CDER Computational Science Center

Better Data, Better Tools, Better Decisions

Improving Efficiency and Consistency in the FDA Review Process

CERSI

September 5, 2013

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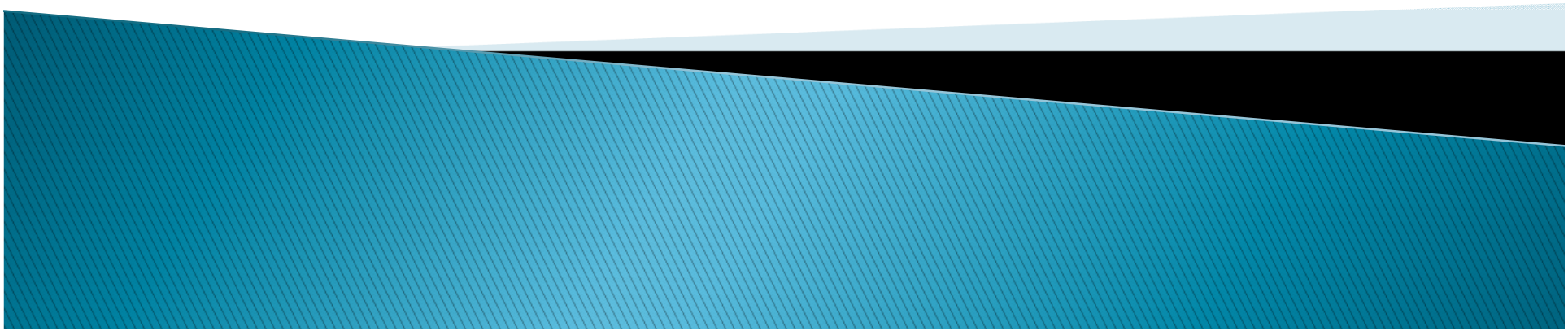
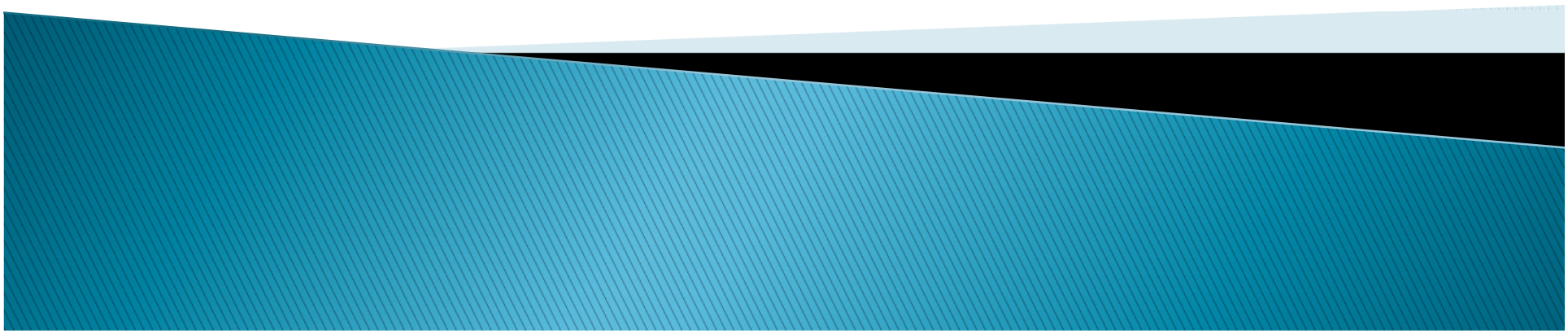
Computational Science Center
Office of Translational Sciences
CDER, FDA



Disclaimer:

The views presented here represent those of the presenter and should not be interpreted to represent policy or guidance on behalf of the FDA.



Outline

- Background
- Review Standards
- Challenges of current review environment
- Data standards
- Modern Review Environment
- Conclusion

CDER's Mission

- Ensure the safety and efficacy of the products it regulates
  - Drug and biologic therapeutics
- How?
  - Assessment of vast amount of information
    - Chemistry, manufacturing
    - Pre-clinical data
    - Phase 1, 2 safety data (IND)
    - NDA/BLA application
    - Marketing, advertising
    - Post-market adverse event reports, PSURs
    - Other sources
      - Published literature
      - Meta-analysis
      - Observational studies

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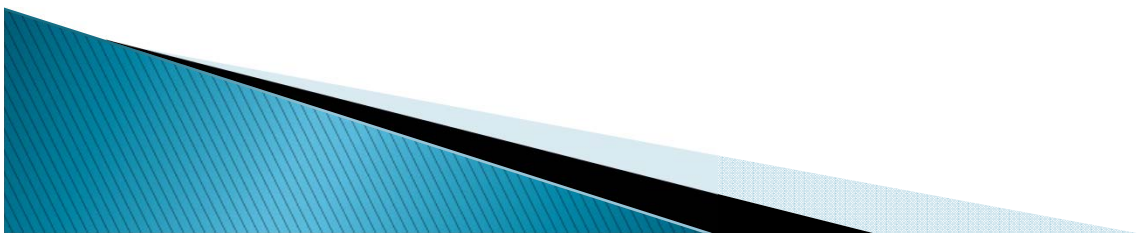
Challenge to Reviewers

- Review timelines
  - Required meetings
  - Advisory Committee meetings
  - Other work
    - INDs, other NDA, sponsor meetings, post-market safety…..
- Validate/confirm sponsors' assessment using clinical trial data
  - why?
  - example



Sponsor's Proposed Labeling

Table 4. Incidence (%) of Treatment Emergent Adverse Events Reported in ≥2% of Patients Treated in Phase 3 Clinical Studies

Body System Adverse Events	Drug X (N=1415)	Comparator[b] (N=1382)
Metabolic and Nutritional		
Alkaline Phosphatase Increased	3.1	2.1
Amylase Increased	2.7	1.2
Bilirubinemia	2.3	0.8
BUN Increased	2.0	
Healing Abnormal	2.	
Hyperglycemia		
Hypokalemia	1.	
Hypoproteinemia	4.4	
Lactic Dehydrogenase Increased	3.6	3.1
Peripheral Edema	3.1	3.0
SGOT Increased	2.5	4.1
SGPT Increased	2.5	4.1

Drug X with 40% less ALT Adverse Events than Comparator

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Final Approved Label

Table 4. Incidence (%) of Treatment-Emergent Adverse Events Through Test of Cure Reported in ≥2% of Patients Treated in Phase 3 Clinical Studies

Body System Adverse Events	Drug X (N=1415)	Comparators[b] (N=1382)
Metabolic and Nutritional		
Alkaline Phosphatase Increased	3.5	2.6
Amylase Increased	3.1	1.4
Bilirubinemia	2.3	0.9
BUN Increased	2.1	
Healing Abnormal	3.5	
Hyperglycemia		
Hypokalemia		
Hypoproteinemia		
Lactic Dehydrogenase Increased	4.0	
Peripheral Edema	3.3	
SGOT Increased[c]	4.3	4.4
SGPT Increased[c]	5.6	4.7

Now the rate has more than doubled over sponsor's proposed rate and now higher than comparator

[c] LFT abnormalities in Drug X-treated patients were reported more frequently in the post therapy period than those in comparator-treated patients, which occurred more often on therapy.

