

Innovation Through Collaboration: Why the CSS Working Groups are Important to the FDA

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Director, FDA/CDER/OTS/OB/DBIII

2014 Computational Science Symposium

March 16th – 18th, 2014

Silver Spring Civic Center, Silver Spring, MD

Our Grand Experiment in Collaboration:
“Opportunities Disguised as Problems” in this
Fast-Paced, Complex
Scientific/Regulatory/Technical
Decision-Making World

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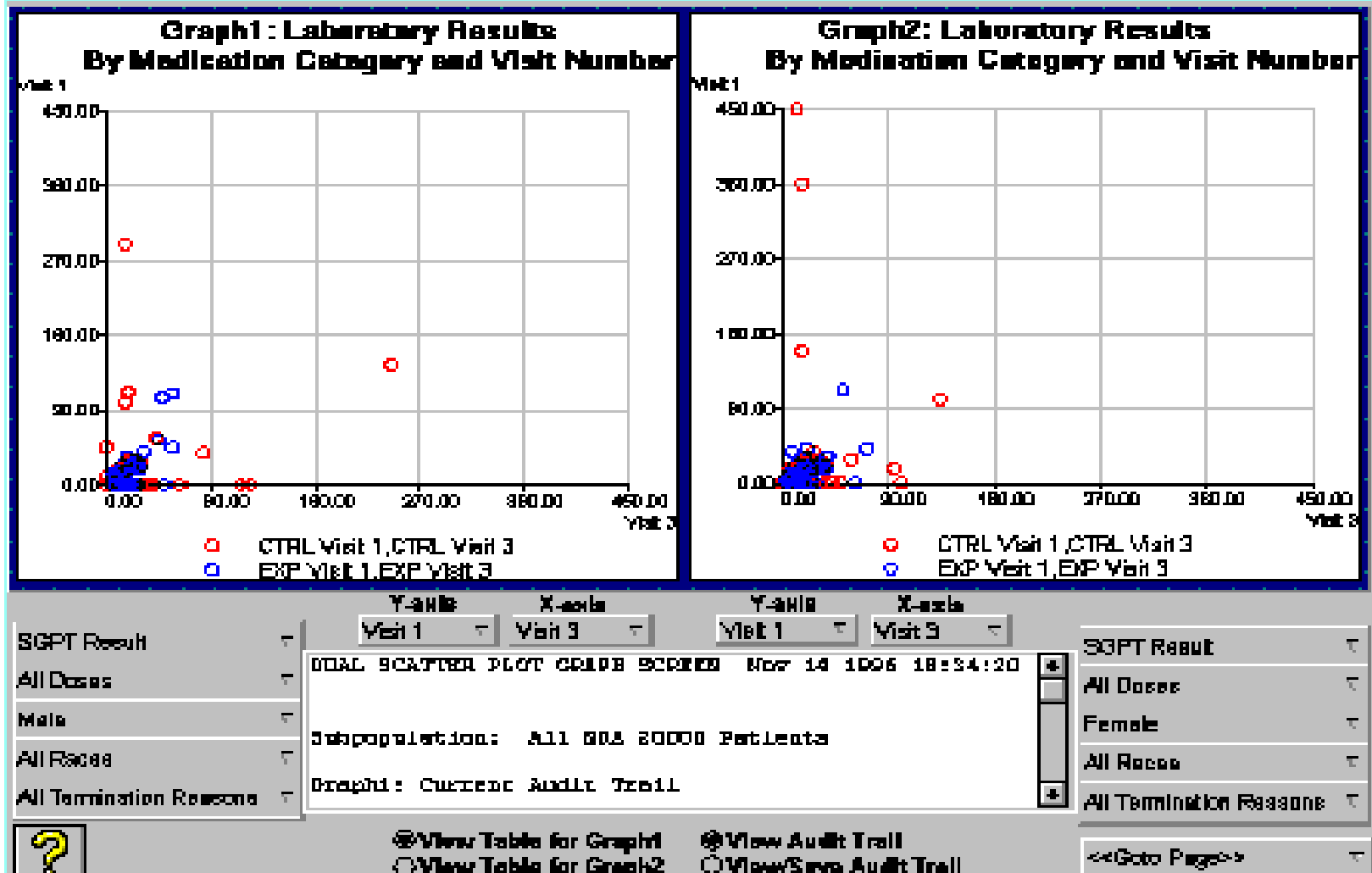
Silver Spring Civic Center, Silver Spring, MD

