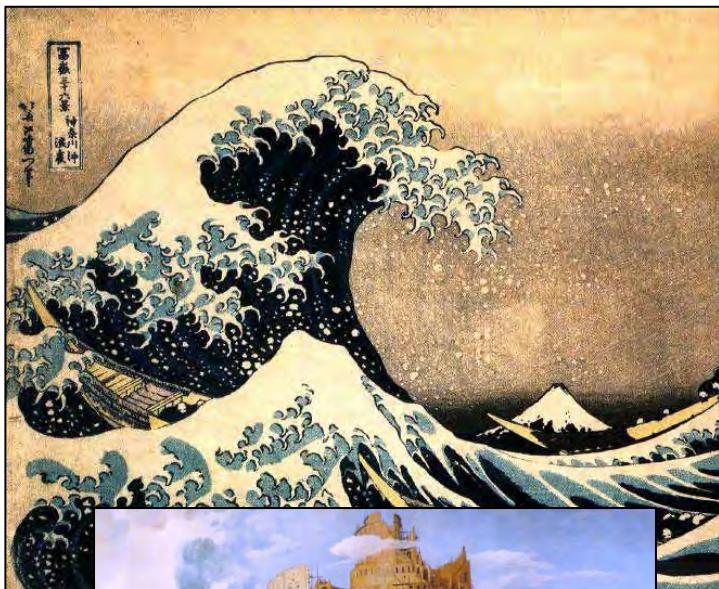


Defining the Problem...



Together, we face:

- A Biomedical Information Tsunami

- ☐ Overwhelming volume of data
- ☐ Multitude of sources

AND

- An Informatics Tower of Babel

- ☐ Each research community speaks its own scientific “dialect”
- ☐ Integration critical to achieve promise of molecular medicine



The Challenge

- The FDA receives **massive** amounts of study data
 - in extremely disparate formats
 - using a variety of proprietary standards
 - mostly in paper or pdf formats
- This makes it extremely difficult, if not impossible, to do cross-study and application reviews

FDA

CBER

CDRH

CDER

CFSAN

CVM

NCTR

ORA

CTP

Challenges/Mandate	Means to Address	Anticipated Impact
Health Crisis (Melamine, Vioxx, Peanut Butter)	<ul style="list-style-type: none"> ■ Automated information mgmt (LIMS, Janus) ■ Safety signal detection tools ■ Best practice → Tools 	<ul style="list-style-type: none"> ■ ↑ Speed, Quality ■ ↑ Protect public health ■ ↑ Confidence <ul style="list-style-type: none"> □ Inside □ Outside
Regulatory Decisions	<ul style="list-style-type: none"> ■ Janus implementation ■ Best practice → Tools <ul style="list-style-type: none"> □ Efficacy-Safety □ Risk-Benefit 	<ul style="list-style-type: none"> ■ ↑ Productivity-Quality ■ ↓ Time-resource ■ Move resource to other ↑ priority topics
Regulatory Science Research <ul style="list-style-type: none"> ■ Biomarker qualification ■ Approval endpoints ■ Clinical trial design ■ Benefit-Risk patient communication tools 	<ul style="list-style-type: none"> ■ Janus implementation ■ Targeted exploratory analysis ■ Modeling & simulation driven trial design ■ New tool qualification 	<ul style="list-style-type: none"> ■ Critical Path success ■ ↑ Development efficiency-productivity ■ ↑ Communication clarity to patients

Scientific Computing Support Services including Collaboration

Computing Platform (Large storage, Fast network, Fast Processors)

The screenshot displays the SAS JMP software interface with several data tables open. The tables and their columns are as follows:

- ADVERSE**: UNIQ_SUB, AEPTX, STARTDT
- NSMED**: UNIQ_SUB, MEDX, STARTDT, STOPDT
- MEDHIST**: UNIQ_SUB, CPENM, CONDTN, PATIENT, DRUGID, STUDYID, STDYSITE, PROTID
- LABTEST2**: STUDYID, SITE, UNIQ_SUB, DCM, LPARM, LVALN, PATIENT, DRUG
- LABTEST3**: STUDYID, SITE, UNIQ_SUB, DCM, LPARM, LVALN, PATIENT, DRUG
- LABTEST1**: STUDYID, SITE, UNIQ_SUB, DCM, LPARM, LVALN, PATIENT, DRUG
- DEMOWIDE**: UNIQ_SUB, SEX, ETHNIC, AGE, PATIENT, DRUGID, TPNAME

Arrows indicate the following data relationships:

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- Concomitant Meds data here**: Points to the **NSMED** table.
- Prior Medical History data here**: Points to the **MEDHIST** table.
- Lab data here**: Points to the **LABTEST2** table.
- Demographic data here**: Points to the **DEMOWIDE** table.