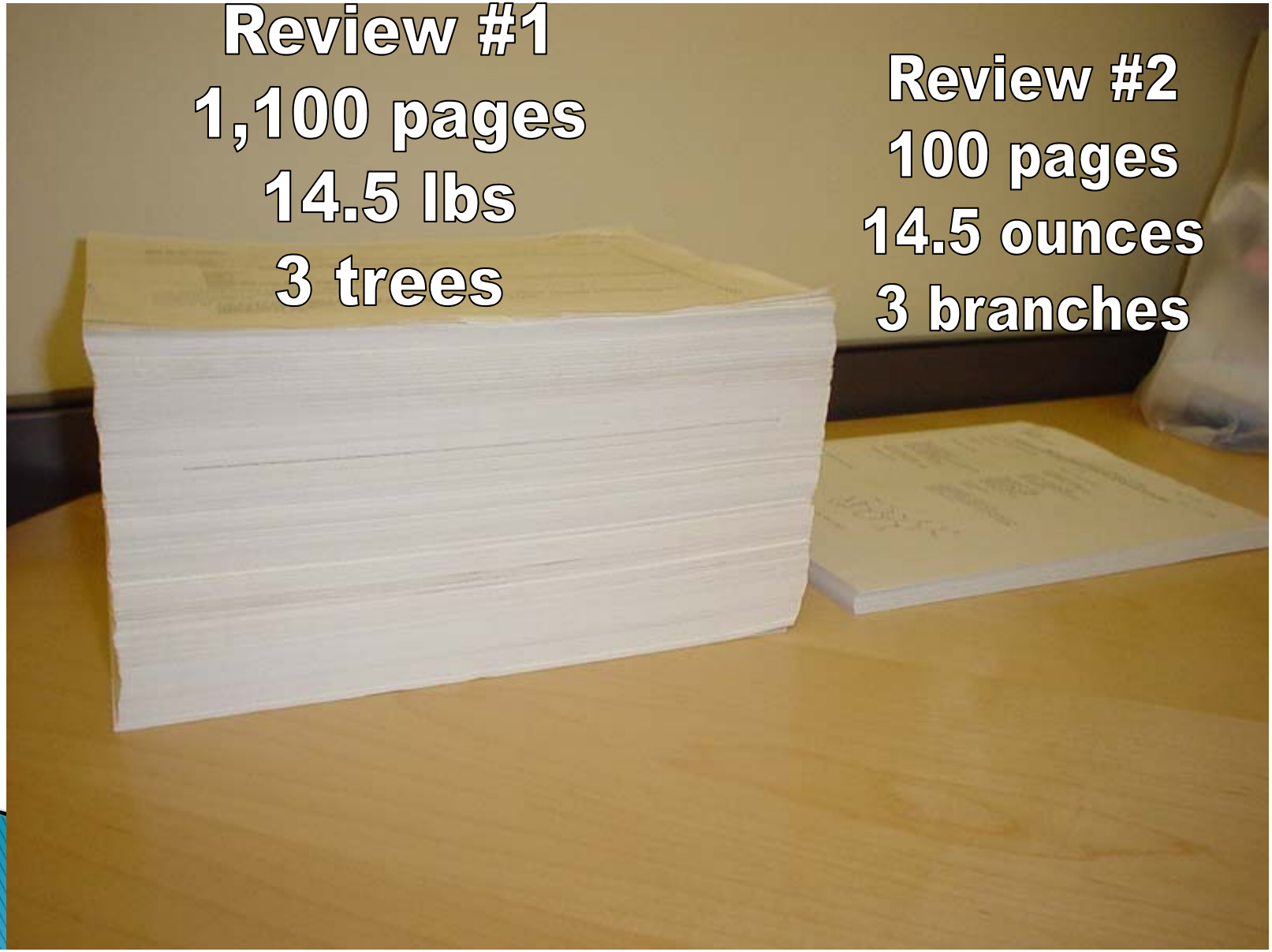
Also, now, delayed onset of ALT rise is mentioned

What Happened?

- Sponsor restricted analysis to include events only occurring up to 5 days after last dose
  - No mention of this in sponsor's submission
  - No explanation for this decision
  - Clinical reviewer unaware that this was done at time of submission
- Is this a reasonable decision?
  - Drug X – ½ life of 55.8 hours
    - measurable plasma levels present at 7-9 days after last dose
    - Even longer tissue ½ life with very large volume of distribution
  - Other Liver adverse events were excluded from analysis

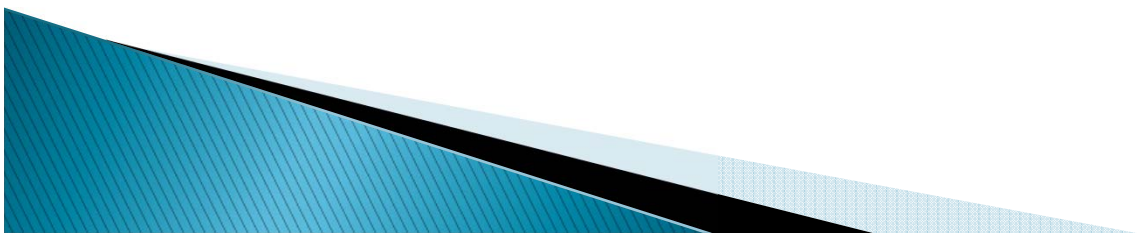
What the review process looks like in 2000:

Consistency Across Reviews?



Establishing Review Standards

- New standards for Safety Review have been established
  - Clinical Review Template (2004)
    - annotated
  - Good Review Practices
    - Review Guidance: Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review, February 2005
      - 84 pages
  - 21st Century Review Process



Clinical Reviewer Template

Table of Contents

Reviewer Guidance

Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review

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

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

February 2005
Good Review Practices

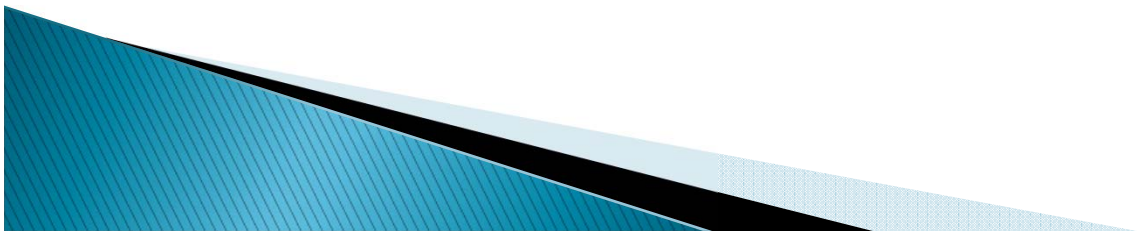
Result:
More consistency across reviewers regarding <u>what</u> reviewers are supposed to be doing, but not <u>how</u>….

Conducting a Clinical Safety Review

- Deaths
  - Overall mortality
  - Cause specific
  - Expected vs unexpected
  - Dose response
  - Time to death analysis
  - Subgroup analysis
  - Interaction analysis
- SAEs
  - Overall rates
  - Rates by event
  - Dose response
  - By duration of exposure
  - By person-time exposure as denominator
  - Assessment according to alternative explanation
  - Assessment of interaction by subgroup
- Dropouts and other SAEs
  - Overall rates
  - Profile of dropouts (by reason)
  - AEs associated with Dropouts
  - Exposure response
  - Time dependency
- Other significant AEs as defined by ICH
  - Marked lab abnormalities
  - Any AE leading to dropout or intervention
  - Potentially important abnormalities not meeting above definition
- Construct of algorithms of combo's of clinical findings
  - Identify possible combinations of clinical findings that may be a marker for a particular toxicity
- Identify possible consequences of a safety signal from any source
- Common AEs
  - Incidence for subsets -controlled studies
  - LLT's should be compared to mapped PT's
  - Assess for causality
  - Comparison of severity between treatment arms
- Dose dependency for AEs
  - Titration studies
- Time to onset for AEs
  - Particularly for events that occur commonly
- AE incidence by interaction
  - demographic
    - race, gender, age
  - Drug-drug interaction
  - Underlying medical problems such as DM or renal disease
  - Dose response
    - body weight-adjustted dose
    - cumulative dose
    - Body surface area-adjusted dose
    - dosing schedule
  - Exposure adjusted event rates "person-time approach"
    - When hazard rate is constant over time
    - Break observation period into intervals