Disclaimer

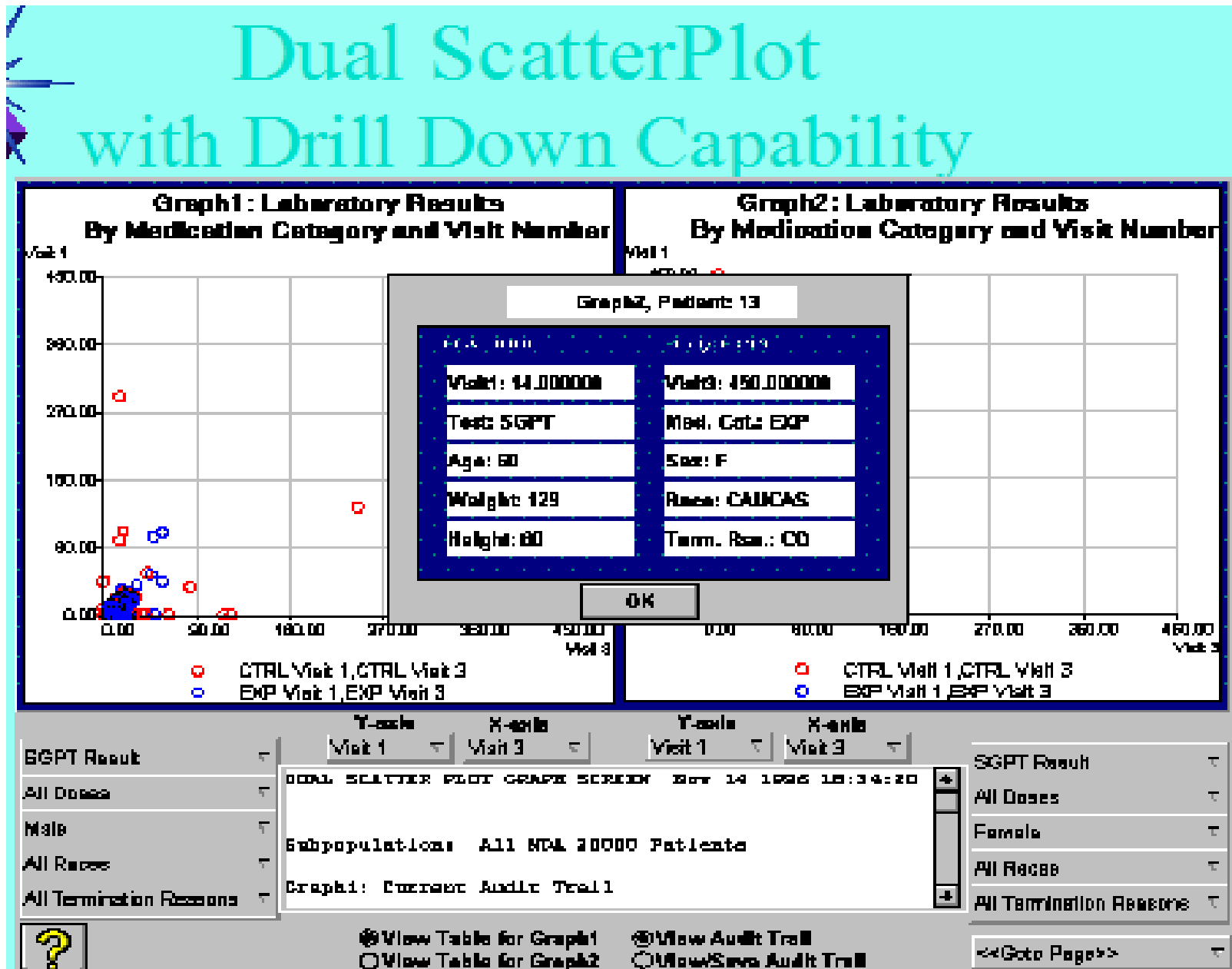
- This presentation reflects the views of the authors and should not be construed to represent FDA's views or policies