The screenshot displays the SAS JMP software interface with several data tables open. The tables and their columns are as follows:

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End Result of 5 Weeks of Data Manipulation – 50 pages taped together

Demographic
data here from
DEM dataset

Adverse Event
data here from
AE dataset

Past Medical
History data
here from
MEDH dataset

Laboratory
data here from
LAB dataset

Concomitant
Meds data here
from Conmed
dataset

The image shows a large, multi-page document, likely a medical chart or a data compilation, with various sections highlighted in yellow and red. The document is annotated with white arrows and brackets pointing to specific sections, which are labeled in blue boxes. The sections include:

- Demographic data here from DEM dataset
- Adverse Event data here from AE dataset
- Past Medical History data here from MEDH dataset
- Laboratory data here from LAB dataset
- Concomitant Meds data here from Conmed dataset

The document appears to be a complex medical record or a data compilation, with various sections highlighted in yellow and red. The annotations and arrows indicate the source of the data for each section.

We Need Standardization: The need to speak a common “Language”

Study #2 – dm9.xpt

ID	GENDER
A1	Male
A2	Male
A3	Female
A4	Female
A5	Male

Study #1 – demog.xpt

SUBJID	SEX
0001	M
0002	F
0003	F
0004	M
0005	F

Study #3 – axd222.xpt

USUBID	SEX
00011	0
00012	1
00013	1
00014	0
00015	1

Study #4 – dm9ph.xpt

PTID	GENDER
0001	1
0002	1
0003	2
0004	2
0005	1



FDA Science and Mission at Risk

- “FDA must be able to put an IT infrastructure in place so that it can regulate these fast-developing “new science” fields, such as panomics, wireless health care devices, medical imaging and nanotechnology.” page 55

- “The FDA must invest in the development of large-scale, sustainable data sharing infrastructures that can support clinical trials and pharmacovigilance...” page K-11

Recommendation 4



The Vision

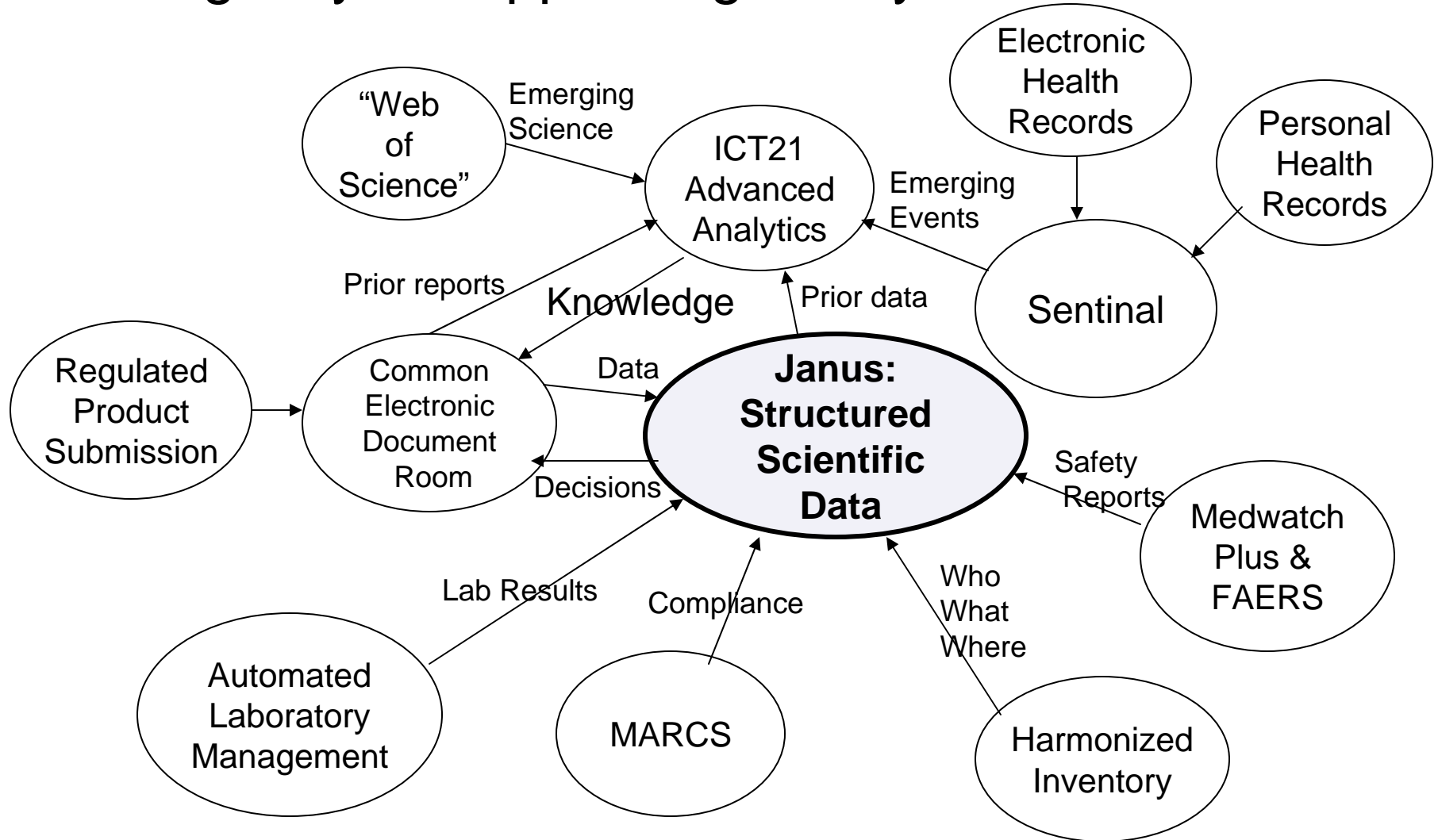
- FDA has been working towards a standardized approach to acquire, receive, and analyze study data
- Standardization of study data is vital to integrate pre-marketing study data and post-marketing safety data to improve public health and patient safety



