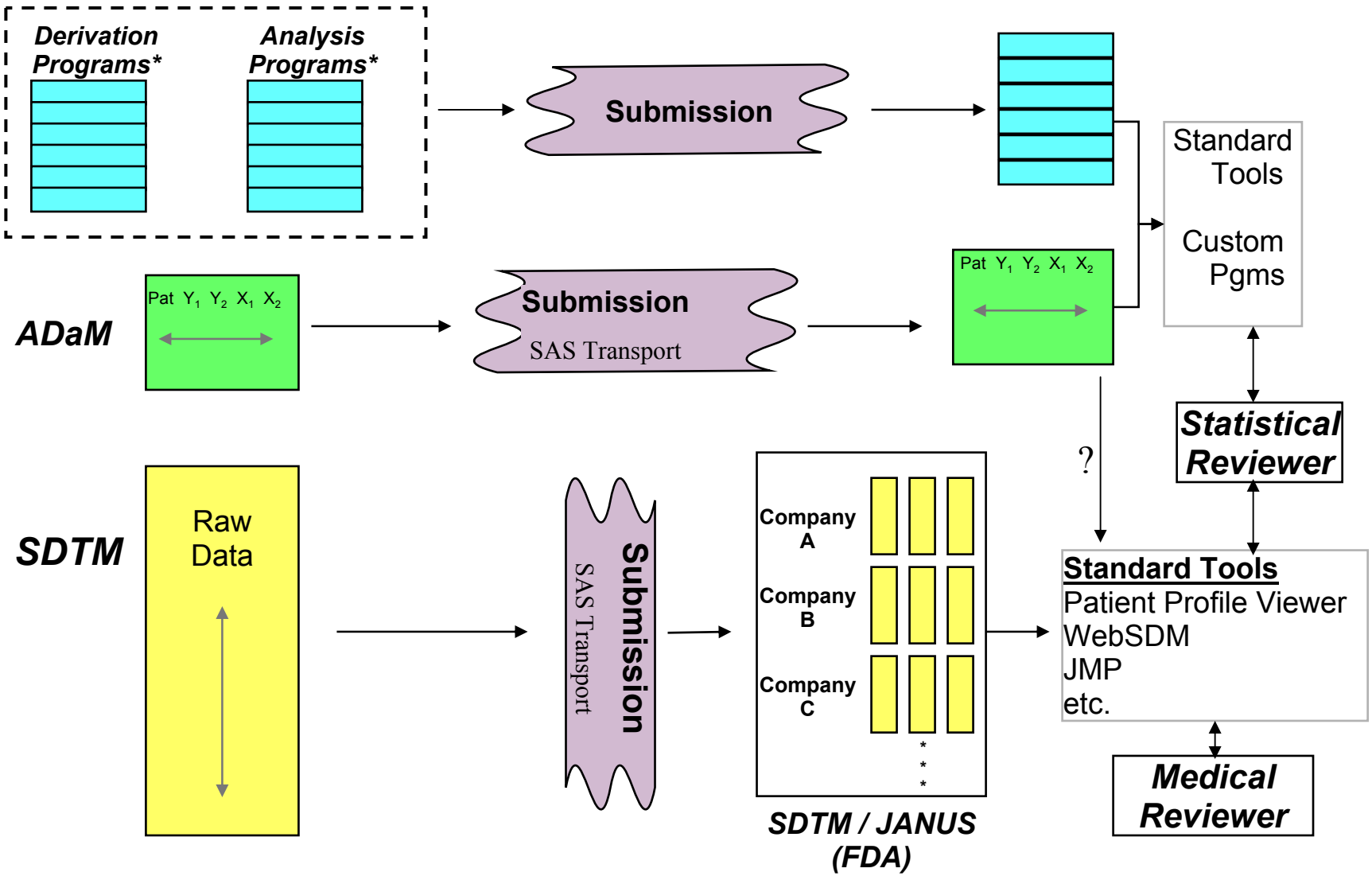
Some Principles

- Minimize redundant data sets and data flows
  - Reduce chances of errors and inconsistencies
  - “Neither seek nor avoid complexity.” (R. A. Fisher)
- Statistical Reviewers need data sets that can be readily analyzable (i.e. minimize programming)
  - “one PROC away” is desirable
- All Reviewers need derived data
  - Minimize Reviewers doing programming
- Data is stored in a common way/warehouse using standard formats and content
  - Facilitates communication for review and regulatory approval
  - Support integration across studies/companies
  - Facilitate automation and use of common tools
  - Supports traceability from collected to analyzed data

Some Considerations

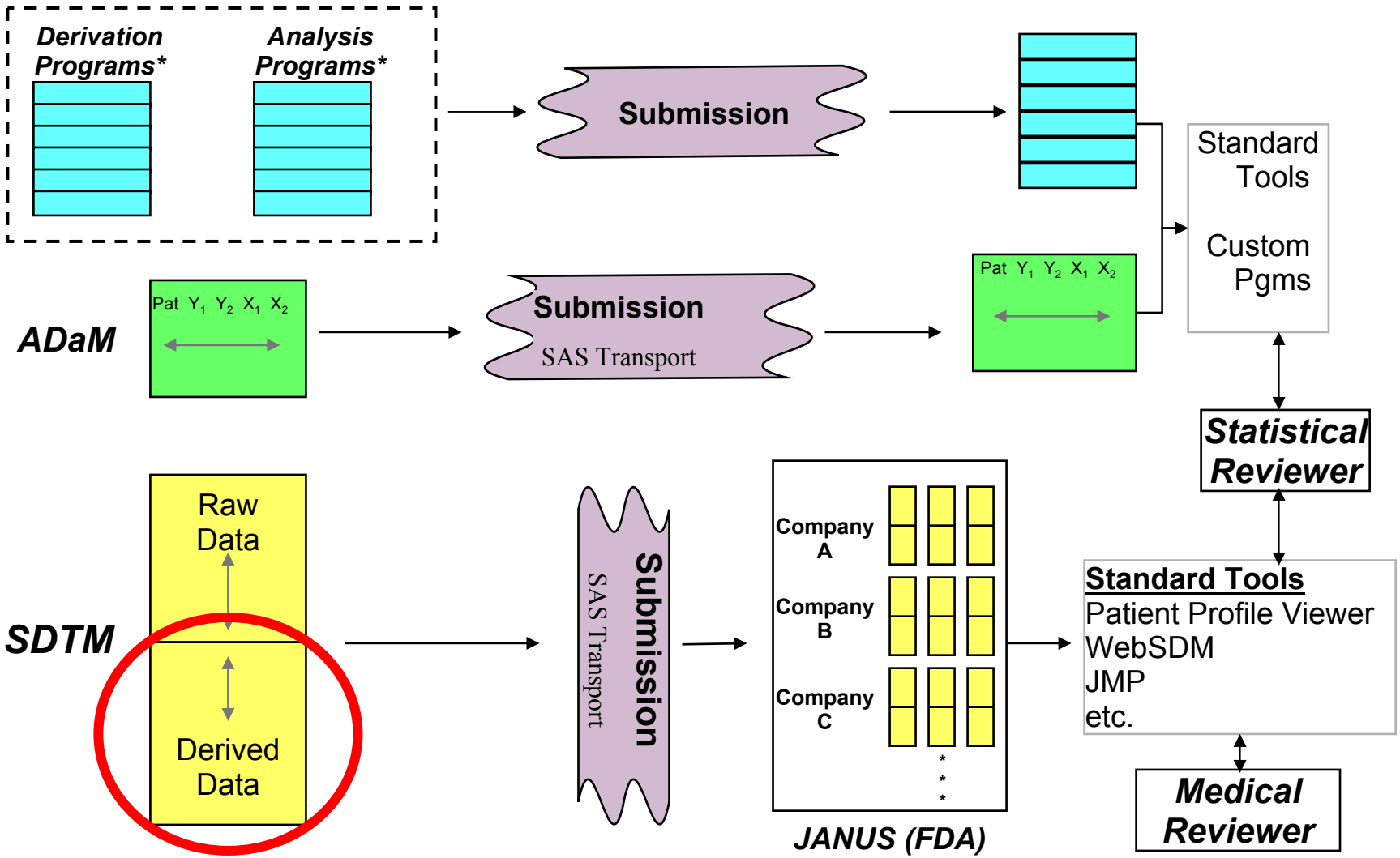
Scope / Primary Purpose	Individual Study/Submission	Integration Across Submissions
Review Data As Reported		
Verify Data As Analyzed		