Computer-Assisted Review of Safety (CARS)

Dual ScatterPlot Graph



Computer-Assisted Review of Safety (CARS)



Outline

- Mission/Vision
- The Landscape
 - Motivation
 - PDUFA/FDASIA
 - 21st Century Review
 - CDER says -- “Show Me the Data”
 - Our “Computational Science”: Is Something Missing?
 - How Are We Going To “Get There” – CDER/OTS and “Pre-competitive” Collaboration
 - Consortia and Institutional Collaboration
 - Computational Science Symposium (CSS)
- The Experiment
 - Some Challenges
 - Progress
- Bottom Line

Mission / Vision

- FDA's mission is to protect and advance public health **by helping to speed innovations** that provide our nation with safe and effective medical products and that keep our food safe.
- The Agency achieves this by applying the **latest technology and science-based standards to the regulatory challenges** presented by drugs, biologics (vaccines, blood products, cell and gene therapy products, and tissues), medical devices, food additives, and, since 2009, tobacco Innovation

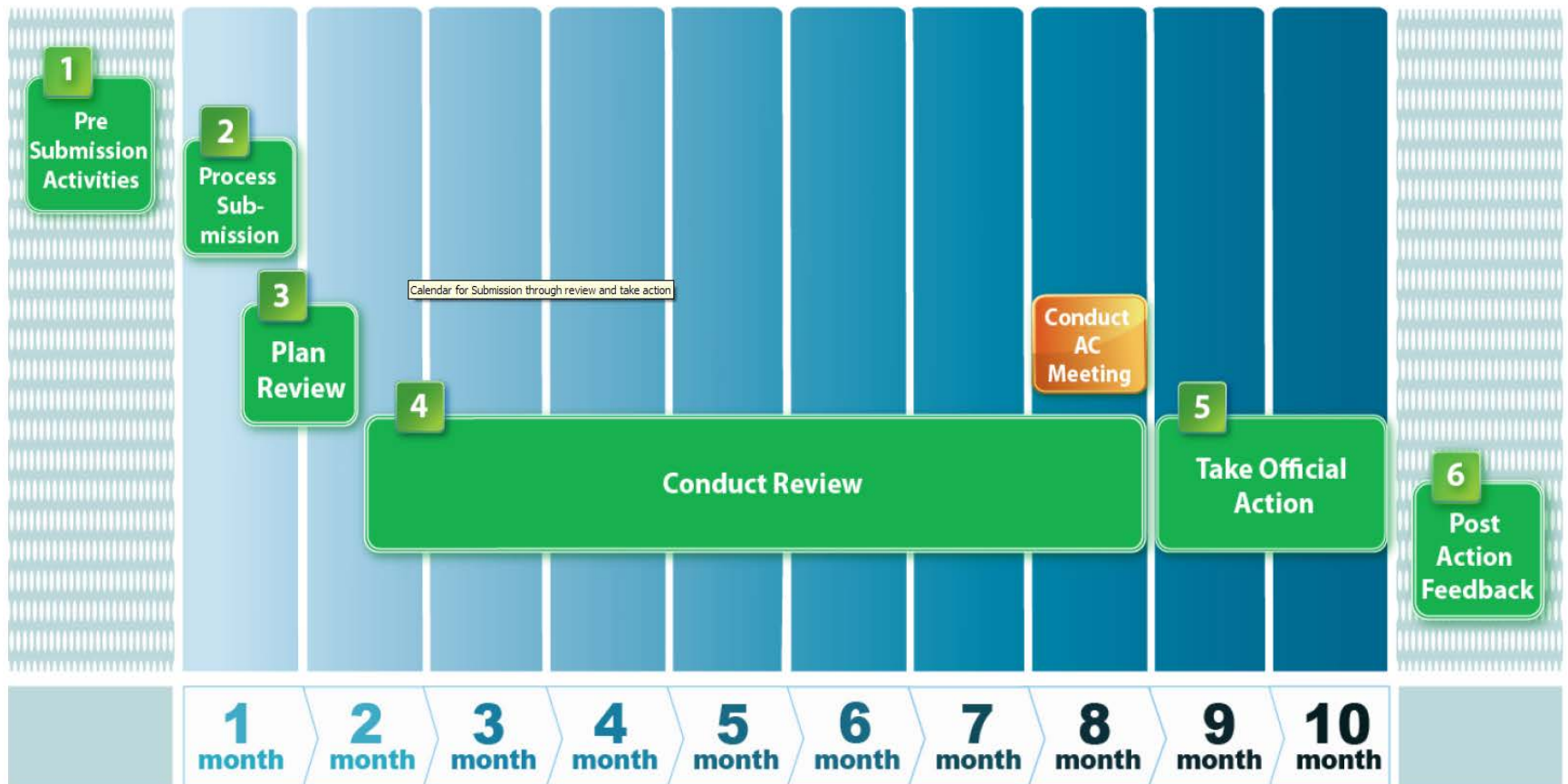
PDUFA / FDASIA

- Efficiency/Predictability of processes
- Promote innovation
- Goals Letter:
 - **B. Assessment of the Program ...** “be evaluated by an independent contractor with expertise in assessing the quality and efficiency of biopharmaceutical development and regulatory review programs.”
 - **XII. IMPROVING THE EFFICIENCY OF HUMAN DRUG REVIEW THROUGH REQUIRED ELECTRONIC SUBMISSIONS AND STANDARDIZATION OF ELECTRONIC DRUG APPLICATION DATA**

21st Century Review

CDER 21st Century Review Process

Desk Reference Guide



21st Century Review

Summary of Review Team Responsibilities

Primary Reviewer	Discipline Team Leader (DTL)	Cross-Discipline Team Leader (CDTL)	Regulatory Project Manager (RPM)	Discipline Director	OND Division Director (includes Deputy)	OND ODE Director (includes Deputy)
<ul style="list-style-type: none"> • Performs scientific review, labeling review, and recommends action. • Consults with TL, peers, and others while developing the review. • Works collaboratively within a team setting. • Raises issues and identifies to management potential solutions throughout the review. • Attends and participates in review team meetings as needed. • Organizes work to meet deadlines. 	<ul style="list-style-type: none"> • Assigns and provides guidance and feedback to primary reviewer. • Provides clear direction to the primary reviewer; meeting regularly to provide feedback and discuss issues. • Resolves conflicts related to discipline area. • Attends review team meetings, as needed. • Attends and participates in key milestone team meetings. • Advises CDTL of potential schedule slippage and issues. • Signs off on primary review and writes a DTL secondary review, as needed. • Organizes work to meet deadlines. 	