Janus: Central to the Vision

- Janus is an enterprise initiative to improve FDA's management of structured scientific data about regulated products in support of regulatory decision-making
- Establish data architecture and standards to facilitate integration of structured scientific data
- Create structured scientific data repositories that support the acquisition, validation, integration, and extraction of data from the increasingly large and complex datasets received by the Agency
- Make use of enhanced analytical tools and techniques that enable reviewers to search, model, and analyze data to conduct better safety and efficacy analyses.

Janus will provide a hub for integrating data within the Agency to support regulatory decisions



Janus supports:

■ FDA Strategic Action Plan

- Objective 3.2: Improve the medical product review process to increase the predictability and transparency of decisions using the best available science
- Objective 2.2: Improve information systems for problem detection...
- Objective 4.3: Respond more quickly and effectively to emerging safety problems, through better information...

■ Strategic Activities

- M1.1 Science to improve medical product safety and development: Use new science and analysis to improve the safety of medical products. In some cases, new science creates opportunities to leverage advances from one product area to promote safety in a different area.
- M1.2 Data analysis Tools to Identify Safety Issues: Develop and implement quantitative decision-making tools to assess the safety and effectiveness of drugs, biologics, and devices throughout their lifecycle.

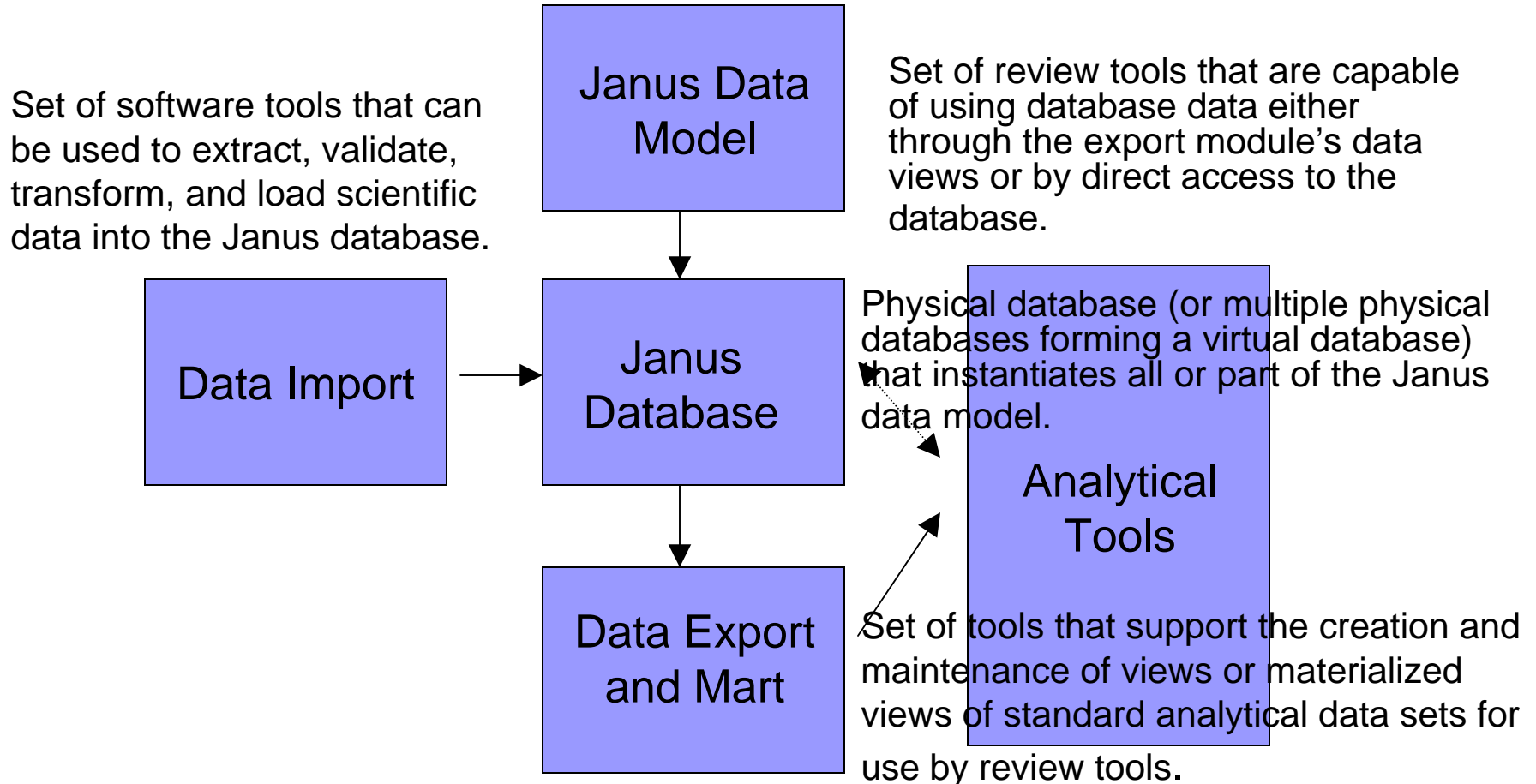


Data Standards are Fundamental to the Janus Vision

- Data standards can be divided into three broad categories:
 - Exchange standards
 - Analysis/data presentation standards
 - Terminology standards

