

Interactive Visualization of SEND Clinical Pathology Data Using R Shiny

Paper DV03

PhUSE US Connect 2019

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Silver Spring, MD

February 25, 2019

Disclaimer

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

Outline

- How have clinical pathology data been traditionally represented in toxicology study reports?
- How can dynamic visualization of electronic data aid in the interpretation of clinical pathology data?
- What opportunities has the adoption of electronic data standards, e.g. SEND, by FDA and other organizations created for the collaborative development of dynamic data visualization?
- How can you contribute to open source data visualization software projects via the PhUSE consortium?

What is Clinical Pathology?

- Laboratory test results from samples collected during a nonclinical toxicology study:
 - Hematology
e.g., red blood cell count, hemoglobin concentration, differential white blood cell count
 - Clinical Chemistry
e.g., liver enzyme levels, electrolyte concentrations, glucose, cholesterol
 - Urinalysis
e.g., pH, specific gravity, volume

Traditional Static Tabular Representation of Clinical Pathology Data



TABLE 4
Selected Clinical Chemistry and Urinalysis Data for Group C Rats in the 6-Month Feed Study of Chitosan^a

	0%	1%	3%	9%
Male				
Clinical Chemistry				
n	10	10	10	10
Calcium (mg/dL)				
Week 13	12.6 ± 0.1	12.5 ± 0.1	12.3 ± 0.2	12.4 ± 0.2
Week 19	12.5 ± 0.1	12.3 ± 0.2	12.3 ± 0.1	12.0 ± 0.1*
Week 25	12.1 ± 0.1	12.1 ± 0.2	12.0 ± 0.1	11.6 ± 0.1*
Phosphorus (mg/dL)				
Week 13	8.4 ± 0.3	8.1 ± 0.3	7.2 ± 0.3**	7.4 ± 0.4*
Week 19	8.2 ± 0.4	7.7 ± 0.2	7.4 ± 0.3	6.7 ± 0.2**
Week 25	6.9 ± 0.3	6.8 ± 0.2	6.7 ± 0.1	5.8 ± 0.3**
Cholesterol (mg/dL)				
Week 7	82 ± 5	75 ± 8	80 ± 6	53 ± 3**
Week 13	95 ± 7	84 ± 8	90 ± 7	53 ± 2**
Week 19	101 ± 6	87 ± 10	94 ± 8	59 ± 4**
Week 25	95 ± 6	81 ± 8	90 ± 6	49 ± 4**
Triglycerides (mg/dL)				
Week 7	202 ± 28	234 ± 43	226 ± 30	88 ± 15*
Week 13	198 ± 33	202 ± 38	195 ± 24	86 ± 8**
Week 19	180 ± 26	218 ± 43	210 ± 29	95 ± 13*
Week 25	173 ± 18	207 ± 30	218 ± 24	109 ± 13

Shortcomings of Static Tabular Representation of Clinical Pathology Data



- Difficult to integrate analysis across several independent variables:
e.g., test, treatment, sex, day
- Difficult to assess treatment effects in individual subjects.
- Impossible to assess correlation of treatment effects across tests.
- Difficult to assess relative changes via data transformations:
e.g., percent change from control, change from baseline