Figure 1A
Submission Data Flow – Emerging State



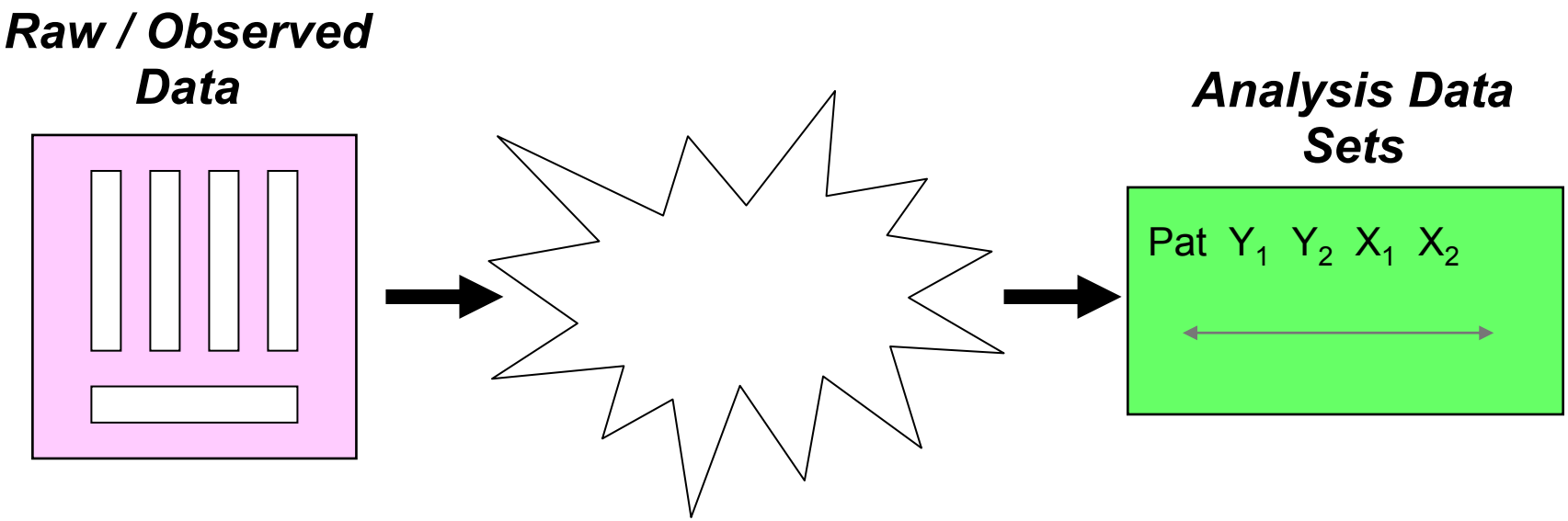
*Structure and process is the discretion of the Sponsor.

Figure 1B
Submission Data Flow – Emerging State



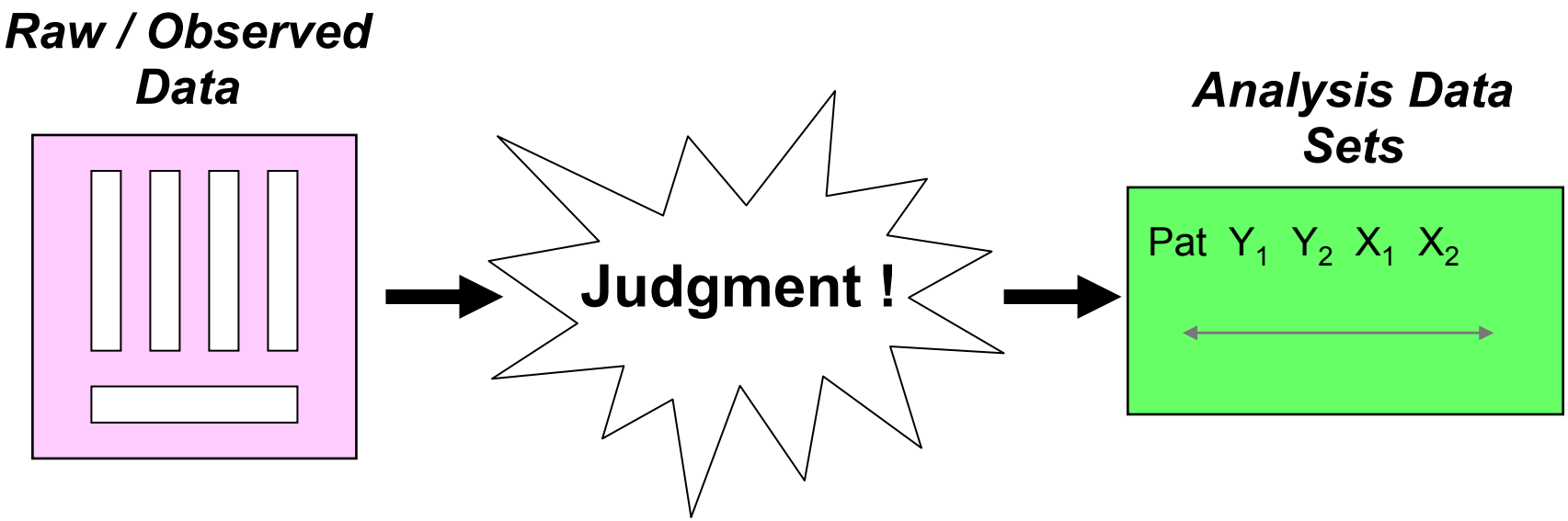
*Structure and process is the discretion of the Sponsor.

Some Considerations



What happens in this space is company specific

Some Considerations

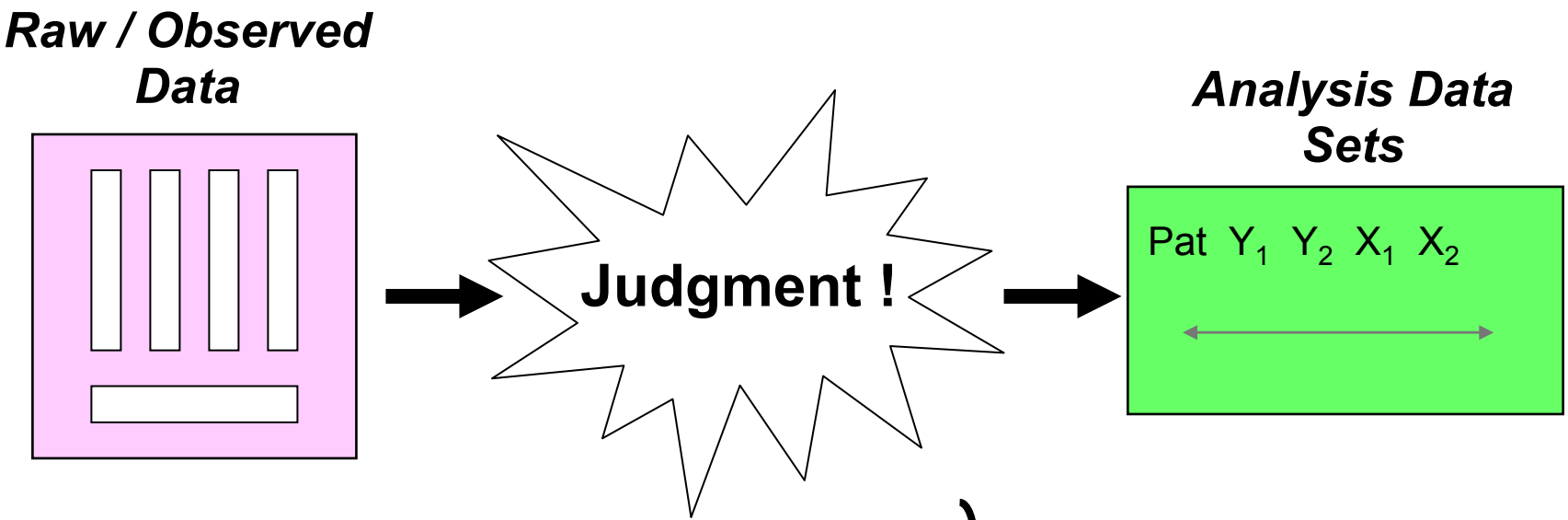


How do we capture all these judgments?

Text? Code? Machine-readable metadata?

What judgments can be turned into rules?