<ul style="list-style-type: none"> • Provides day-to-day leadership to team and oversight of the review. • Works with the RPM and DTLs to address issues and resolve conflicts that arise within and across disciplines and to ensure efficient and timely reviews. • Attends all team meetings. • With RPM, monitors review progress and keeps OND management apprised of review status. • Writes a CDTL Review for each application bringing together highlights and perspectives of all disciplines. • Organizes work to meet deadlines. 	<ul style="list-style-type: none"> • Serves as regulatory leader for review team. • Performs PLR format review of label and includes deficiencies in 74-day letter. • With the CDTL, manages day-to-day review activities. • Organizes and attends all review-related meetings -- usually facilitates meeting. • Tracks review progress, addresses potential review process issues, and resolves obstacles, keeping the CDTL informed. • Serves as the point of contact for communication with the applicant. • Maintains an accurate administrative record of the review. • Organizes work to meet deadlines. 	<ul style="list-style-type: none"> • Is responsible for ensuring the quality and consistency of the discipline's review and recommendation for action. • Attends key milestone team meetings, as needed. 	<ul style="list-style-type: none"> • Has signatory authority for non-NME applications. • Attends key milestone review team meetings. • Is responsible for ensuring the quality of the review decision, approved labeling, and associated administrative record. • Appoints and mentors the CDTL and works with the CDTL and RPM to ensure that review goals are being met. • With the CDTL handles conflicts that arise during the review. • Writes a tertiary "summary" review that includes a decision or recommendation for regulatory action. • Keeps Office Director apprised of review status and significant issues and organizes work to meet deadlines. 	<ul style="list-style-type: none"> • Has signatory authority for NMEs, original BLAs, and other applications such as novel public health issues. • Attends key milestone review team meetings. • Writes a decisional memorandum for applications. • With the Division Director, ensures the quality of the review decision, approved labeling, and associated administrative record. • Organizes work to meet deadlines.