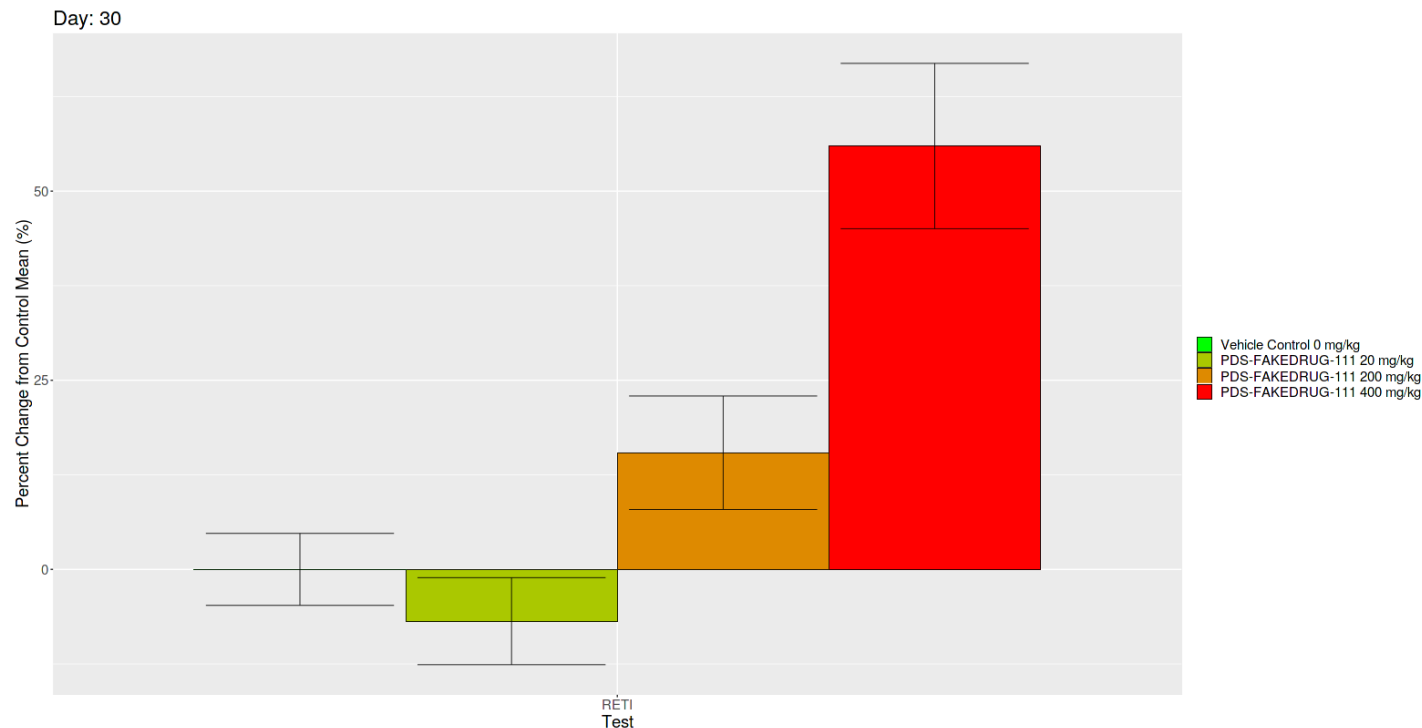
Standard for Exchange of Nonclinical Data (SEND)

- SEND is a data standard created by the Clinical Data Interchange Standards Consortium (CDISC) to enable collection and presentation of nonclinical data in a consistent format.
- In December 2014, the FDA finalized a binding guidance requiring that certain clinical and nonclinical studies be submitted with standardized electronic data, formatted in accordance with the standards recognized in FDA Data Standards Catalog, which currently includes SEND versions 3.0 and 3.1.
 - Clinical pathology data from repeat-dose toxicology and carcinogenicity studies are currently modeled in SEND.

Advantages of SEND-Formatted Clinical Pathology Data



- Tables and figures can be dynamically generated to allow each dataset to tell its own story.