Some Considerations



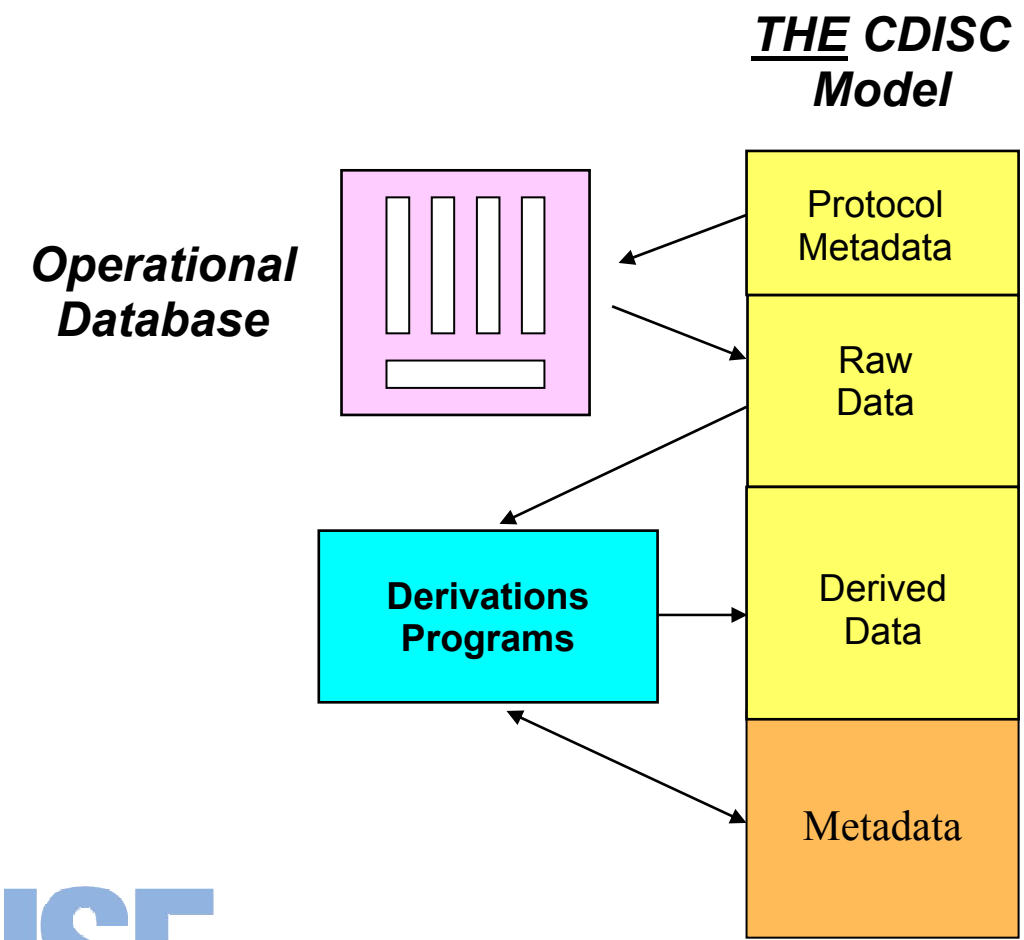
What metadata can be captured?

What can be standardized? automated?

Can metadata help with integration across studies?

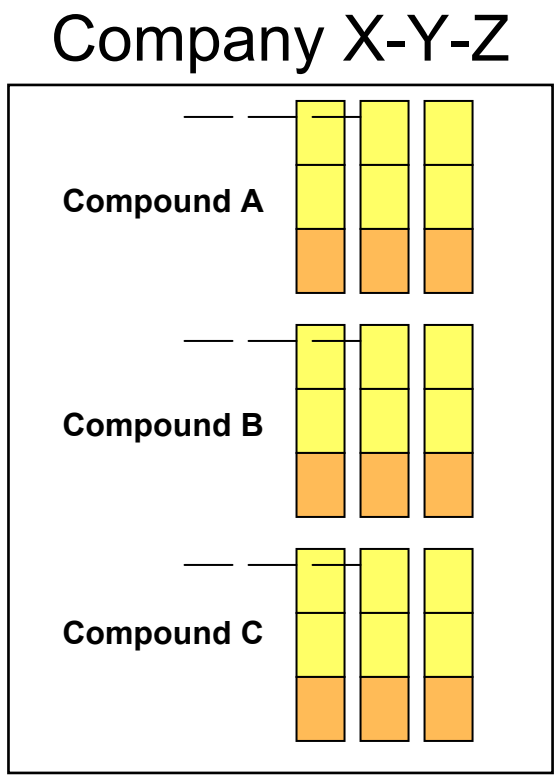
These questions are relevant regardless of how derived data are structured in an analysis data set.

Creating THE CDISC Model



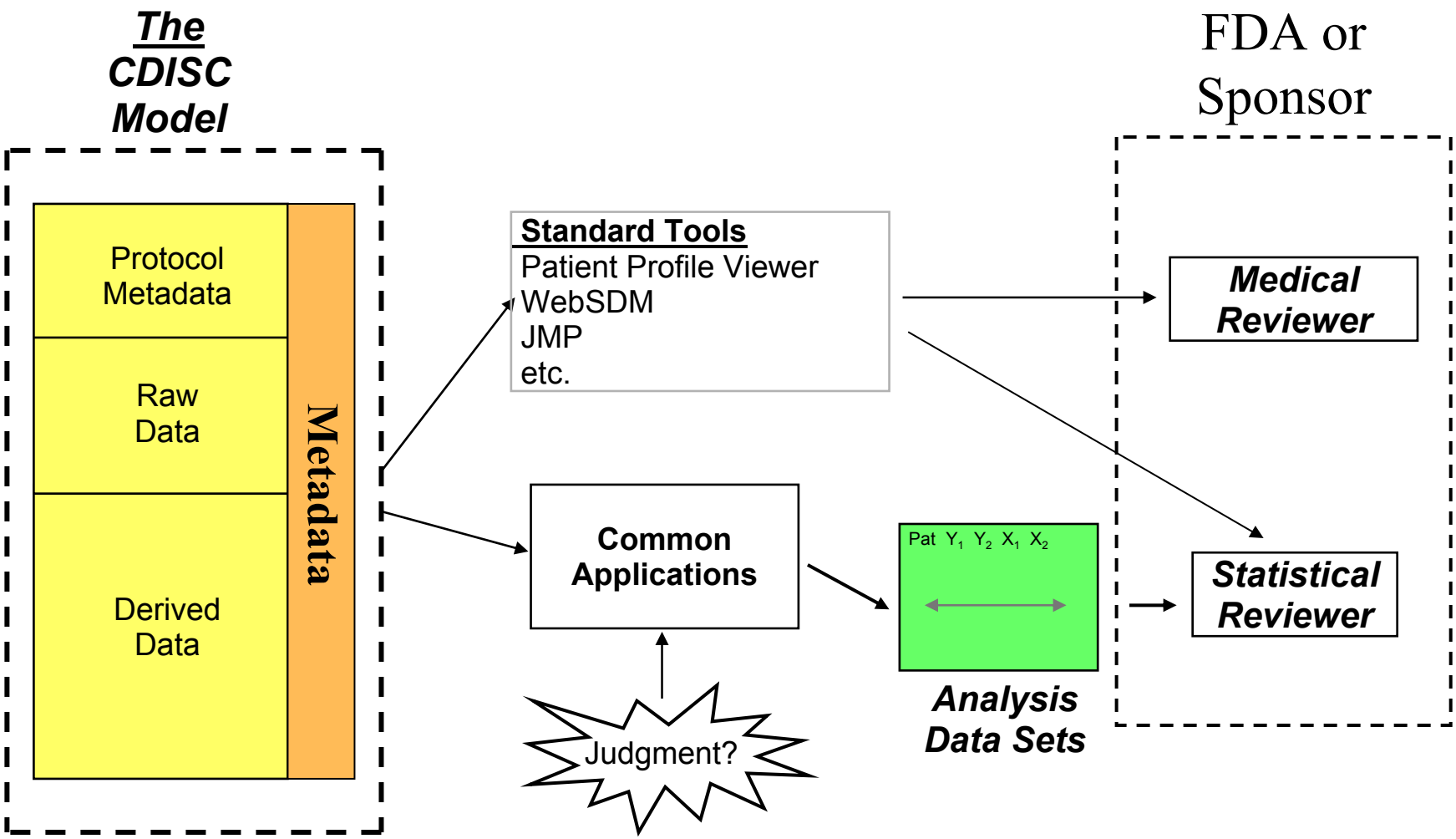
Creating the CDISC Warehouse

- Companies can more easily build internal warehouses of clinical data using CDISC standard content, structures, metadata



There is no need to have multiple archives of data (protocol, raw derived and meta) and programs.

Creating the CDISC Submission



What else do we need?