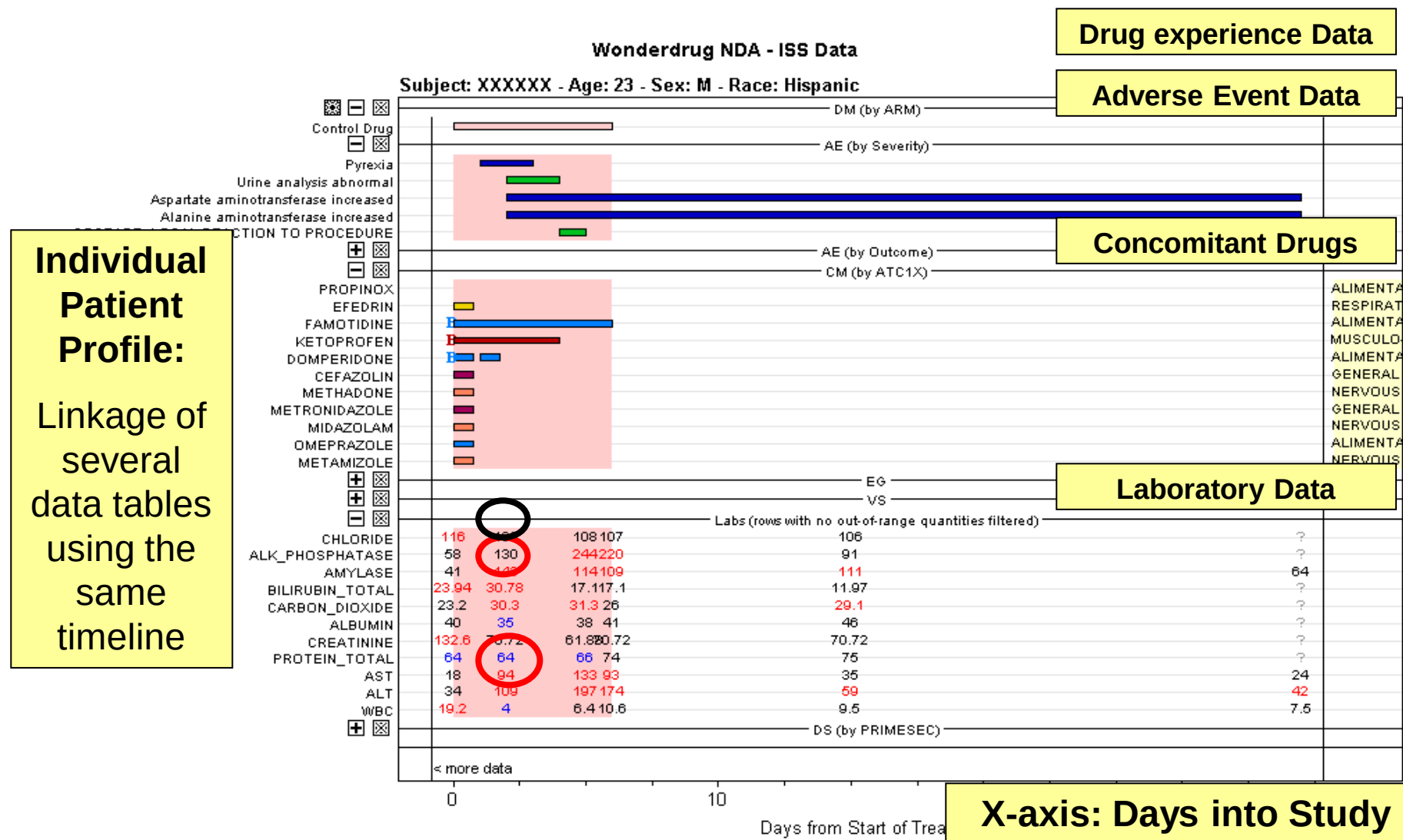
CDER says --

“Show Me the Data”

CDER says – Show me the data!

Assessing Potential Liver Injury

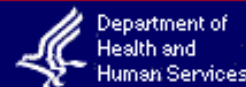
[by Analyzing Increases in Serum Alanine Aminotransferase (ALT) and Total Serum Bilirubin (TBILI)]



The Critical Path— Data Standards



U.S. Food and Drug Administration



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FDA News

FOR IMMEDIATE RELEASE
P04-73
July 21, 2004

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-
INFO-FDA

FDA Announces Standard Format That Drug Sponsors Can Use to Submit Human Drug Clinical Trial Data

The Food and Drug Administration (FDA) today announced a standard format, called the Study Data Tabulation Model (SDTM) developed by the Clinical Data Interchange Standards Consortium (CDISC), that sponsors of human drug clinical trials can use to submit data to the agency. It is expected that this step will lead to greater efficiencies in clinical research and FDA reviews of New Drug Applications (NDAs).

Our “Computational Science”: Is Something Missing?

- Tool development / standards – on-going
- Data quality / documentation / language
- Submission processes
- Application: Relevant Science and Decision-Making
- Training
- Acceptance by Regulatory Agencies, Industry, Academia