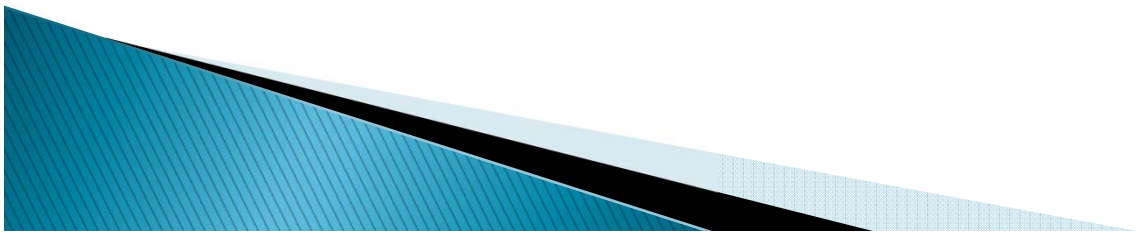
Conducting a Clinical Safety Review

- AE incidence by interaction (cont.)
  - Relative risks and attributable risks for subgroup differences
  - Life table/ time-to-event analyses/ cumulative incidence anlayses
  - Hazard rates – risk over time estimation
- Less common AEs
  - Identify and group by body system for rates
- Laboratories
  - Overview of testing methodology
  - Analysis of measures of central tendency
  - Analysis of outliers or shifts to abnormal
  - Marked outliters and dropouts due to lab abn
  - Dose dependency
  - Time dependency
  - Demographic interactions
  - Drug-drug interactions
  - Underlying medical condition interactions
  - Special section on Liver laboratory abn
  - Shift tables
  - Scatter plots
  - Box plots
  - Cumulative distribution displays
  - Tables of deviation in >1 parameter
- Vital signs
  - Overview of testing
  - Analysis of measures of central tendency
  - Analysis of outliers or shifts to abnormal
  - Marked outliters and dropouts due to lab abn
- ECG's
  - Describe baseline and number of on-study ECGs
  - Analysis of measures of central tendency
  - Analysis of outliers or shifts to abnormal
  - Marked outliters and dropouts due to lab abn
- Immunogenicity
  - Summarize and assess available data
- Carcinogenicity
  - Summarize and assess
- Special Safety Studies
  - Summarize any such studies
  - Similar to other drugs in pharmacological class?
  - Studies on cumulative irritancy, sensitizing potential
  - Photosensitivity, photoallergenicity
  - Special Thorough QT study
    - To be done on all NMEs
  - Studies to demonstrate a safety advantage over existing therapeutics
- Withdrawal phenomenon or Abuse potential
  - Reivew/summary of relevant studies
  - Scheduling recommendations
- Human Repro and Pregnancy data
- Assessment of Effect on Growth
- Overdose Experience
- Post-marketing experience
- Causality determination
- Adequacy of patient exposure and Safety assessments
  - Refer to ICH
  - Adequate numbers of various demogrpahic subsets
  - Doses and durations of exposrue were adequate to assess safety for intended use
  - Were study designs adequate to answer critical questions
  - Were potential class effects evaluated
  - Did patient exclusions from studies limit relevance of satey assessments
- Review of secondary clinical data sources
  - IND data
  - Post-marketing data
    - Literature reports



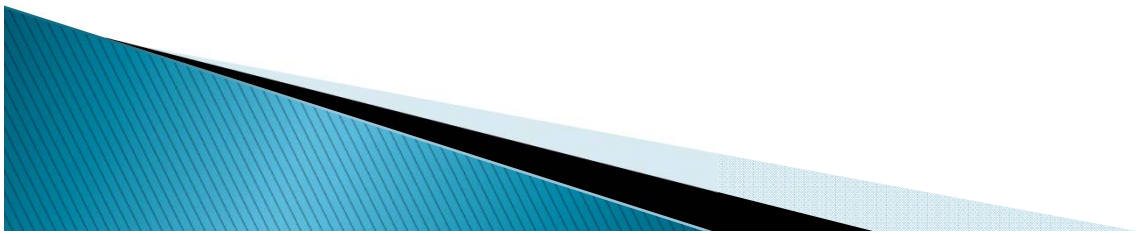
Conducting a Clinical Safety Review

- Additional Clinical Issues
  - Level of confidence for dose/regimen
  - Dose-toxicity and dose response relationships
  - Dose modification for special populations
- General assessment of adequacy of Special Animal and/or In Vitro testing
  - Pre-clinical animal models
  - QT studies
- Adequacy of routine clinical testing
  - Labs, vital signs, ECGs, assessment of certain events
- Adequacy of metabolic, clearance, and interaction workup
  - P450 and p-glycoprotien pathways
  - Other drug-drug interaction studies
  - Specify potential safety consequences
- Adequacy of evaluation for potentially problematic AEs that might be expected for a new drug
  - Assess adequacy and note pertinant negative findings (absences of findings)
- Assessment of Quality and completeness of data
  - Generall overall assessment of the quality an dcompleteness of data with a description of the basis for this assessment
- Additional submissions, including safety update
  - Particularly those submission whose data were not incorporated into the rest of the review
- Summary assessment of important identified adverse events
  - Not important limitations of data and make conclusions
- General Methodology
  - Discussion of general methodological issues
- Pooled data vs. individual study data
- Causality determination
- Exploration of predictive factors
  - Plasma levels, duration of treatment, concom meds, concom illnesses, age, sex, race
- Special populations
- Pediatrics
- AC meeting
- Literature review
- Post-marketing Risk management plan
- Other relevant materials
  - Result of consultations with DDMAC, ODS reviews, actual use and labeling comprehension studies, marketing studies
- Overall assessment
  - Conclusions
  - Recommendation (regulatory)
  - Recommendations on post-marketing actions
- Risk management activity
  - Include all such recommended activity with rationale
- Required phase 4 commitments
  - Include the agreed upon studies, the timeline for submission, and basis for each phase 4 commitment
- Labeling review



Review Improvements

- Scope and size of the review process significant
  - Variability now exists in review approach
    - Driven by individual reviewer technical abilities
- Other challenges remain
  - Ability to answer simple questions still can difficult
  - No ability to introduce automation or advanced graphical visualization tools
    - Data is extremely variable



What is the Solution?

- Create a Modern Bioinformatics Review Environment

- Data Standards – Foundational Prerequisite
  - Allow us to integrate data automatically
    - Clinical Trial Repository (Janus)
  - Develop re-useable tools and analytic capabilities that automate common assessments, support data exploration

- CDISC Data Standards
  - Approved for submission to FDA 2004
  - Uptake by sponsors has increased over past few years
    - Now over 50% of product submissions

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What is the Solution?

Computational Science Center

- Create governance structure
- Develop policy
- Define review requirements
- Create data validation system

High Quality Standard Data

- Analysis code library
- Create new solutions (MAED)
- Extend, modify existing COTS