- Can we have a comprehensive/robust enough vocabulary to integrate data across studies easily?
  - Raw data is hard enough; derived data is ?
- Can we have comprehensive metadata to describe trial design, judgments and analysis?
  - Judgments for a single analysis
  - Judgments for integrated summary across a compound
  - Judgments for integrated summary across companies
- Some alchemy

Conclusion 1

- CDISC committed to unambiguous communications for submissions
  - Data structures and content
  - Derivations, analysis programs
- Levels of complexity / sophistication
  - For an individual study
  - For studies across a submission
  - For submissions across companies

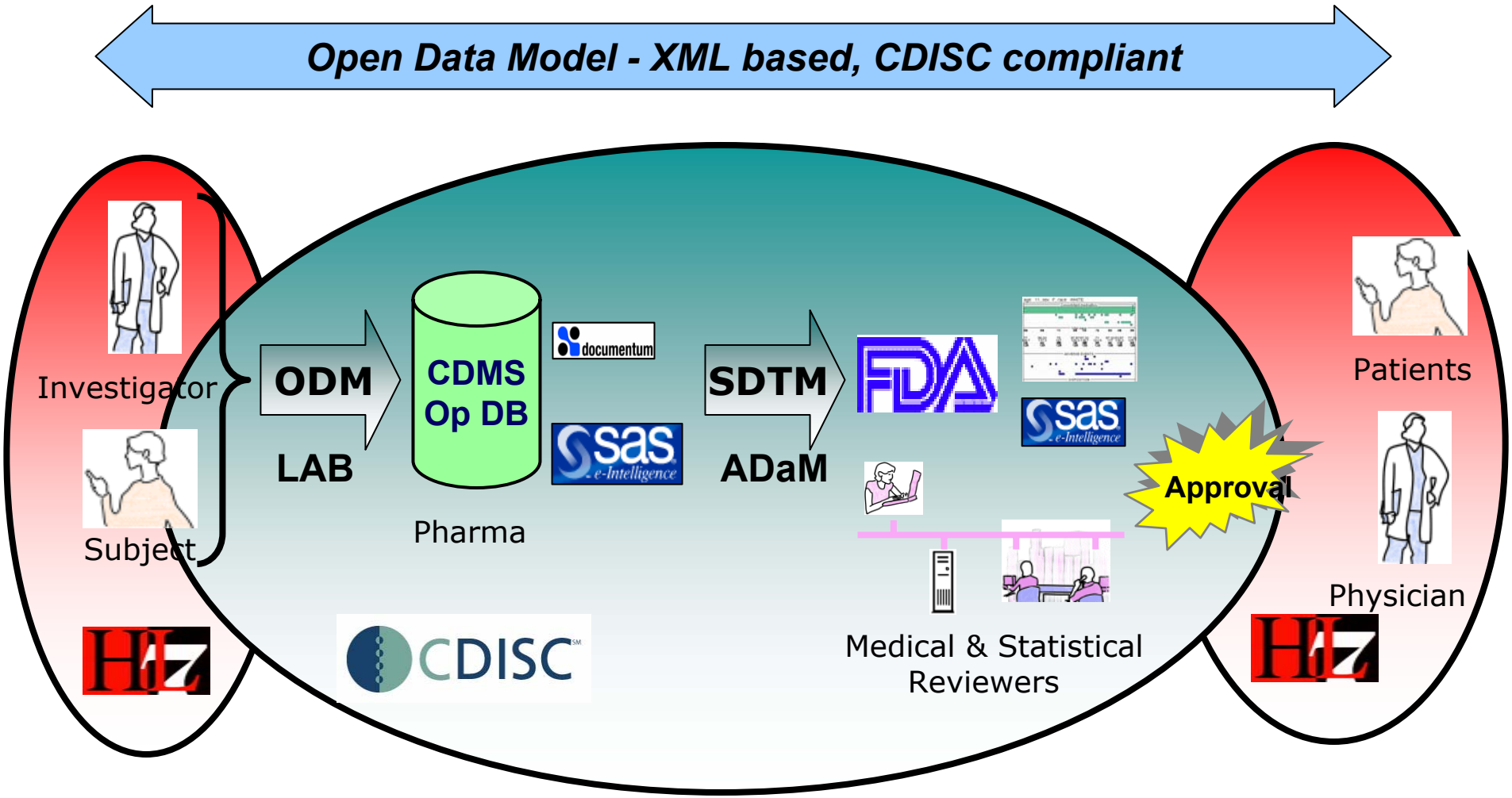
Conclusion 2

- Analysis datasets will not go away
  - How they are created and documented may
- Can we simplify/streamline unambiguous communication on analyses
  - An integrated CDISC model that can accommodate raw and derived data
  - Common tools available to create analysis data sets

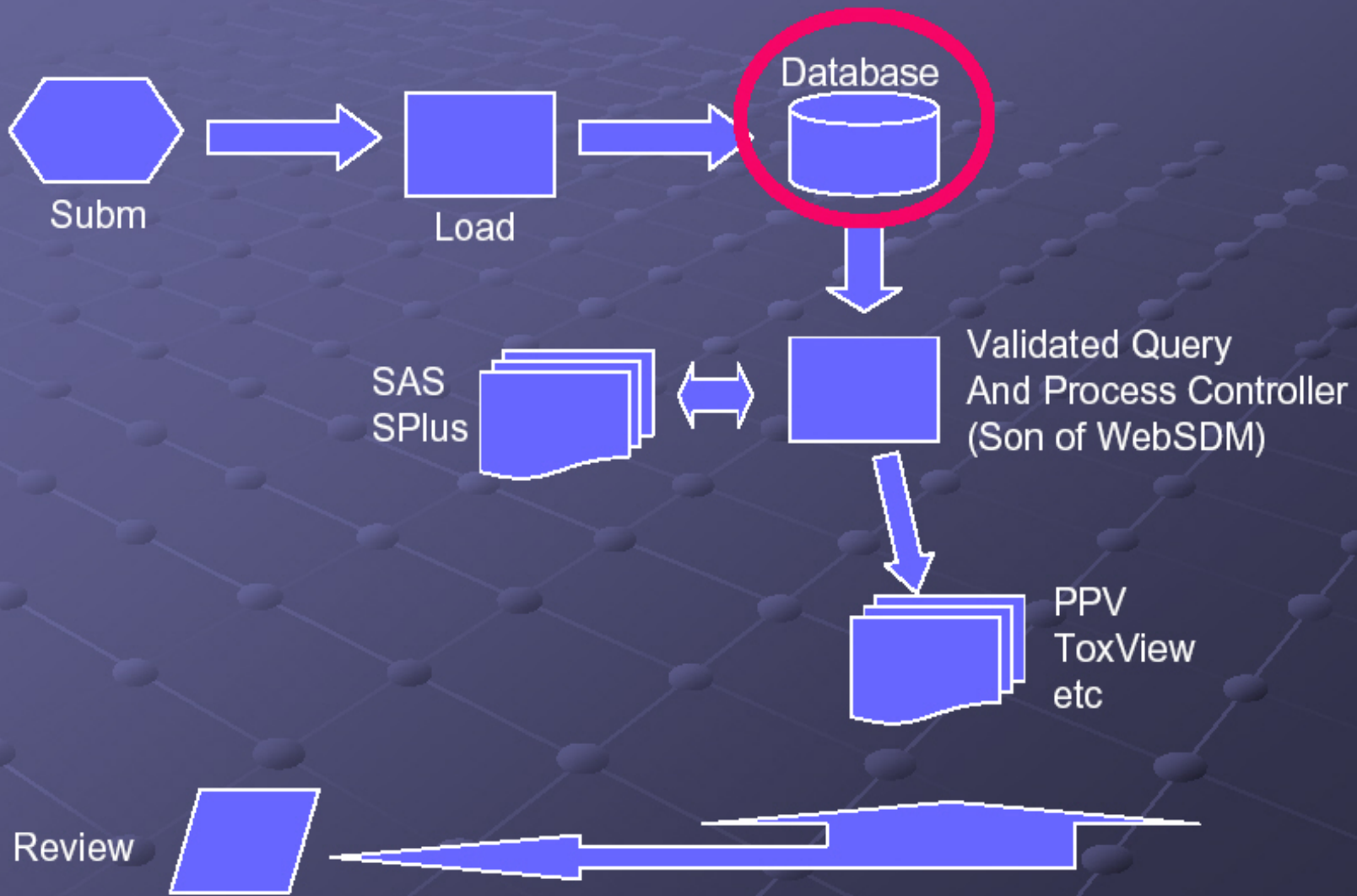
Conclusion 3

- Individual companies need to make business decisions about when and how to implement CDISC standards
  - Embed SDTM into internal systems and data flows?
  - How SDTM and ADaM operate with each other
  - Create company-specific extensions to CDISC metadata and/or vocabularies
  - Etc.