SO ...

How Are We Going to “Get
There”?

CDER/OTS and “Pre-competitive”
Collaboration

Examples of Public-Private Partnerships with CDER Participation

Analgesic Clinical Trial Translations, Innovations,
Opportunities, and Networks (ACTTION) Initiative

Biomarker Consortium (BC)
fNIH

Cardiac Safety Research
Consortium (CSRC)

International Serious Adverse
Events Consortium (iSAEC)

Pediatric Anesthesia
Safety Initiative (PASI)

Clinical Trials Transformation
Initiative (CTTI)

Critical Path Institute (CPath)

Coalition Against
Major Diseases
Consortium (CAMD)

Patient Reported
Outcomes
Consortium (PRO)

Predictive Safety
Testing Consortium
(PSTC)

Polycystic Kidney Disease
Consortium (PKD)

Critical Path to TB Drug
Regimens Consortium (CPTR)

Computational Science Symposium (CSS)

- 2014 CSS is the 5th in a Series of Annual Computational Science Meetings established to support the work of FDA's Center for Drug Evaluation and Research (CDER), Office of Computational Science (OSC)
- 3rd Year working with PhUSE (first two were with the DIA)
- Intention: To work collaboratively with industry, vendors and regulators in a “non-competitive space” to find solutions and advance the computational sciences/technology associated with the development and regulation of new medical products (drugs, biologics, etc.)