Leveraging Standard Data

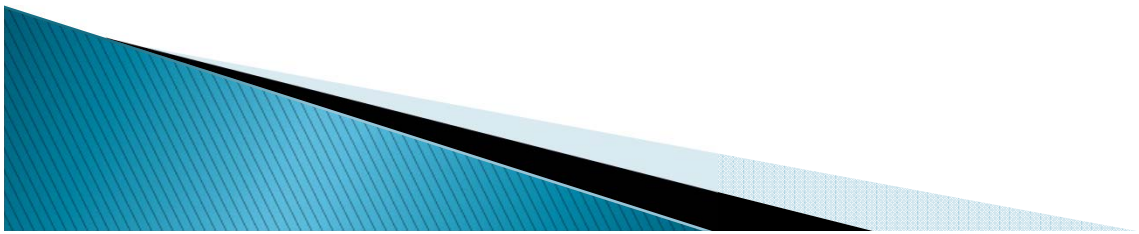
Tool Development

- Create reviewer expertise
- General training
- Buy-in from senior leadership

Training, Change Management

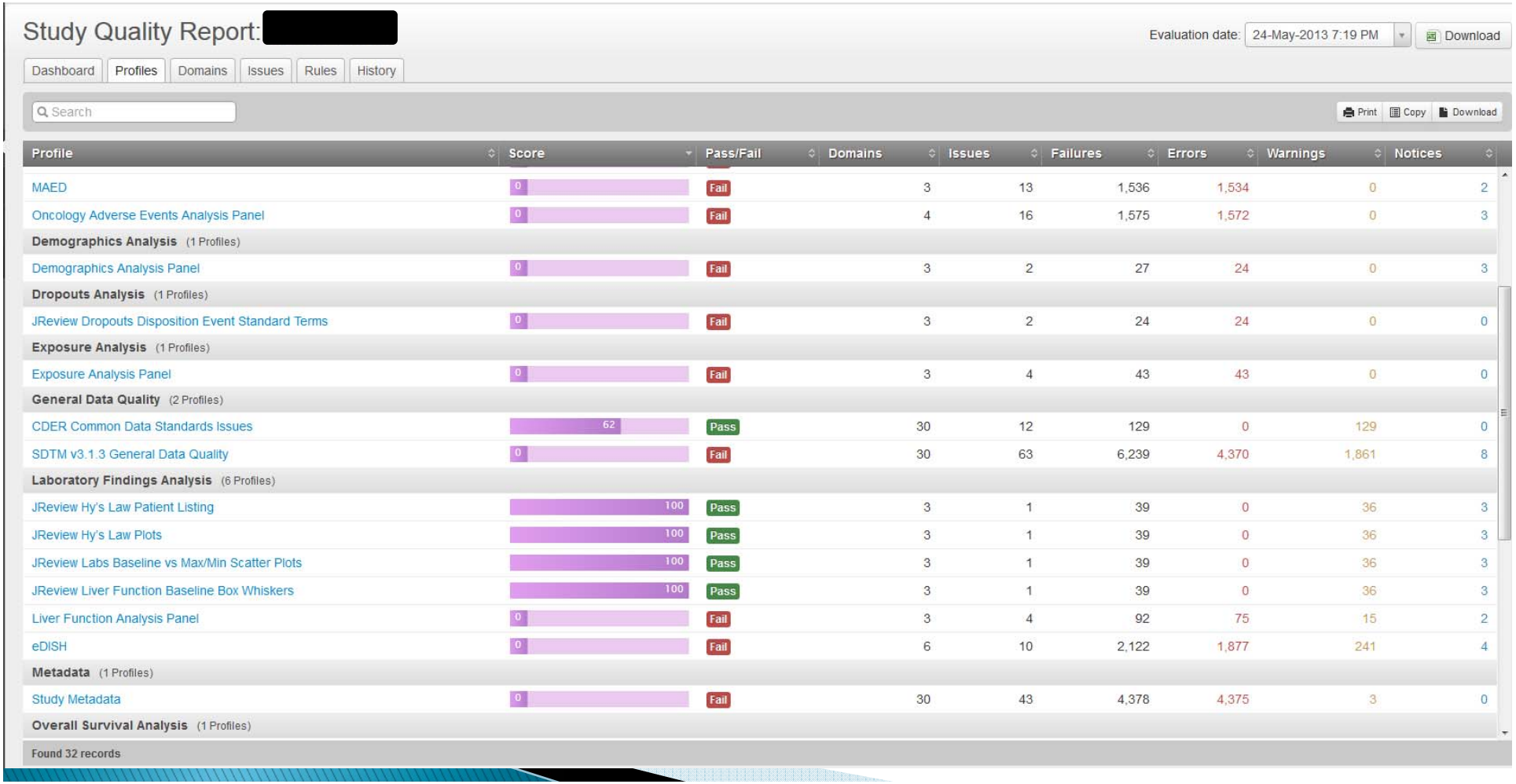
Data Standards and Validation

- CDER Governance Structure
- PDUFA5 agreement
  - Standardized data requirement to be phased in
- Guidance Development
- CDER DataFit Program
- CDER FIRRS Program



DataFit

- Validate sponsor study data on arrival



Study Quality Report: [redacted]

Evaluation date: 24-May-2013 7:19 PM | Download

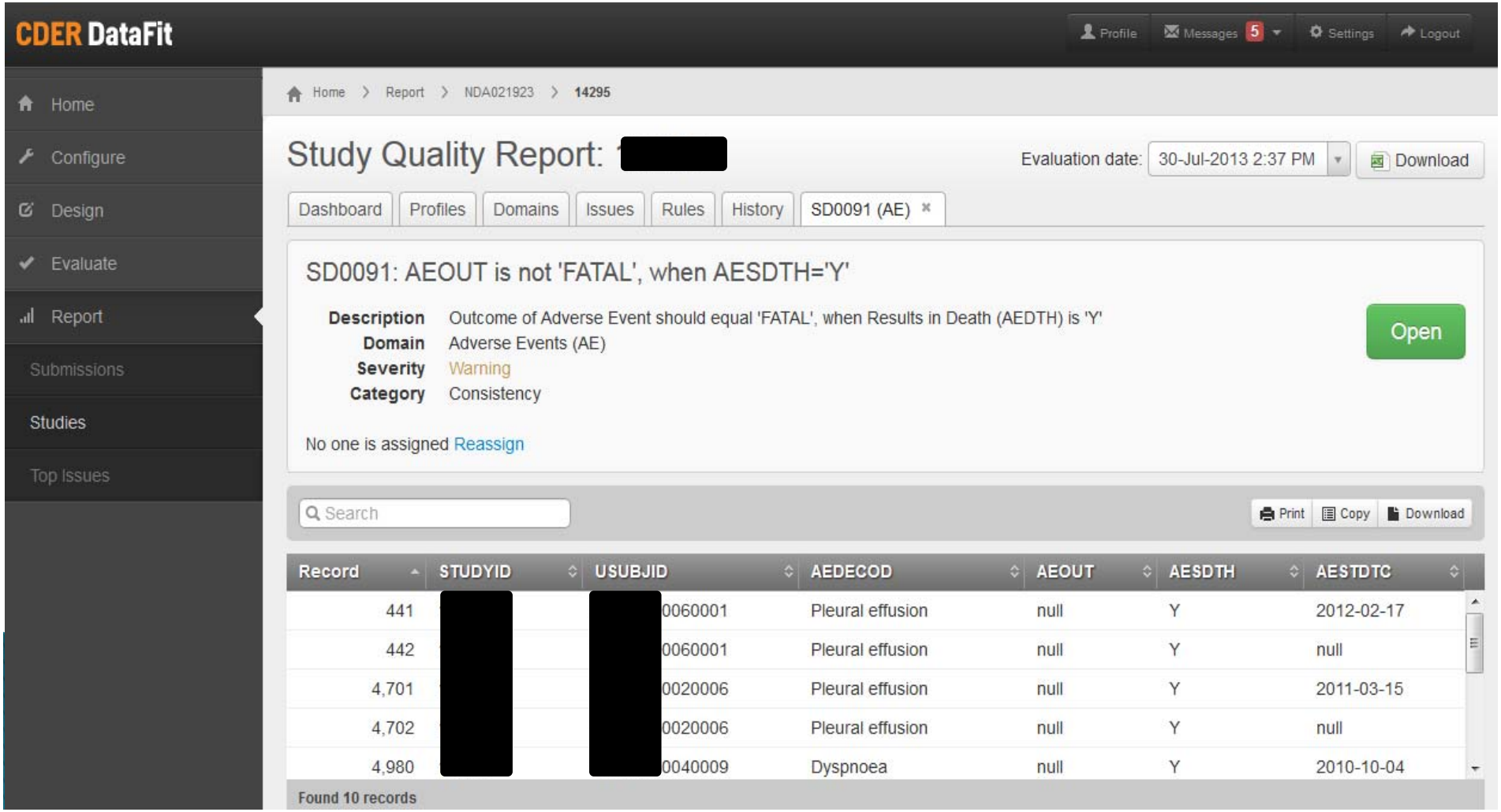
Dashboard | Profiles | Domains | Issues | Rules | History

Search | Print | Copy | Download

Profile	Score	Pass/Fail	Domains	Issues	Failures	Errors	Warnings	Notices
MAED	0	Fail	3	13	1,536	1,534	0	2
Oncology Adverse Events Analysis Panel	0	Fail	4	16	1,575	1,572	0	3
Demographics Analysis (1 Profiles)								
Demographics Analysis Panel	0	Fail	3	2	27	24	0	3
Dropouts Analysis (1 Profiles)								
JReview Dropouts Disposition Event Standard Terms	0	Fail	3	2	24	24	0	0
Exposure Analysis (1 Profiles)								
Exposure Analysis Panel	0	Fail	3	4	43	43	0	0
General Data Quality (2 Profiles)								
CDER Common Data Standards Issues	62	Pass	30	12	129	0	129	0
SDTM v3.1.3 General Data Quality	0	Fail	30	63	6,239	4,370	1,861	8
Laboratory Findings Analysis (6 Profiles)								
JReview Hy's Law Patient Listing	100	Pass	3	1	39	0	36	3
JReview Hy's Law Plots	100	Pass	3	1	39	0	36	3
JReview Labs Baseline vs Max/Min Scatter Plots	100	Pass	3	1	39	0	36	3
JReview Liver Function Baseline Box Whiskers	100	Pass	3	1	39	0	36	3
Liver Function Analysis Panel	0	Fail	3	4	92	75	15	2
eDISH	0	Fail	6	10	2,122	1,877	241	4
Metadata (1 Profiles)								
Study Metadata	0	Fail	30	43	4,378	4,375	3	0
Overall Survival Analysis (1 Profiles)								