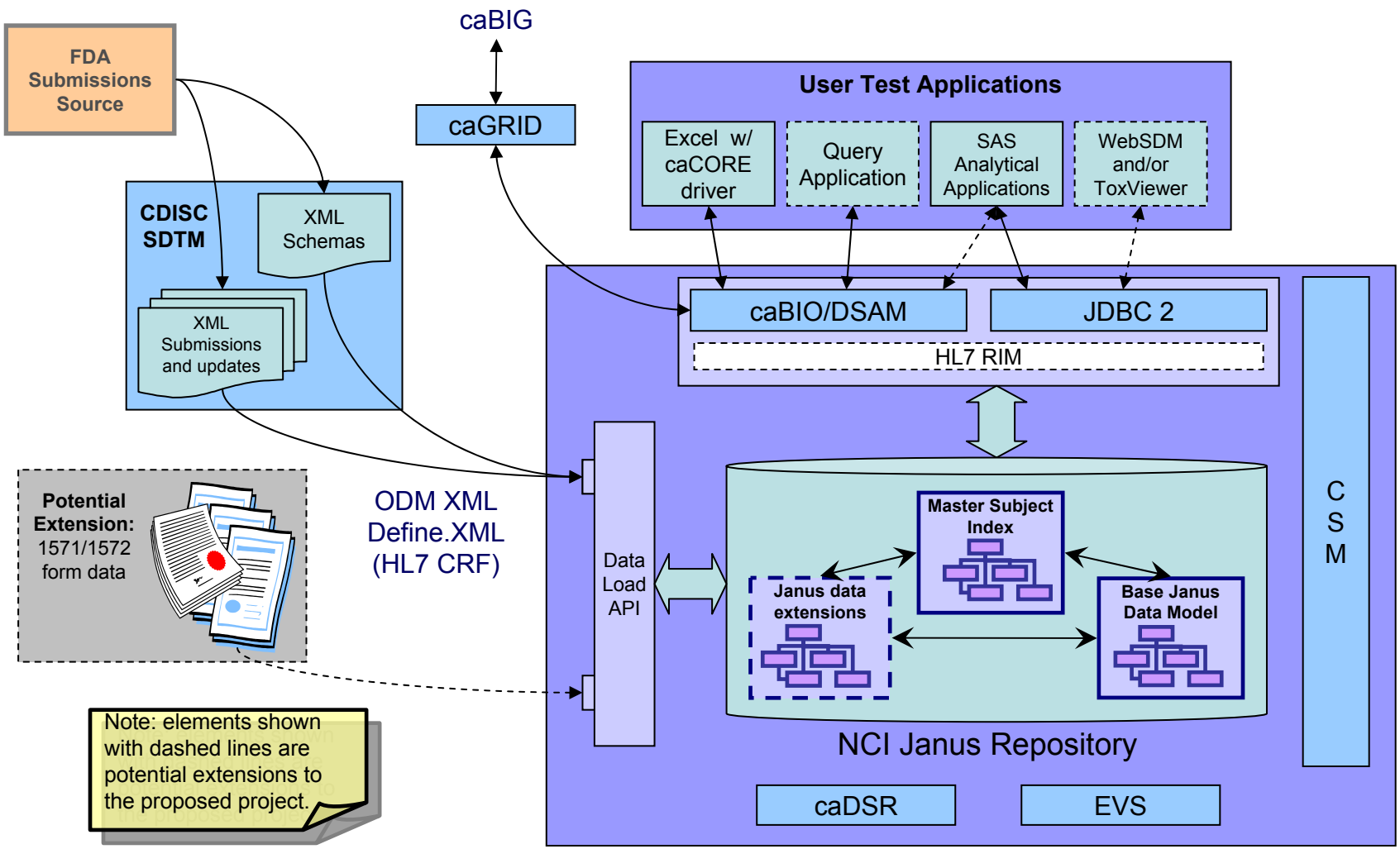
End-to-End Seamless Integration; Semantic Interoperability

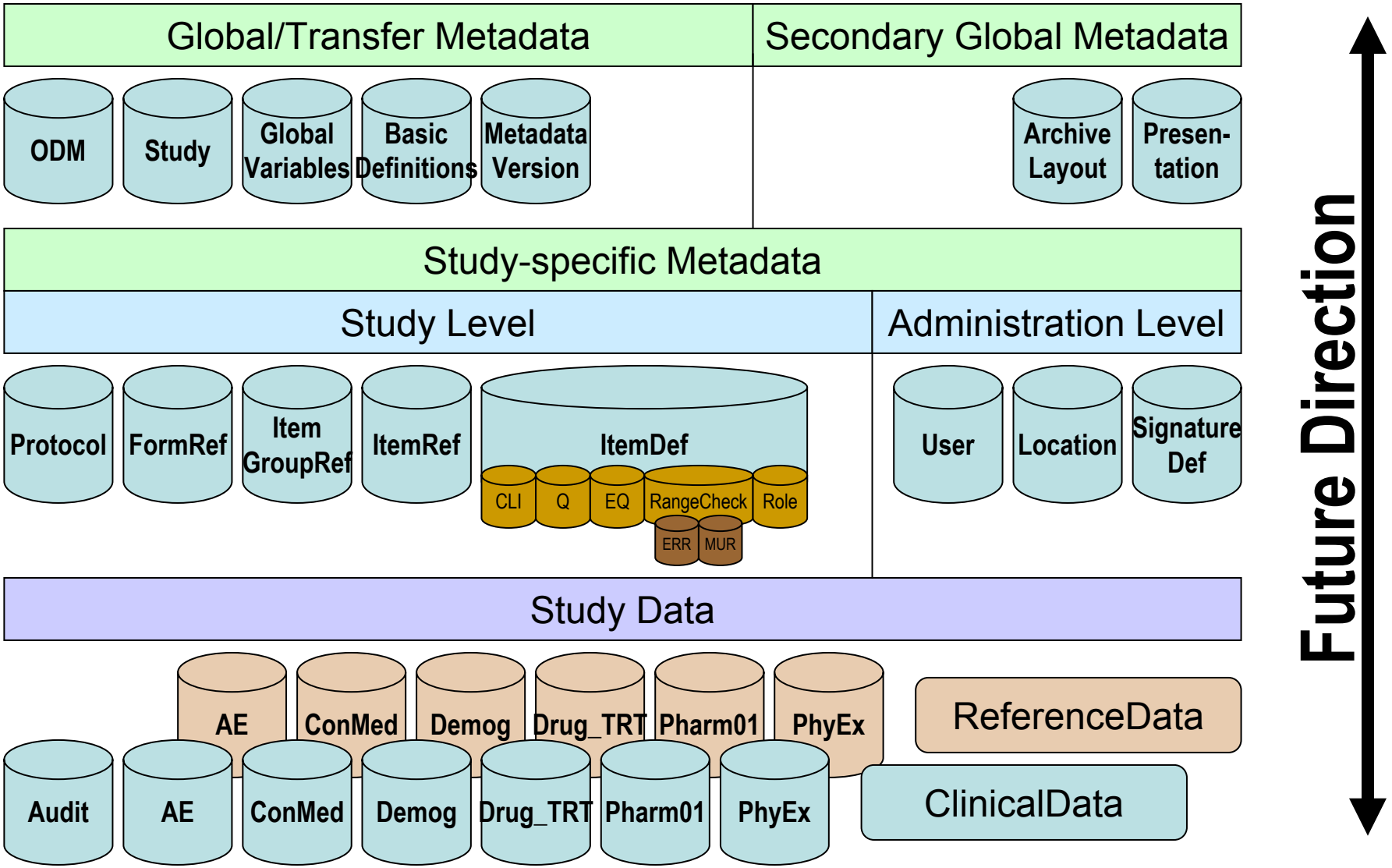


Final


Database
Subm
Load
SAS
SPlus
Validated Query
And Process Controller
(Son of WebSDM)
PPV
ToxView
etc
Review

Janus Solution Overview




Global/Transfer Metadata
Secondary Global Metadata
ODM
Study
Global Variables
Basic Definitions
Metadata Version
Archive Layout
Presen-tation
Study-specific Metadata
Study Level
Administration Level
Protocol
FormRef
Item GroupRef
ItemRef
ItemDef
CLI
Q
EQ
RangeCheck
Role
ERR
MUR
User
Location
Signature Def
Study Data
AE
ConMed
Demog
Drug_TRT
Pharm01
PhyEx
ReferenceData
Audit
AE
ConMed
Demog
Drug_TRT
Pharm01
PhyEx
ClinicalData
Future Direction