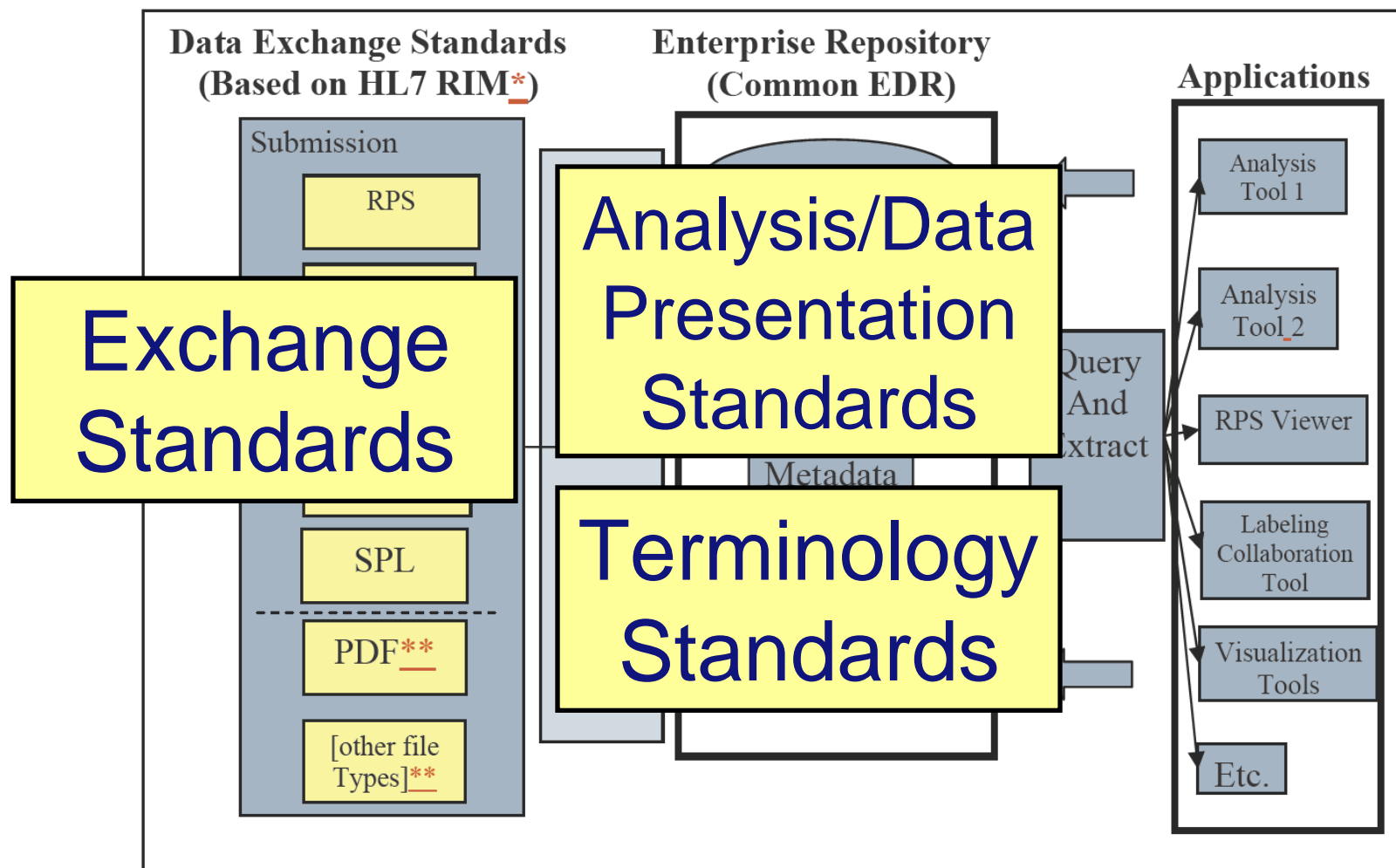
Janus Functional Components

Comprehensive logical data model for the scientific data



FDA's Conceptual Target Data Flow for Regulated Product Information

PDUFA IT Plan 2008



*The following depicts a conceptual framework for Janus. The final implementation may change as this conceptual framework is further vetted and refined within FDA As stated in the PDUFA IT Plan 2008

Janus Goals

- Institute a regulated product information data warehouse
 - Electronically acquire, validate, integrate, and extract standardized, structured scientific data
 - Synthesize information across product applications, across classes of products, and across product lifecycle
 - For example, new nephrotoxicity biomarker approved in one area could be used for a different product area
 - Ingredient found unsafe or component found defective may be found in other product areas (e.g., combination products, kits, inactive ingredients)
- Transform the regulatory review and decision process
 - Transition to interactive, electronic reviews
 - Support quantitative decision-making to assess safety and effectiveness throughout a product's life cycle (e.g., data mining to detect possible safety signal)
 - Leverage analysis tools across product areas improving consistency and efficiency
 - Provide springboard to environment of the future that enables
 - Enriched scientific interpretations that integrate latest domain knowledge
 - Advanced analytics (e.g., virtual clinical trials, disease models)

Here comes ARRA CER and Janus

■ HHS Programs Funded by the Recovery Act*

- HHS funded projects in new areas, including:
 - Health information technology,
 - Healthcare-acquired infections,
 - Community-based prevention and wellness programs to fight obesity and tobacco use,
 - Patient-centered health research.

■ Provides funding opportunity for FDA to develop infrastructure, capabilities and tools

*Excerpted from webcast presentation 5/2010 to regional speakers and OPDIV public affairs staff in an effort to inform the public about the results of the Recovery Act.



Patient-Centered Health Research

- The Recovery Act provided \$1.1 billion for patient-centered health research, also known as comparative effectiveness research.
 - \$400 million to NIH
 - \$400 million to the Office of the Secretary
 - \$300 million to the Agency for Healthcare Research and Quality (AHRQ).
- The goal of this research is to promote high quality care by providing scientific information that helps clinicians and patients determine the best care that suits their needs.