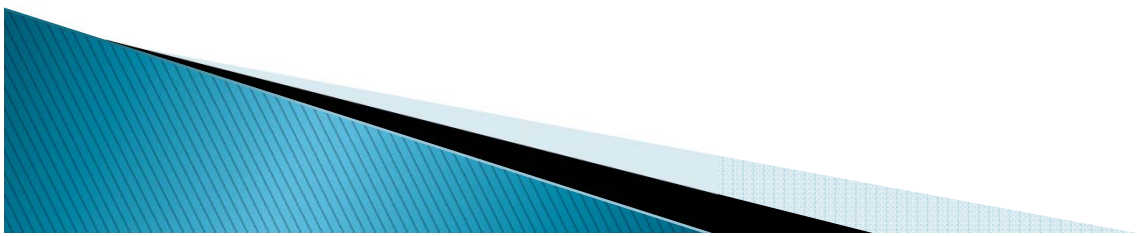
Found 32 records

CDER DataFit

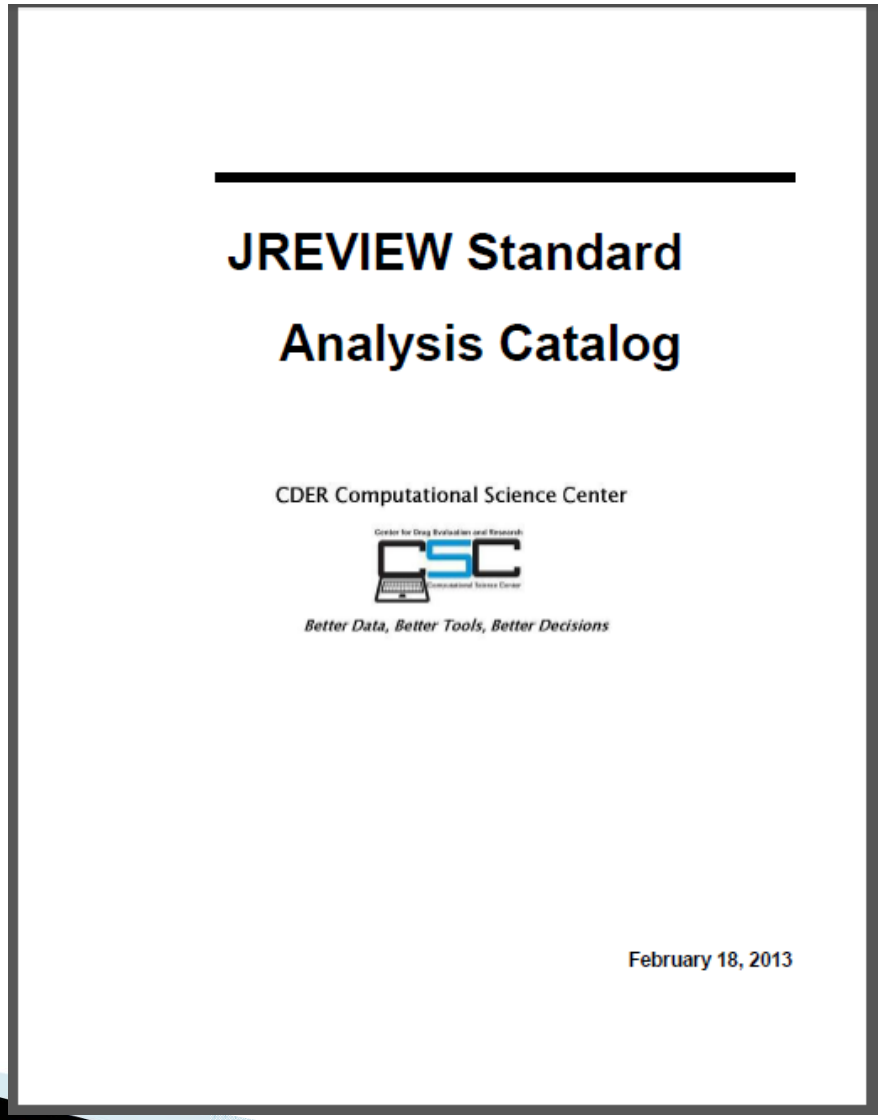


Examples of Standardized/Automated Analyses

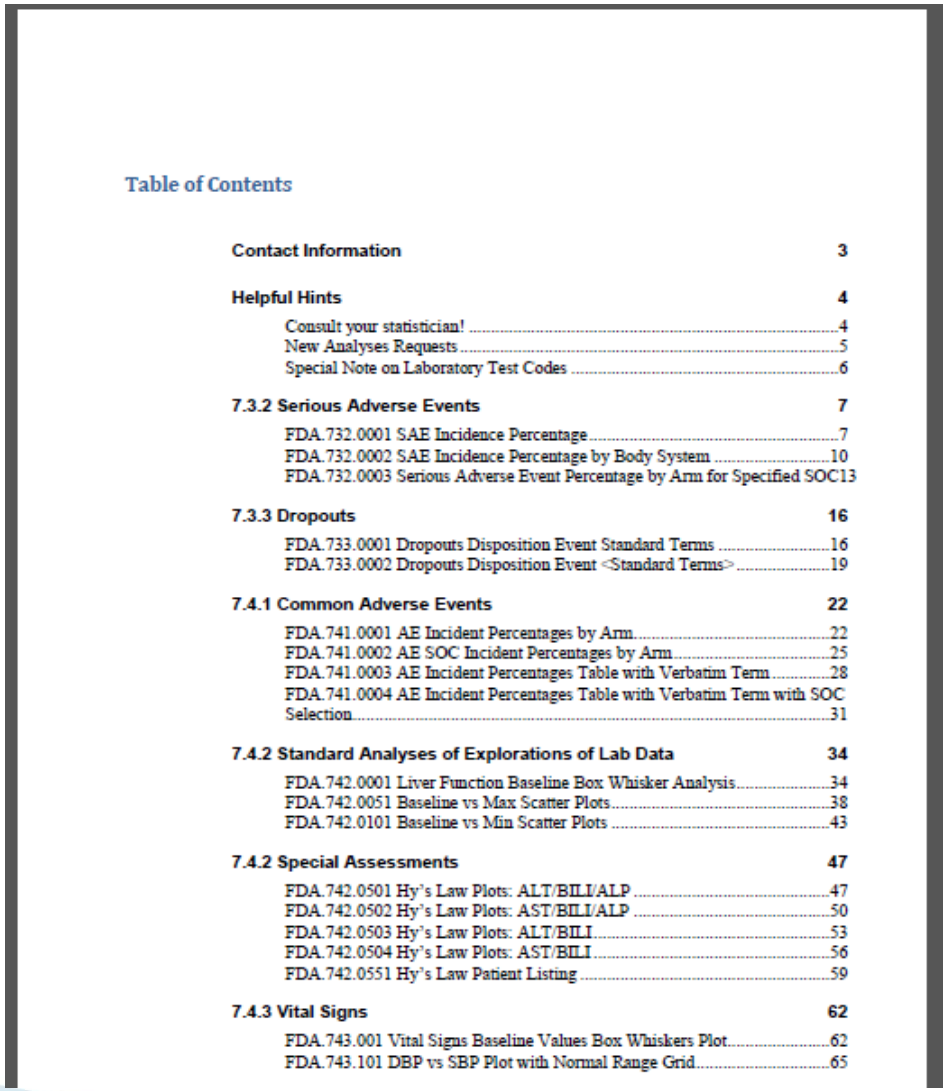
- JReview Standard Analysis Catalog
- SAS macro library
- MAED program
  - MedDRA Adverse Events Diagnostics



JReview Standard Analysis Catalog



JReview Standard Analysis Catalog



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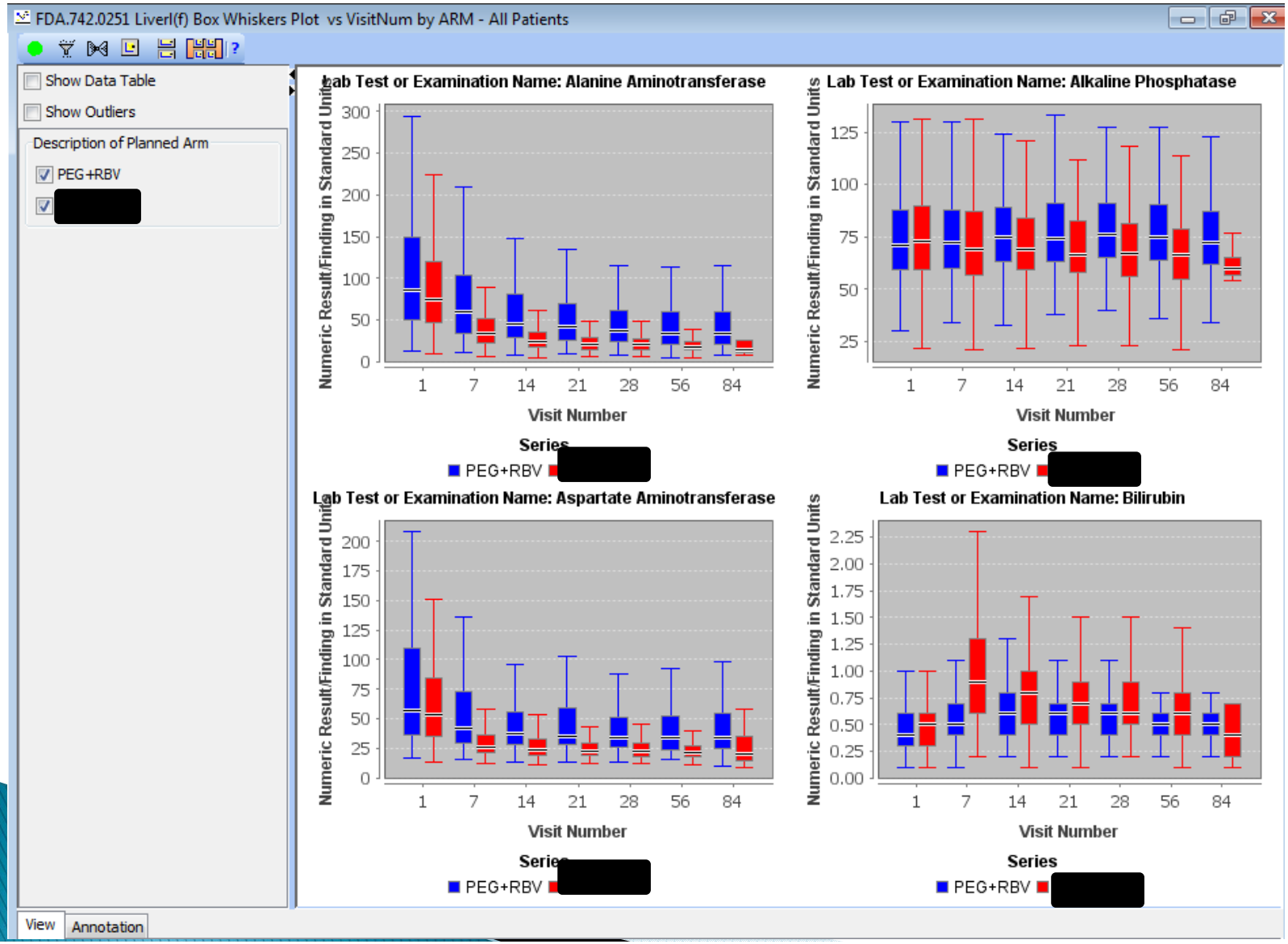
Standard Analyses in Jreview Examples:

FDA742.0251 Liver Box Whiskers vs. VisitNum



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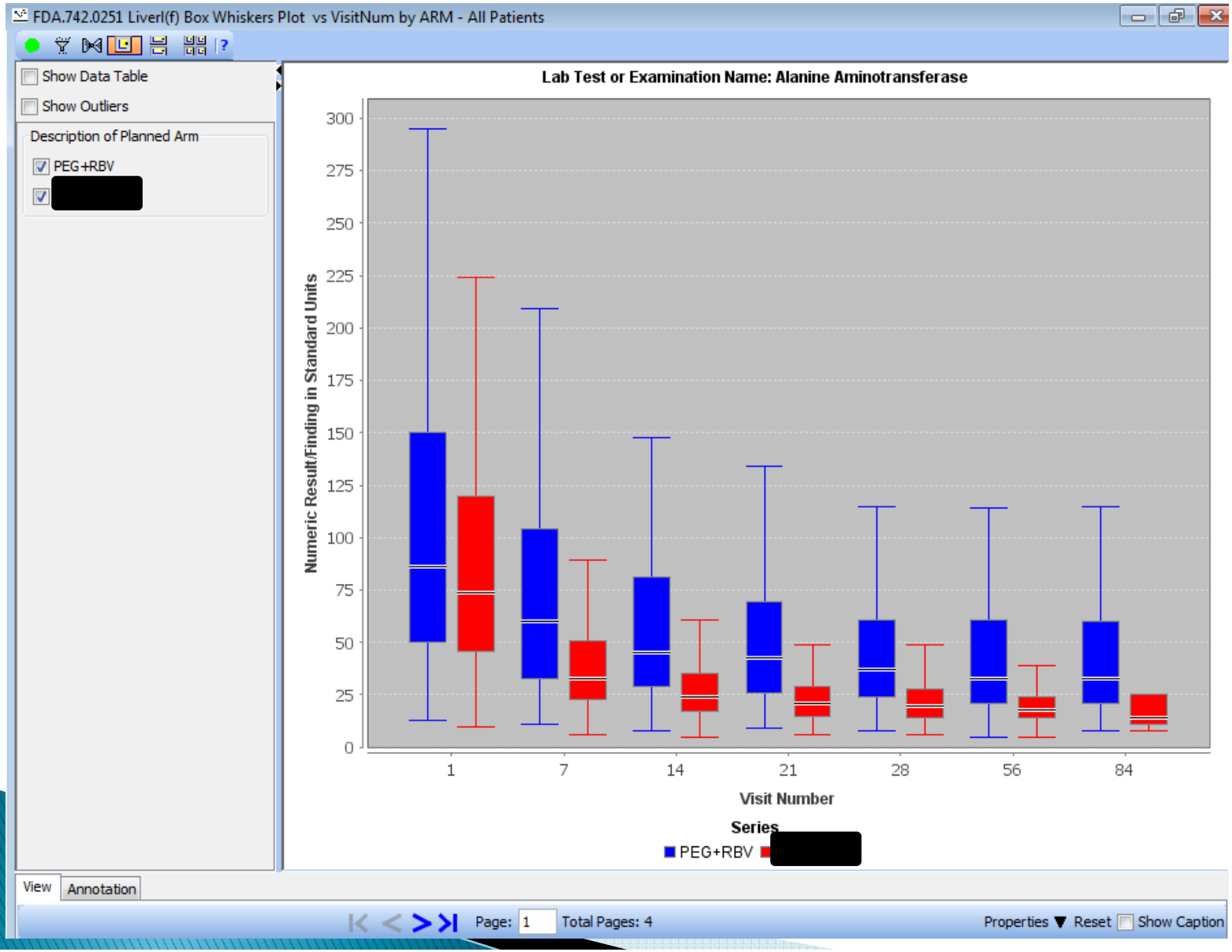
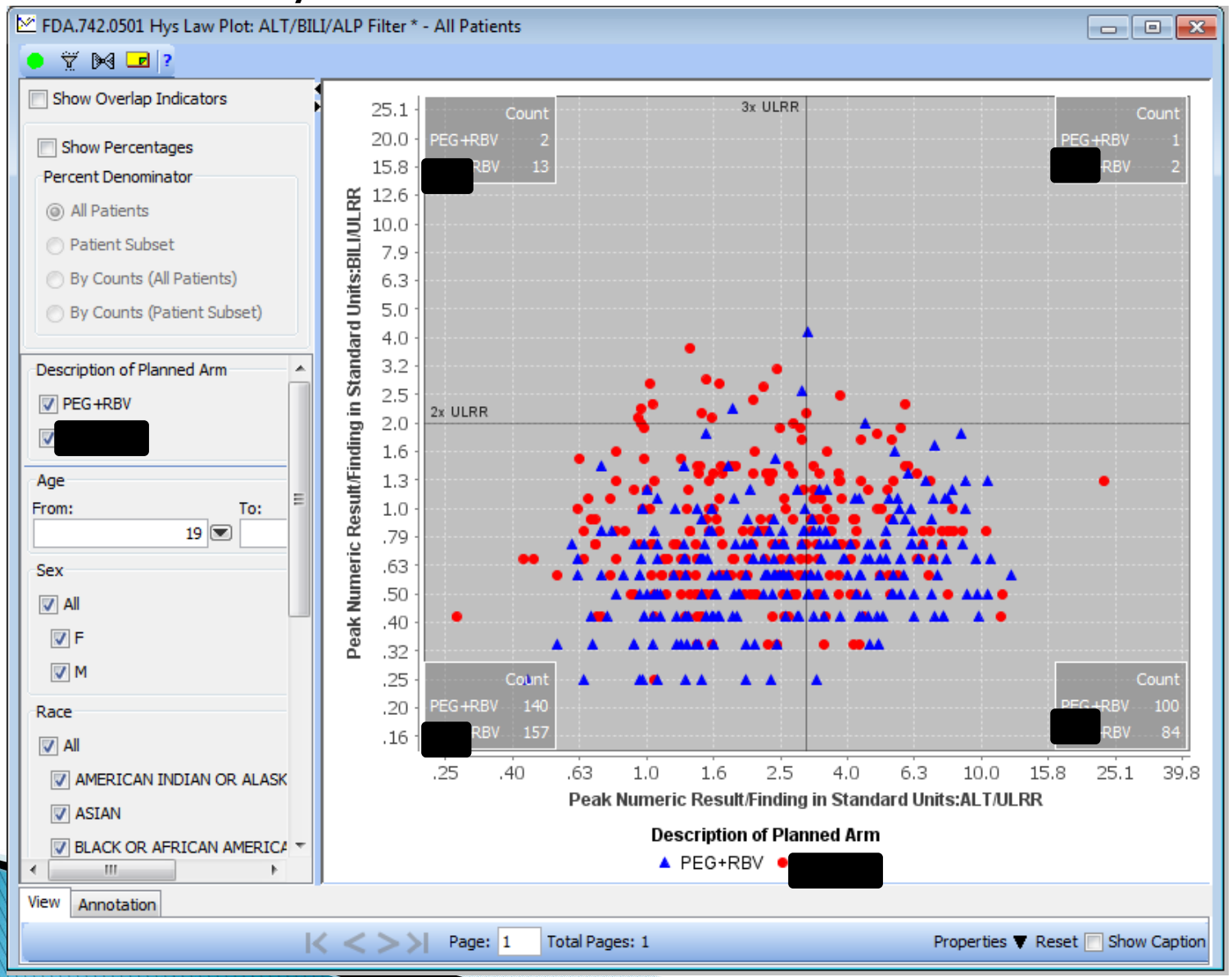