AERS II RFI Functions	Pre-marketing Risk (*Guid.) Assessment	Risk (*Guid.) Minimization Action Plan	NDA Clinical Safety Review GRP (*Guid.)	PV Practices & PE (*Guid.) Assessment
1) Safety data monitoring 2) Data Analysis capabilities 3) Data mining activities 4) Report generation 5) Automated monitoring 6) Alarm functionality 7) Early detection of AE reaction patterns 8) Enhance signal detection analysis 10) Complex query and data mining (eg – passive signals of drug-drug interaction, polytherapy, poly pharmacy)	1) Pre clinical tox data and reports 2) Clinical pharmacology and PK 3) Temporal relationships 4) Population diversity 5) Drug – drug interaction 6) Demographic relationships 7) Disease interactions and intercurrent events 8) Dietary supplements 9) Dose effects 10) Laboratory safety data 11) Coding 12) ICSRs and PSURs	1) Benefit risk management (BRM) plan 2) Tools to minimize and assess risk 3) Strategic safety program - education - controlled prescribing - prescription monitoring 4) and re-assessment of BRM updates 5) performance linked access to laboratory safety data, etc 6) Reminder systems & prompts 7) Is risk - predictable - preventable - reversible - time limited - continuous - cumulative - when risk is highest	1) Establish data quality 2) Standard data content PROFILE: deaths, SAEs, ADOs, AEs, dropouts (frequency & count) 3) Laboratory safety data - central tendency - outliers & - shifts 4) Vital signs 5) ECG(waveform) 6) Pre-clinical data and results 7) Demography & extent of exposure 8) Predictive factors - dose dependency - time dependency -demography interactions - drug and disease interactions - exploration of drug-drug interaction	1) Good reporting practices -case reports -case series assessing causality -summary descriptive analysis 2) Data Mining - product & event comb. -spontaneous reports - relative risk/odds ratios - biological effects - controlled safety findings - marketing experience - severity 3) Safety Signal Investigation 4) Signal detection rates and incidence 5) Background rates (external data sources) 6) PE studies - safety - registries - surveys - literature ***FDA Guidance**

Guidance for Industry
Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2005

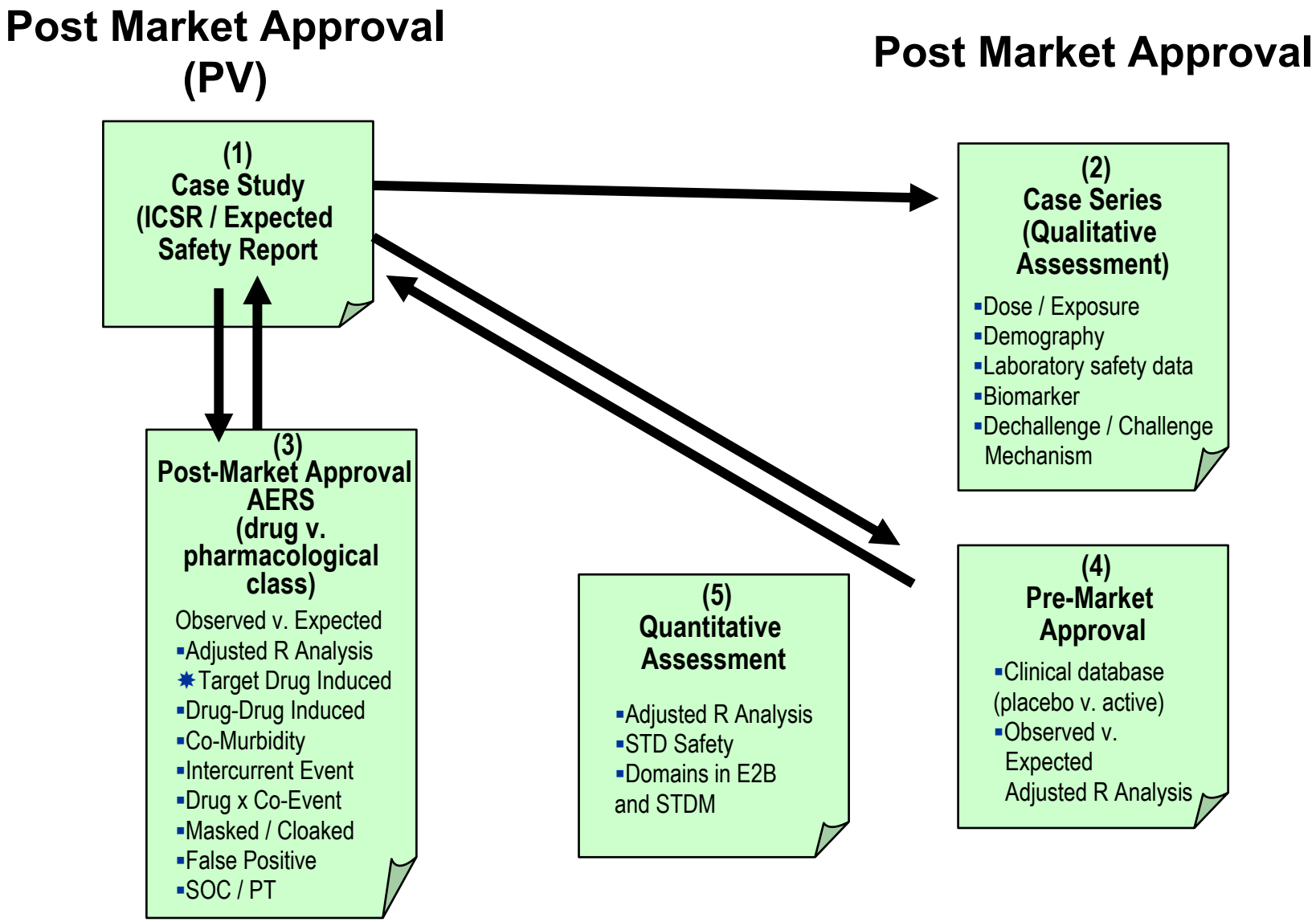
Clinical Medical

Additional copies are available from:
Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573

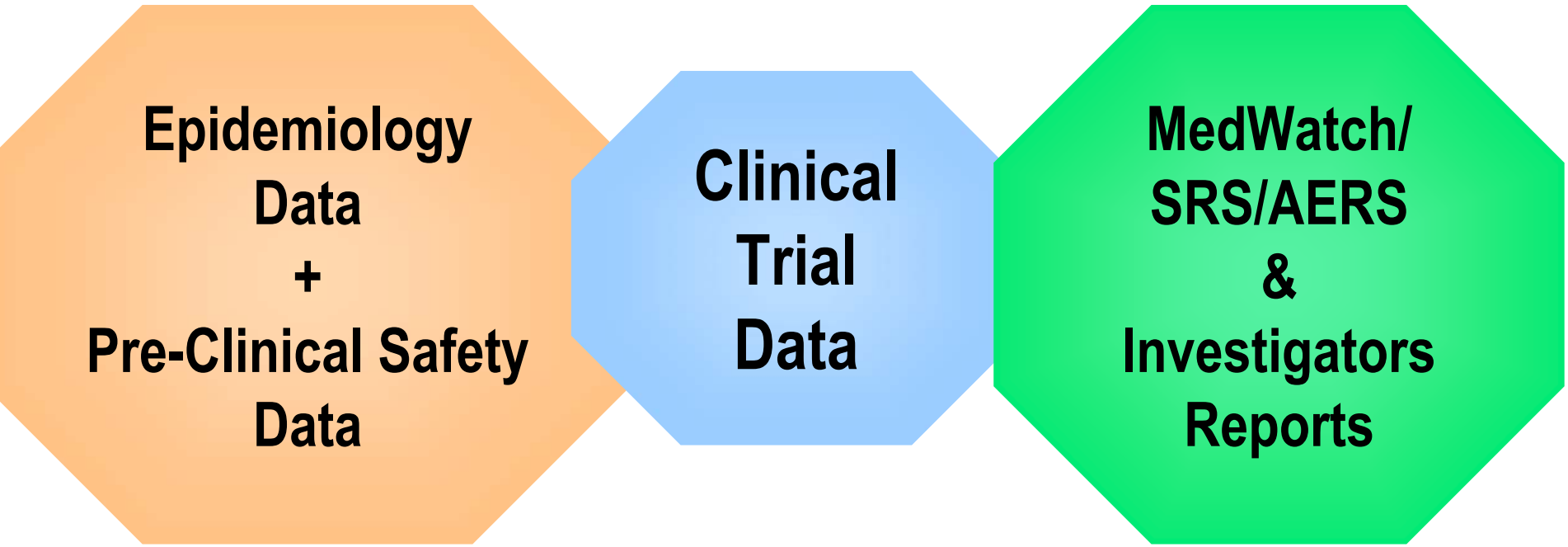
http://www.fda.gov/cder/guidance/index.htm