Meetings 2.0 – Computational Science Symposium

- A different kind of conference: A Collaborative Workgroup Symposium
- Organizing Committee: Currently defined 4 “working groups” to continue the work throughout the year
- Supporting collaborative workgroups that will continue until all of the work is done.
- Technical “Stakeholder Workgroups” – but we are asking you to move beyond “your stake” ... act as knowledgeable professionals seeking solutions
- Work Products, timelines, next steps
- Job much bigger than these workgroups – this is a start

The Experiment: Tom Sawyer & The Fence



The Experiment

- Progress
- Some Challenges

Progress: Current Workgroups

- Optimizing the Use of Data Standards
- Development of Standard Scripts for Analysis and Programming
- Non-Clinical Road-map and Impacts on Implementation Emerging Technologies
- Emerging Technologies

Progress: Deliverables



PhUSE CSS Deliverables Catalog

The PhUSE CSS Working Groups bring together academia, industry, technology providers and the FDA to collaborate on projects to address unmet computational science needs. This catalog provides a single point of reference for content developed by the PhUSE CSS Working Group Projects. Hyperlinks will redirect users from the PhUSE website to the specific location of the work package.

[Handling SEND References in Study Documentation:](#) Recommendations for handling references to SEND in study documentation (e.g. protocol, contracts, etc.)

[PhUSE CSS Google Code Repository:](#) Repository for storing standard scripts for data transformations and analyses across and/or within a therapeutic area and exploratory analysis.

[Representation of CDISC Foundational Standards in RDF \(draft\):](#) Representation of CDASH v1.1, SDTM v1.2/IG v3.1.2, SDTM v1.3/IG v3.1.3, SEND IG v3.0, ADaM v2.1/IG v1.0 and an example of CDISC Controlled Terminology in Resource Description Framework (RDF)

[Semantic Technology Primer:](#) Resources for obtaining additional information about Semantic technologies including books, websites and free ontology editors.

[SEND Implementation Wiki:](#) Knowledge base for SEND implementers including reference articles and links, modeling basics and FAQs.

[Study Data Reviewer's \(SDRG\) Guide Work Package:](#) The SDRG proves FDA Reviewers with additional context for SDTM datasets received as part of a regulatory submission. The SDRG Work Package includes a SDRG Completion Guidelines, SDRG Template and example SDRGs.

[Traceability References :](#) Summarizes and interprets traceability references found in the public domain (e.g. conference papers, CDER Common Data Standards Issues Document, etc.)

[White Paper: Best Practices for Data Sizing \(Under public review\):](#) Provides recommendations managing the length of character variables in a submission, handling SAS transport files that exceed the maximum allowable size and documenting split domains in define.xml

[White Paper: Analyses and Displays Associated with Measures of Central Tendency:](#) Provide advice on displaying, summarizing and/or analyzing measures of central tendency, with a focus on vital sign, electrocardiogram (ECG) quantitative findings and laboratory analyte measurements in Phase 2-4 clinical trials and integrated submission documents.

[White Paper: Current State of Traceability and Data Flow:](#) Provides a high-level definition of traceability and analysis of the current common data flows in human clinical trials.

[White Paper: Roadmap for Nonclinical data Standards and Elements to Improve Data Access:](#) Identifies points to consider when implementing Nonclinical Standards, sets priorities for Nonclinical data types and considerations for future Nonclinical Standards development. Documents key Standards resources.

[White Paper: Traceability. Preliminary Recommendations for Traceability Documentation using Define-XML 2.0:](#) Overview of define.xml 2.0 and traceability implications.

[White Paper: Traceability. Best Practices for Linear Data Flow :](#) Describe traceability needs pertinent to regulatory agency review of electronic clinical data for collected data to tabulation data (SDTM) to analysis datasets to analysis

Progress: The Wiki

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Navigation trail: Annual Conference » CSS Working Groups » PhUSE Wiki

PhUSE Wiki

Welcome to the  Wiki

Currently 605 users are helping to **Share, Contribute and Advance** clinical informatics.

CSS Working Groups



Annual Conference London



Good Programming Practice Guidance



All content on this wiki is non-binding. All content expresses opinions of users and not necessarily that of their employer nor PhUSE. See our [Disclaimers](#) page.