CE is NOT

- Solely about effectiveness
- Cost-effectiveness
- Intended as regulatory or directive
- Restricted to randomized controlled trials
- Exclusionary of clinical judgment or the circumstances of the individual patient
- Aimed at limiting or restricting health services

Comparative Effectiveness IS...

- Focused on real-world circumstances and decisions
- Intended to help make decisions more consistent, transparent and rational
- Useful in identifying gaps and uncertainties
- Fruitful ground for statistical involvement
 - Meta-analyses
 - Analyses of retrospective or observational data
 - Design/analysis of pragmatic, adaptive trials
 - Consideration of heterogeneity in treatment effects

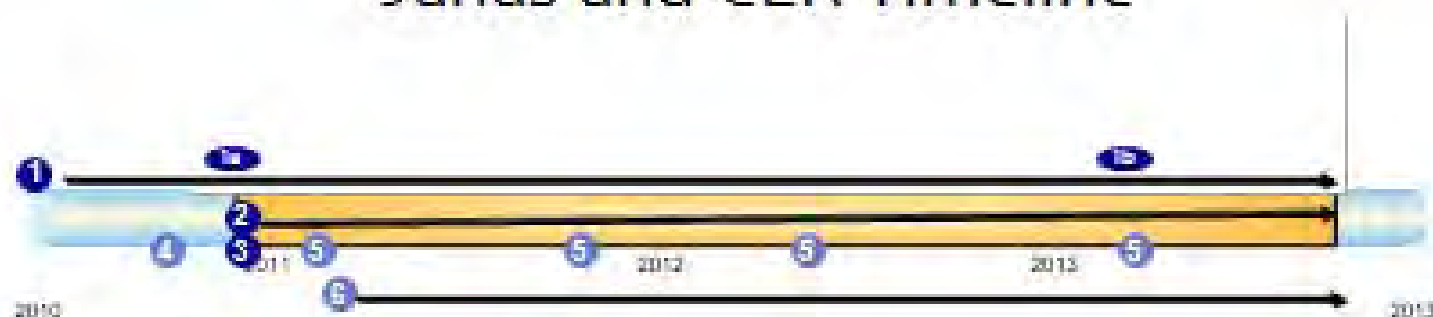


ARRA CER and FDA

- Goal is to build FDA CER clinical data and standards infrastructure, tools, skills, and capacity
 - Harness the capacity of large study data repositories to answer questions about care for priority interventions through infrastructure development
 - Enable pilots of comparative effectiveness and other complex research and evaluation using the agency's vast, but untapped, stores of patient safety and clinical efficacy data.
 - Support building needed expertise across the Agency, as well as FDA interactions with NIH, AHRQ and sponsors, as they design and evaluate CER, including needed guidance.
 - Evaluate policy approaches
 - Inform and improve medical and regulatory decision making and improve patient outcomes

Activity	FDA ARRA CER Scope Description
Create Janus Repository	<p>Update the Janus physical database design</p> <ul style="list-style-type: none"> Support the software development life-cycle phases of requirements and design analysis, development/enhancement, testing, training, and implementation
Convert Legacy Data	<p>Convert legacy data from clinical studies relevant to specific questions of comparative efficacy to a standard format harmonizing terminologies as needed and storing the standardized data in the data repository.</p>
Implement Modern Analytical Tools	<p>Support comparative effectiveness research using the clinical study data repository.</p> <p>Provide integration and implementation support for selected tools.</p>
PACES	<p>Facilitate comparative analysis pilots to conduct advanced and robust analysis for detecting clinical trends to understand which interventions are most effective for which patients under specific circumstances.</p> <ul style="list-style-type: none"> Establish Partnership in Applied Comparative Effectiveness Science for Medical Products (PACES). Host public scientific workshops to discuss analytic tools, methods, and best practices for analyzing data across multiple clinical studies

Janus and CER Timeline



1 Create Janus Repository for Clinical Data

1a Janus Repository Development

1b Janus Repository Deployment to FDA reviewers


2 Convert Legacy Data

3 Analytic Tools to support CER

4 PACES contract award

5 Workshops

6 Conduct comparative analysis and clinical trial designs



HHS Program Accomplishments for Recovery Act*

□ Health Information Technology.