or

FDA Pharmacovigilance Path



Assessment of the Drug Safety



PharmacoStatistical Modeling

Predictable Drug Safety

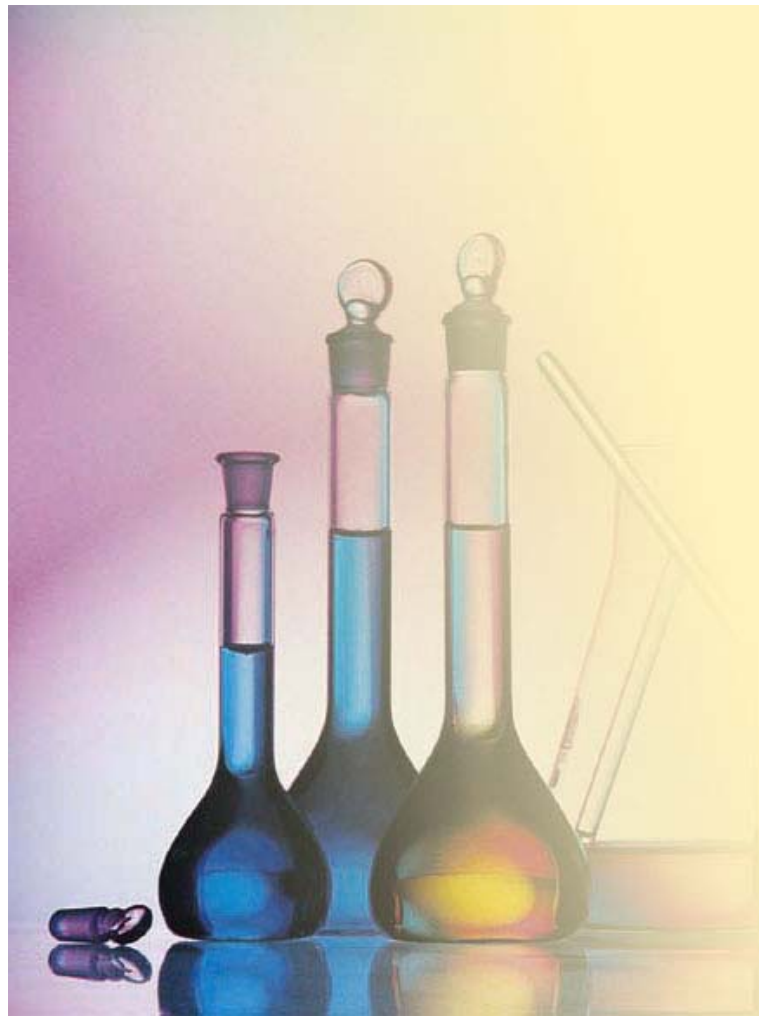
- Dose Linear/Dose Proportional
- Across the entire patient population
- Good structure/activity relationship
- Relational to clearance and metabolism

Unpredictable Drug Safety

- Idiopathic
- Idiosyncratic
- Iatrogenic

Standards and Systems

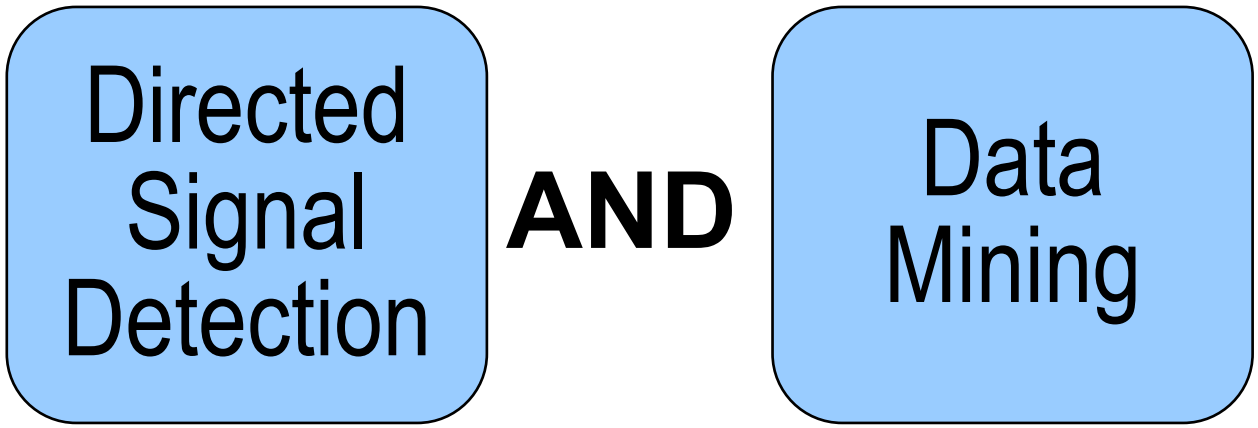
- MedDRA
- CDISC
- MedWatch
- AERS
- SNOMED