What is this place?

The PhUSE Wiki is an [PhUSE](#) [eFDA](#)/Industry collaboration to provide a medium to share information specifically relating to clinical trial informatics. The wiki has three main goals:

1. To support the [Computational Science Symposium \(CSS\) Working Groups](#) by creating an online collaboration environment.
2. To support the [sharing](#) of statistical and informatics software code (SAS,R etc).
3. To serve as a medium to share information related to software programming and processes for pharmaceutical, biotech, CRO, medical device and health care programmers.

What can I do here?

Well that depends who you are. If you are an [CSS Working Group member](#) you can [click here](#) to access your specific working group. If you are [authoring a wiki for the Brussel Conference](#) you can [click here](#). Otherwise, if you have something to share, enter the title of your page into the box at the right. If you are looking for something, use the search at the top right of this page.

Start by [creating a User account](#). In order to keep this Wiki transparent for all users it would be great if you could **use your real name as your user name**. Note that you also need to create a User account if you are a PhUSE member. **Your PhUSE login details do not work here**. It might also be good to familiarize yourself with the [wiki language](#). After that, you are welcome to add, edit, read, and discuss anything in this wiki. If you have questions, please [contact us](#). Interested, but don't know which topic to tackle? Check out the [Wanted](#) pages. Make someone's day by answering their question.

Recent Changes

17 March 2014

- [\(diff | hist\)](#) . . [WG5 Project 07](#); 04:54 . . (+214) . . [Dirk Spruck](#) ([Talk](#) | [contribs](#)) (←*Planned Presentations:*)

16 March 2014

- [\(diff | hist\)](#) . . [Metadata Definition Project](#); 20:11 . . (0) . . [Mitarrocca](#) ([Talk](#) | [contribs](#))
- [\(diff | hist\)](#) . . [Metadata Definition Project](#); 20:10 . . (-8) . . [Mitarrocca](#) ([Talk](#) | [contribs](#))
- [\(diff | hist\)](#) . . [Metadata Definition Project](#); 20:09 . . (+9) . . [Mitarrocca](#) ([Talk](#) | [contribs](#))
- [\(Upload log\)](#); 20:07 . . [Mitarrocca](#) ([Talk](#) | [contribs](#)) uploaded "[File:ET project MDD 2014-03-12.pptx](#)"
- [\(diff | hist\)](#) . . [Metadata Definition Project](#); 20:04 . . (+221) . . [Mitarrocca](#) ([Talk](#) | [contribs](#))
- [\(Upload log\)](#); 20:02 . . [Mitarrocca](#) ([Talk](#) | [contribs](#)) uploaded "[File:ET MDD v1.0 2014-03-12 final.docx](#)"

15 March 2014

Add a new wiki page

Add new Wiki!

 caption

News

Most Popular Pages



CSS News

- March 11, 2014: Final draft PK White Paper is available for review
- February 7, 2014: Two Draft White Papers on Standard Analyses open for review
- December 8, 2013: CSS Working Group initiates best practices document with recommendation for Data Sizing
- December 8, 2013: White Paper on Central Tendency TFL finalized
- December 8, 2013: CSS 2014 will feature first Script-athon ever

CSS Deliverables

- Data Sizing Best Practices Recommendation

White Paper on Central Tendency TFL finalized

Recent changes on active CSS Projects:

- [WG5 Project 02](#)
- [WG5 Project 04](#)
- [WG5 Project 05](#)
- [WG5 Project 06](#)
- [Top 20 Validation Rule Failures \(CBER\)](#)

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Some Challenges

- Volunteer / Co-Lead
- Right Projects
- Transparency/”Optics”
- Recognition/Appreciation
- FDA Involvement – Disclaimer & “Liaison”
- Wiki and “Agile Communication”
- Testing and “Socialization of Deliverables”

Thank You for your attention!!



SOLDIERS AT ATTENTION.

stephen.wilson@fda.hhs.gov