- To prepare for a new age in health care, HHS has awarded a series of grants to support and accelerate the adoption and “meaningful use” of health IT by health care providers. These include grants totaling \$643 million for health IT Regional Extension Centers; \$548 million for State Health Information Exchanges; \$84 million to train a health IT workforce and \$60 million to support advanced health IT research and development.
- HHS will be providing \$21 billion in incentives to physicians and hospitals, beginning in FY 2011 and continuing through FY 2019, to promote the widespread use of electronic health records.

*Excerpted from webcast presentation 5/2010 to regional speakers and OPDIV public affairs staff in an effort to inform the public about the results of the Recovery Act.



FDA and HIT

- FDA must align and leverage widespread use of electronic health records to effectively fulfill its mission
- FDA is aligning to “meaningful use” initiatives by working with HL7 Standard Development Organization for the exchange of data with FDA
- HHS recently published an Interim Final Rule for Health Information Technology that included an Initial Set of Standards, Implementation Specifications, and Certification Criteria for Electronic Health Record Technology.
 - Four HL7 standards are listed in the HHS' Interim Final Rule.
 - Clinical Document Architecture
 - Continuity of Care Document
 - Messaging Standard Version 2.5.1
 - Messaging Standard Version 2.3.1

Risks: Success Requires Coordination on Several Key Dimensions

Dimension	Current Status	Next Step / Challenges
Data Standards	HL7 RIM and data exchange standards, CDISC, BRIDG	Goal is interoperability with Health IT for personalized medicine and for clinical studies
Policy / Statutory	Need standard electronic data submission- policy or rule	Single regulation for electronic submission per standard with guidance providing standard
Business Process	Scientific Review Processes, Review Templates	Efficiency from standardized data and possible new advanced analytic tools
IT	CRADAs vs Public/Private vs Agency development	Iterative collaborative development needed to evolve data standards;
Financial	“Tin Cup” with CRADAs, NCI’s caBIG, HRSA, Critical Path Program	Dedicated funding and staffing

Janus – Risks

Risk	Response
Data standards have evolved and will continue to evolve	<ul style="list-style-type: none">■ Use a flexible data model (e.g., HL7 RIM)■ Recognize when a standard is close enough to move forward with especially relative to current state
Complex science and complex data supporting the science	<ul style="list-style-type: none">■ Use iterative, collaborative development to evolve solutions
Umbrella of Janus impedes rather than expedites	<ul style="list-style-type: none">■ Recognize and retain the current scientists who are championing a knowledge domain and make it their day job.■ Enable project teams by ensuring adequate resources and by removing stumbling blocks
Reinventing the wheel	<ul style="list-style-type: none">■ Learn from and leverage work of leaders (eg caBIG, VA)■ Actively participate in Standards Development Organization work groups
Progress with external organizations too slow and too cumbersome	<ul style="list-style-type: none">■ Invest in proof of concept prototypes to demonstrate potential and to energize

Janus Long Term Benefits:

Will require major investment over many years

■ To Agency...

- Credibility... improved scientific support for regulatory decisions by
 - ensuring access to all available, relevant data (e.g., all clinical studies with Vioxx) and
 - enhancing analytical, visualization, and other computational tools and techniques
- Efficiency... reuse data and tools

■ To Public...

- Improve product safety
 - Proactive surveillance where data standards move toward interoperability with wide-variety of internal (e.g., marketing application data, adverse event reports) and external (e.g., electronic health record) data sources
 - Correlate animal toxicity studies with the human experience
- Faster, better informed regulatory decisions

How do we reach the vision?

■ Incrementally

- phases can run in parallel or sequentially based on available resources and priorities (CER, regulatory research and reviews)
- Iterative and incremental development and progress
- Initial focus on clinical data- demonstrate success **

■ Modular

- Develop reusable modular components
- Reuse previous components as much as possible

■ Data Standards Strategy

- Aligns with HHS for interoperability
- Establish regulatory mandate for standardized data

■ Potential other options on model

- PCAST report and meta data annotation-discuss

Points for discussion

- Science and policy intersection
 - Impact on new methods and regulatory review
 - Timing
 - Ability to re-analyze data
- Enabling “personalized medicine”
 - Multi-study comparisons
 - Trial design
- Flexibility- entertain approach of meta data annotation within Janus construct
 - Who are the players??



E mail contact: Vicki.Seyfert-Margolis@fda.hhs.gov

THANK YOU.