Standard Analyses in Jreview Examples:

FDA742.0501 Hy's Law Plot



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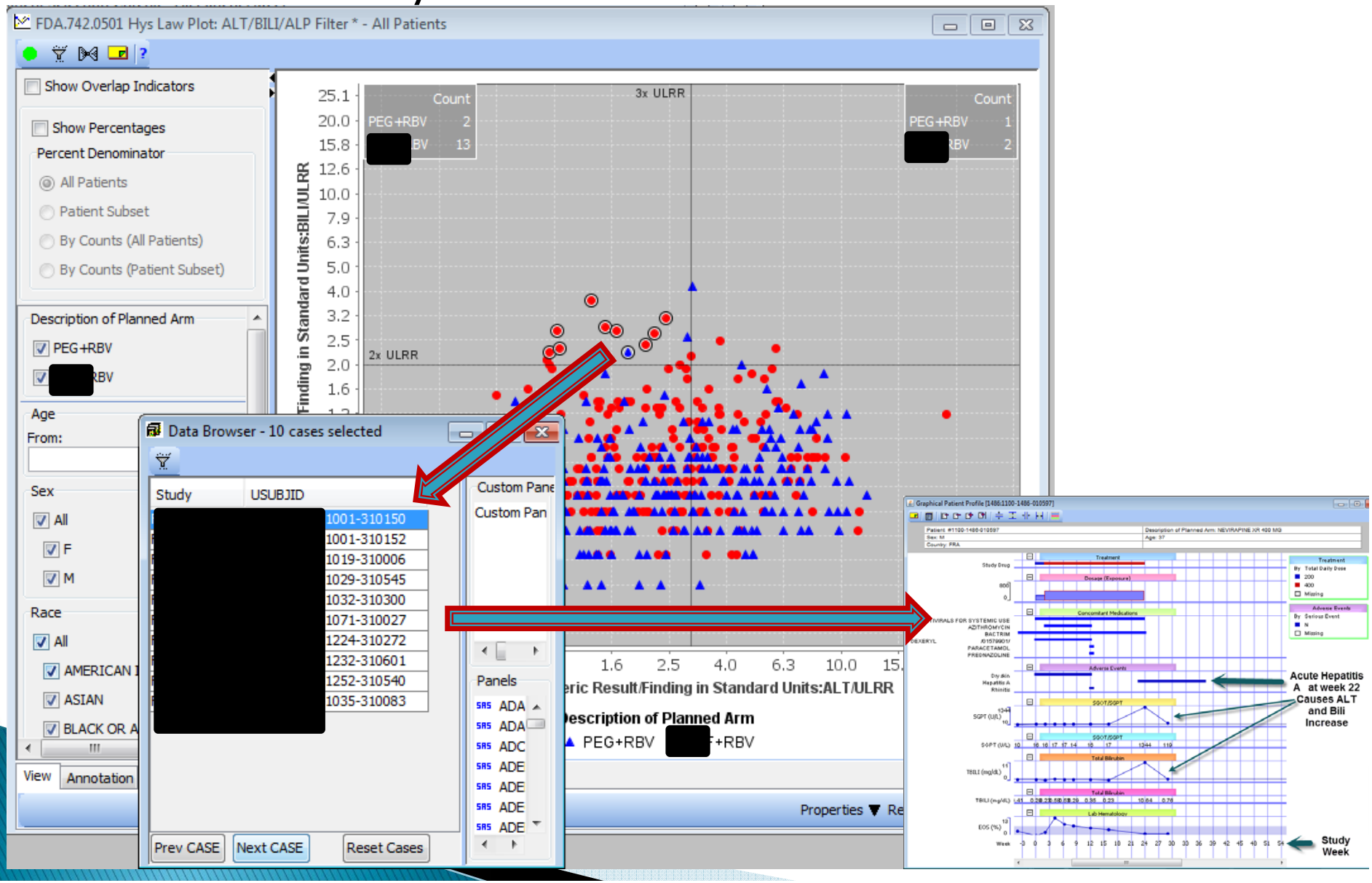
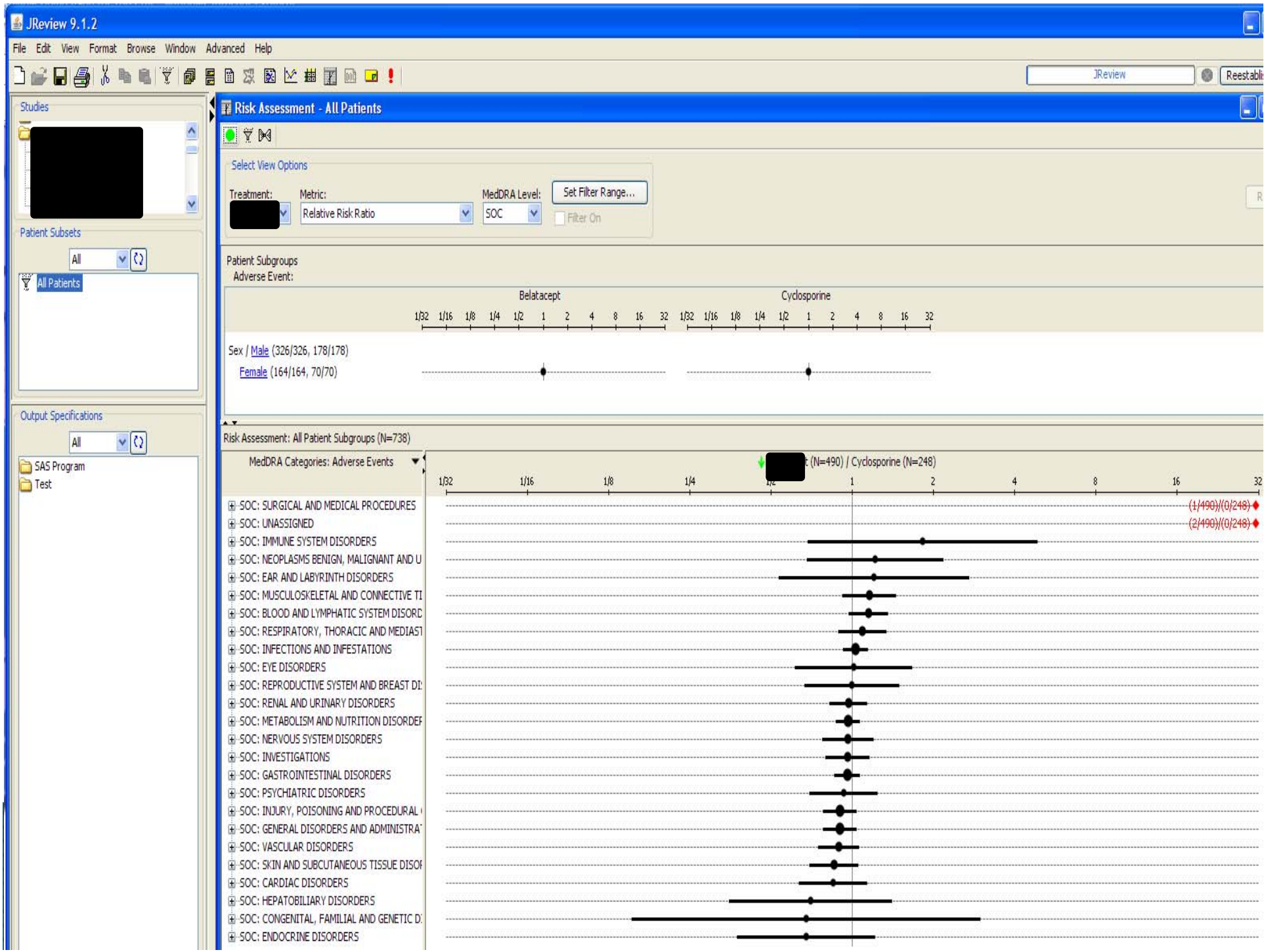
FDA742.0501 Hy's Law Plot