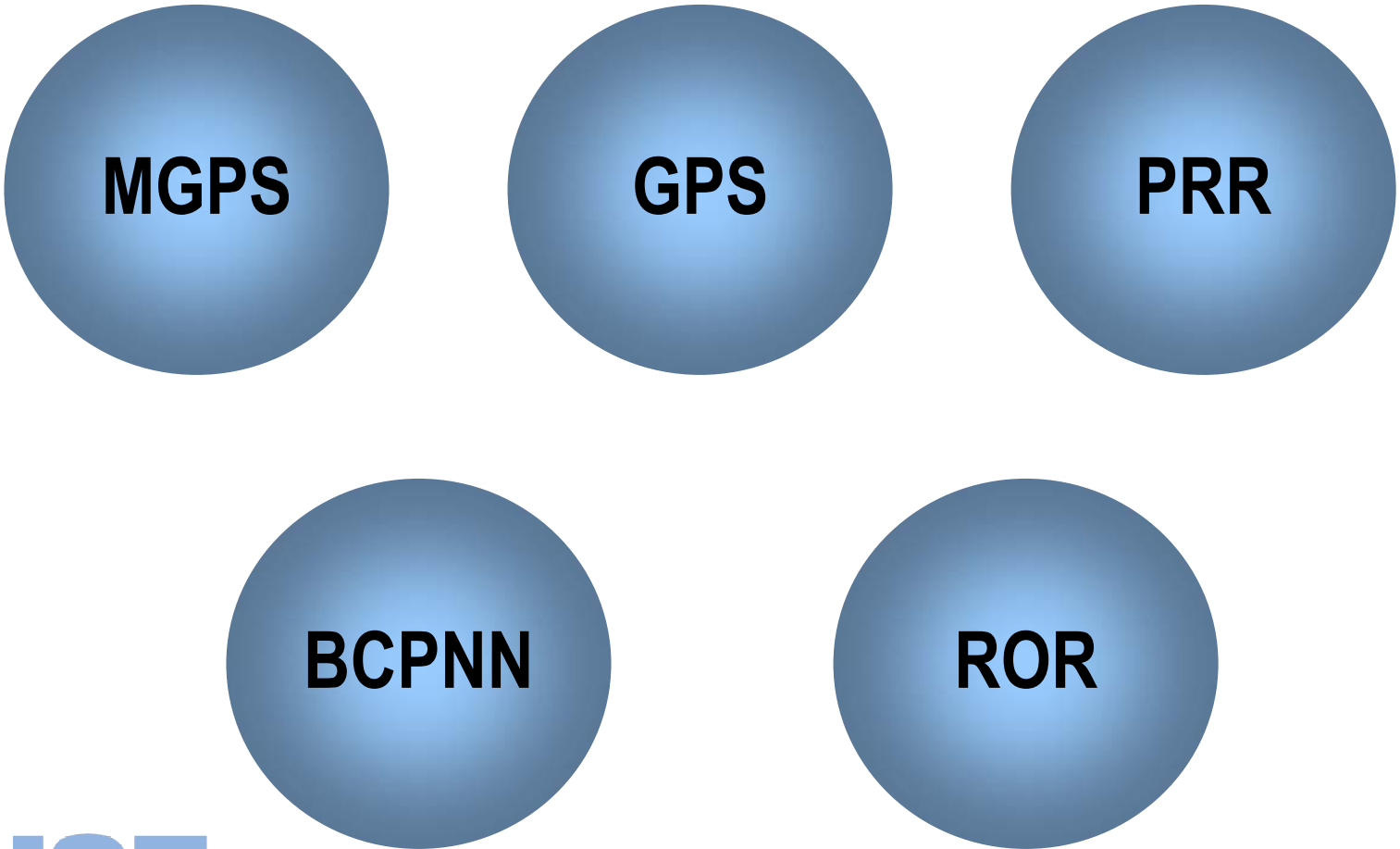
Era of Polytherapy/PolyPharmacy

- Drug/drug interaction
- Passive signals

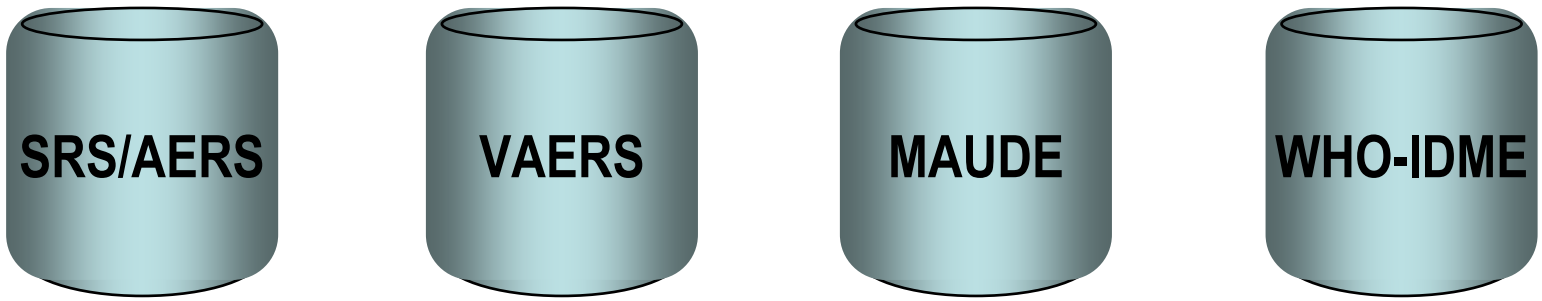
Must have open global databases populated with standard data to intuitively predict untoward effects


Directed Signal Detection
AND
Data Mining

Data Mining Analytics



SRS Databases



Sentinel Considerations of A Signal

- Target Drug Event (drug-event pair)
- Drug – Drug Interaction
- Co-Morbitity
- Intercurrent Event
- Passive Signals (Drug/Drug & Disease/Event)
- Masked/Cloaked
- False Positive

Pharmacovigilance and Drug Safety Reporting Algorithms (Content and Process)

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Gail Kongable, University of Virginia
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ABSTRACT

Using SAS® software we have built out algorithms, content and processes, for pharmacovigilance or post market approval safety reporting. The processes used CDISC data standards, metadata management and data warehousing, pre or post approval spontaneous or case series standard summary safety report (ICSR or PSUR) and data exploration and signal detection. Common and more uncommon adverse events (e.g. -hypotension, kidney dysfunction, etc and pulmonary edema, respectively) were used as selected events for demonstration of these processes. nicardipine control data from two pivotal trials (published in The Journal of Neurosurgery) and the MedWatch AERS data were the pre and post approval data source. AERS (year 2000) data for both nicardipine and comparator calcium channel blockers was explored and mined using new directed signal detection algorithms and evaluated against the controlled data. The basic concepts of WHO signal detection and the FDA Pharmacovigialnce Guidance were guiding principles in the developed algorithms.

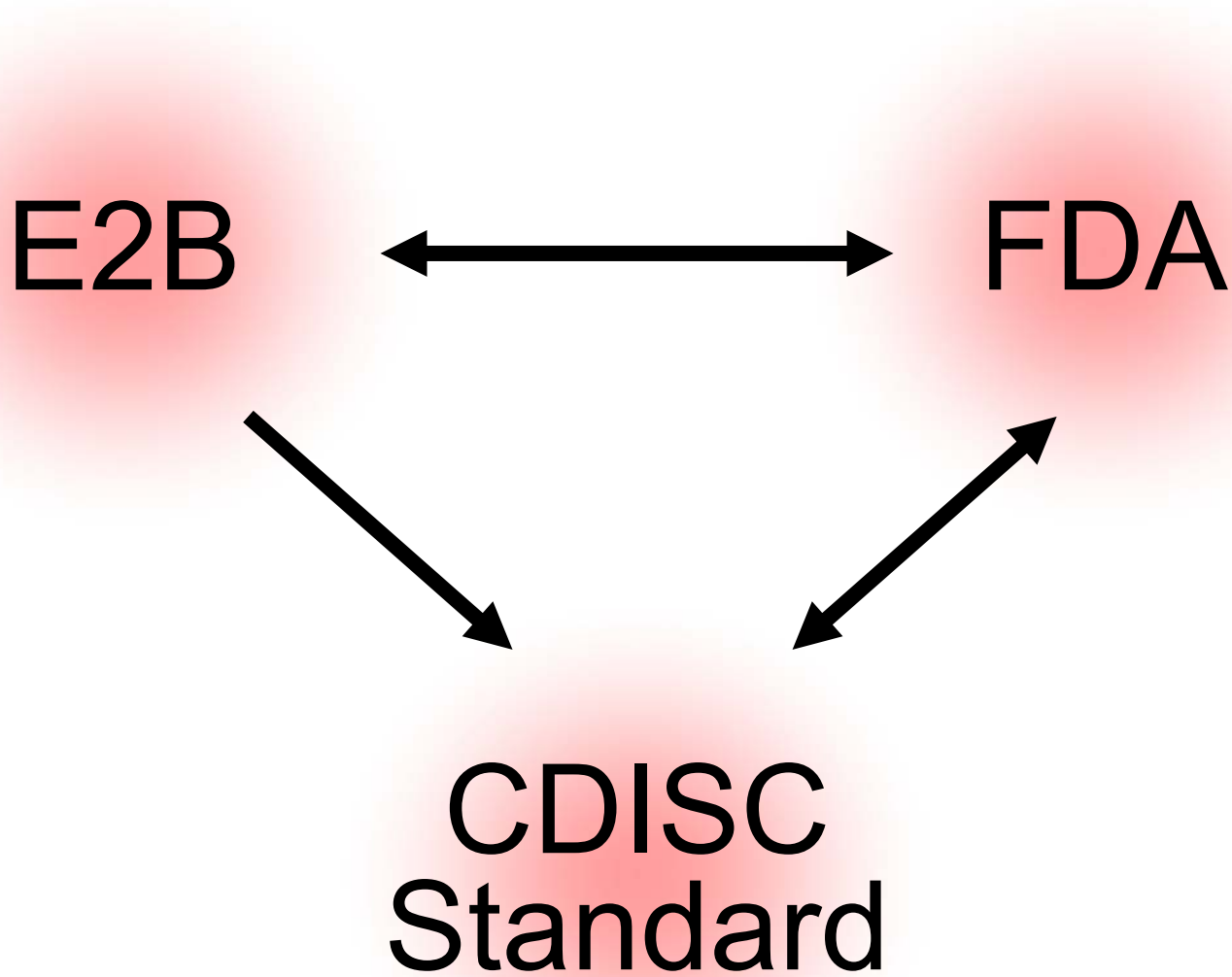
Concomitantly the use of CDISC SDTM safety domains and the ADaM requirements to unambiguously provide compliant analysis were explored. Metadata management (source code, potential imputations, flags and analysis files, etc) was also explored for standard procedures of analysis using SAS software.

INTRODUCTION

Over the past 40 years we have made numerous errors in drug safety approvals to include thalidomide, diethylstilbestrol, Xoma, Rezulin, fen/phen, Vioxx and Baycol. These drugs represent examples of compounds that contributed to untoward effects that were potentially unobserved in the controlled data and not apparent at market approval but generated a stronger signal in the post market approval period.

In 2005, primarily resulting from the Vioxx reported incidences of cardiotoxicity, the Food and Drug Administration (FDA) established two new regulatory processes for the enhanced protection of public health for FDA regulated product. The first is that the same statistical review and approval process of efficacy outcomes will now be applied to the safety data. Second, a new FDA independent Drug Safety Oversight Board (DSB) has been established to further provide an external review of safety data for marketed products. Two completely separate events, but equally important, is that the European Medicines Evaluation Agency is starting a new pharmacovigilance system in which SAS is a participant; and the FDA has initiated the process to develop a new Adverse Event Reporting System (AERS-II) to further enhance collection and analysis of drug safety data.

Adverse event (AE) reporting systems provide drug safety reviewers the opportunity to investigate a variety of drug safety questions. Once a product is marketed, there is generally a large increase in the number of patients exposed, including those with co-morbid conditions and those being treated with concomitant medical products. A thorough understanding of the safety profile of a marketed product requires analyzing


E2B
FDA
CDISC
Standard

Pharmaceutical Users Software Exchange

The Knowledge Exchange for SAS® Professionals