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JReview
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Studies
[redacted]
Patient Subsets
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SAS Program
Test
Risk Assessment - All Patients
Select View Options
Treatment:
[redacted]
Metric:
Relative Risk Ratio
MedDRA Level:
SOC
Set Filter Range...
Filter On
Patient Subgroups
Adverse Event:
Belatacept
Cyclosporine
1/32 1/16 1/8 1/4 1/2 1 2 4 8 16 32
Sex / Male (326/326, 178/178)
Female (164/164, 70/70)
Risk Assessment: All Patient Subgroups (N=738)
MedDRA Categories: Adverse Events
[redacted] (N=490) / Cyclosporine (N=248)
SOC: SURGICAL AND MEDICAL PROCEDURES
SOC: UNASSIGNED
SOC: IMMUNE SYSTEM DISORDERS
SOC: NEOPLASMS BENIGN, MALIGNANT AND U
SOC: EAR AND LABYRINTH DISORDERS
SOC: MUSCULOSKELETAL AND CONNECTIVE TI
SOC: BLOOD AND LYMPHATIC SYSTEM DISORD
SOC: RESPIRATORY, THORACIC AND MEDIAST
SOC: INFECTIONS AND INFESTATIONS
SOC: EYE DISORDERS
SOC: REPRODUCTIVE SYSTEM AND BREAST DI
SOC: RENAL AND URINARY DISORDERS
SOC: METABOLISM AND NUTRITION DISORDEF
SOC: NERVOUS SYSTEM DISORDERS
SOC: INVESTIGATIONS
SOC: GASTROINTESTINAL DISORDERS
SOC: PSYCHIATRIC DISORDERS
SOC: INJURY, POISONING AND PROCEDURAL
SOC: GENERAL DISORDERS AND ADMINISTRA
SOC: VASCULAR DISORDERS
SOC: SKIN AND SUBCUTANEOUS TISSUE DISOI
SOC: CARDIAC DISORDERS
SOC: HEPATOBILIARY DISORDERS
SOC: CONGENITAL, FAMILIAL AND GENETIC D
SOC: ENDOCRINE DISORDERS
(1/490)/(0/248)
(2/490)/(0/248)

SAS Macro Analysis Panels: Division-defined re-usable analyses

Panel	Description of Analysis
Demographics	Produces tables and graphs that show the number and percent of cases that correspond to the demographic variables such as age, race and sex as well as descriptive statistics of the variable age.
Disposition	Details the number and percent of cases that correspond to each disposition category.
Liver	Evaluates specific laboratory measurements that signal the potential for drug induced liver injury (DILI). The analyses include counts/percents of possible Hy's Law candidates; an evaluation of measurements that are major indicators for severe DILI, and graphical analysis of subject's baseline measurement to his/her maximum change in serum measures.
Adverse Events	Provides various analyses to find the most frequent AEs, largest differences in AEs between treatment arms and produce graphs of relative risk/odds ratio.
Enrollment	Produces tables and graphs that details the enrolled study subjects by country and site. In addition demographics, protocol deviations and disposition can be viewed by site.
Exposure	Analyzes exposure on drug such as total number of days on drug, cumulative dose and average daily dose.

Excel Output

Maximum Post-Baseline Lab Tests vs Baseline Lab Tests

NDA/BLA: 12345
Study: 123
Analysis run date: 2011-04-07 1:13:08 PM

ALT Baseline / ALT Maximum	E7389 N= 509									
	ALT < 2x ULN		2x ≤ ALT < 5x ULN		5x ≤ ALT < 10x ULN		10x ≤ ALT < 20x ULN		ALT ≥ 20x ULN	
	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
ALT < 2x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
2x ≤ ALT < 5x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
5x ≤ ALT < 10x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
10x ≤ ALT < 20x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
ALT ≥ 20x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

AST Baseline / AST Maximum	E7389 N= 509									
	AST < 2x ULN		2x ≤ AST < 5x ULN		5x ≤ AST < 10x ULN		10x ≤ AST < 20x ULN		AST ≥ 20x ULN	
	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
AST < 2x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
2x ≤ AST < 5x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
5x ≤ AST < 10x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
10x ≤ AST < 20x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
AST ≥ 20x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

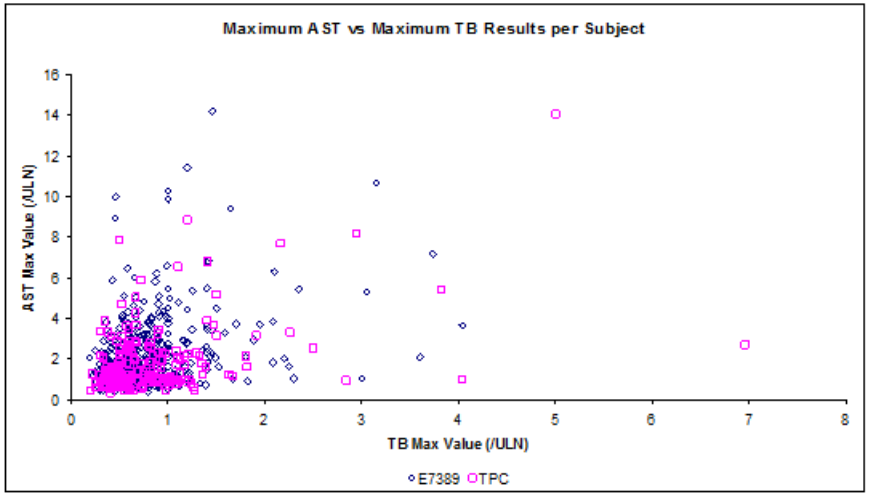
ALP Baseline / ALP Maximum	E7389 N= 509									
	ALP < 2x ULN		2x ≤ ALP < 5x ULN		5x ≤ ALP < 10x ULN		10x ≤ ALP < 20x ULN		ALP ≥ 20x ULN	
	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
ALP < 2x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
2x ≤ ALP < 5x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
5x ≤ ALP < 10x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
10x ≤ ALP < 20x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
ALP ≥ 20x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

E7389

Analysis 4

Maximum AST and ALT vs Maximum TB Lab Test Results per Subject Charts

NDA/BLA: 12345
Study: 123
Analysis run date: 2011-04-27 11:29:30 PM



MAED (MedDRA Adverse Event Diagnostics)

* after SMQ name indicates SMQ with broad terms only. Narrow search will yield no results.

Number in parenthesis before SMQ name represents SMQ level.

P-values should be used for ranking purposes only, not for determining statistical significance.

	Drug A			Drug B					SCREENII
SMQ (Broad Search)	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)	RD (per hundre	RD C.I. (lower boun	RD C.I. (upper boun
(1) Hearing and vestibular disorders	36	35	10.12	133	109	31.32	-21.21	-27.02	-15.39
(1) Anticholinergic syndrome	70	50	14.45	173	127	36.49	-22.04	-28.31	-15.77
(2) Vestibular disorders	35	34	9.83	126	104	29.89	-20.06	-25.8	-14.32
(1) Noninfectious encephalopathy/delirium	37	24	6.94	68	51	14.66	-7.72	-12.3	-3.14
(1) Anaphylactic reaction	76	53	15.32	135	84	24.14	-8.82	-14.7	-2.94
(1) Noninfectious encephalitis	34	21	6.07	60	43	12.36	-6.29	-10.56	-2.01
(1) Noninfectious meningitis	26	19	5.49	53	40	11.49	-6	-10.13	-1.88
(1) Lipodystrophy	17	14	4.05	36	32	9.2	-5.15	-8.83	-1.47
(1) Dementia *	26	18	5.2	42	35	10.06	-4.86	-8.79	-0.92
(1) Acute central respiratory depression	1	1	0.29	10	8	2.3	-2.01	-3.68	-0.34
(1) Dyslipidaemia	20	12	3.47	29	24	6.9	-3.43	-6.72	-0.14
(1) Pseudomembranous colitis	47	39	11.27	72	57	16.38	-5.11	-10.23	0.01
(1) Pulmonary hypertension	1	1	0.29	9	7	2.01	-1.72	-3.3	-0.14
(1) Guillain-Barre syndrome	21	17	4.91	37	30	8.62	-3.71	-7.43	0.02
(2) Hearing impairment	1	1	0.29	7	7	2.01	-1.72	-3.3	-0.14

Introduction SOC HLGT HLT PT **Broad** Narrow

Conclusion

- Rapidly moving towards a modernized, integrated bioinformatics-based review environment
- High quality, standardized data
- Easy data analysis using best practices
- Access to powerful, standard data-based review tools
- Additional efficiency through introduction of business process management

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END