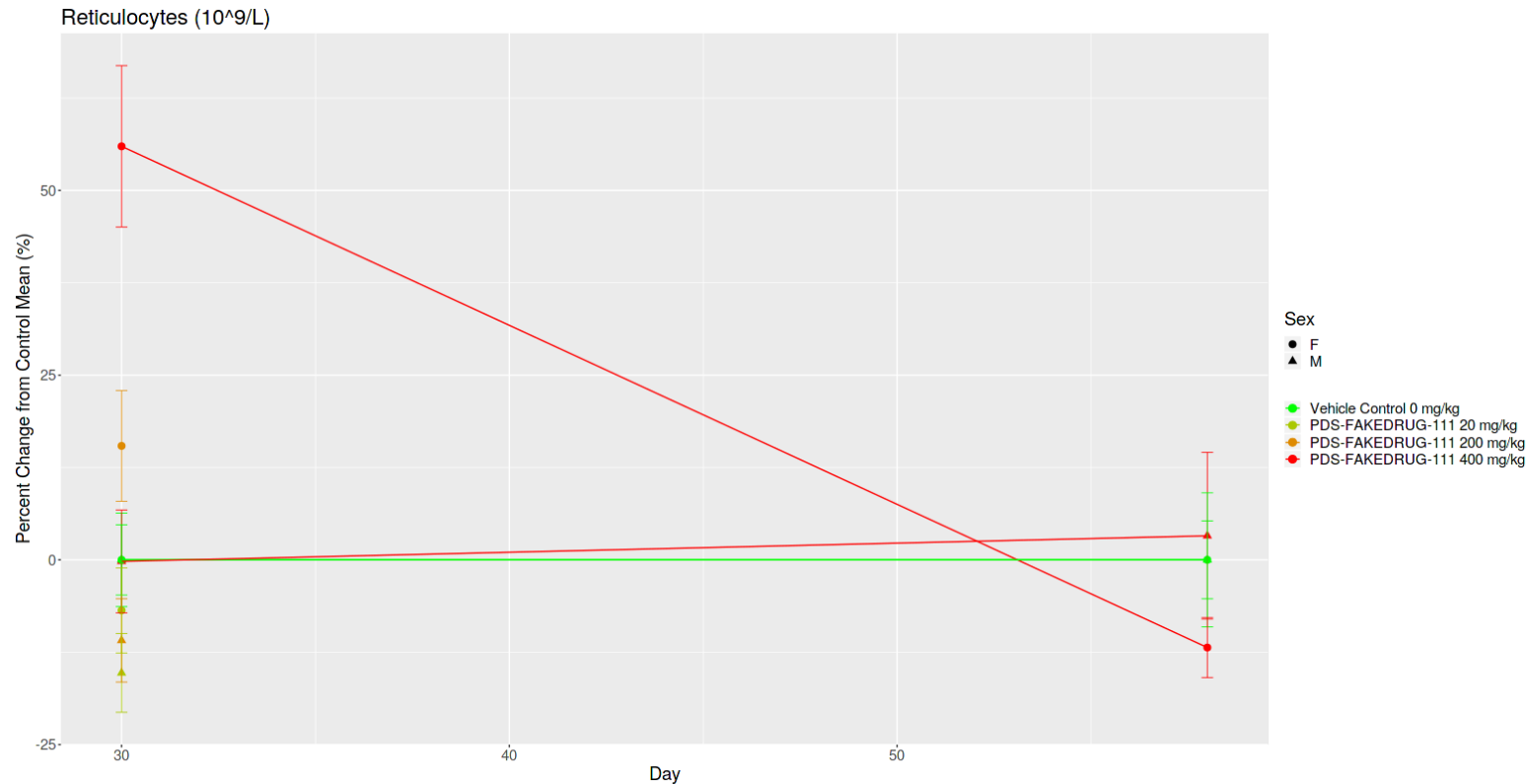


ID	Treatment	Sex	Day	RETI
PDS2014-0161	PDS-FAKEDRUG-111 400 mg/kg	F	30	64
PDS2014-0162	PDS-FAKEDRUG-111 400 mg/kg	F	30	49.4
PDS2014-0163	PDS-FAKEDRUG-111 400 mg/kg	F	30	35.9
PDS2014-0164	PDS-FAKEDRUG-111 400 mg/kg	F	30	62.6
PDS2014-0165	PDS-FAKEDRUG-111 400 mg/kg	F	30	107
PDS2014-0166	PDS-FAKEDRUG-111 400 mg/kg	F	30	13
PDS2014-0167	PDS-FAKEDRUG-111 400 mg/kg	F	30	181
PDS2014-0168	PDS-FAKEDRUG-111 400 mg/kg	F	30	50.9
PDS2014-0169	PDS-FAKEDRUG-111 400 mg/kg	F	30	63
PDS2014-0170	PDS-FAKEDRUG-111 400 mg/kg	F	30	70.1
PDS2014-0171	PDS-FAKEDRUG-111 400 mg/kg	F	30	37
PDS2014-0172	PDS-FAKEDRUG-111 400 mg/kg	F	30	17.9
PDS2014-0173	PDS-FAKEDRUG-111 400 mg/kg	F	30	27.6
PDS2014-0174	PDS-FAKEDRUG-111 400 mg/kg	F	30	19.7
PDS2014-0175	PDS-FAKEDRUG-111 400 mg/kg	F	30	40.8

Advantages of SEND-Formatted Clinical Pathology Data



- Treatment effects can be observed simultaneously across multiple independent variables, e.g. sex and day:

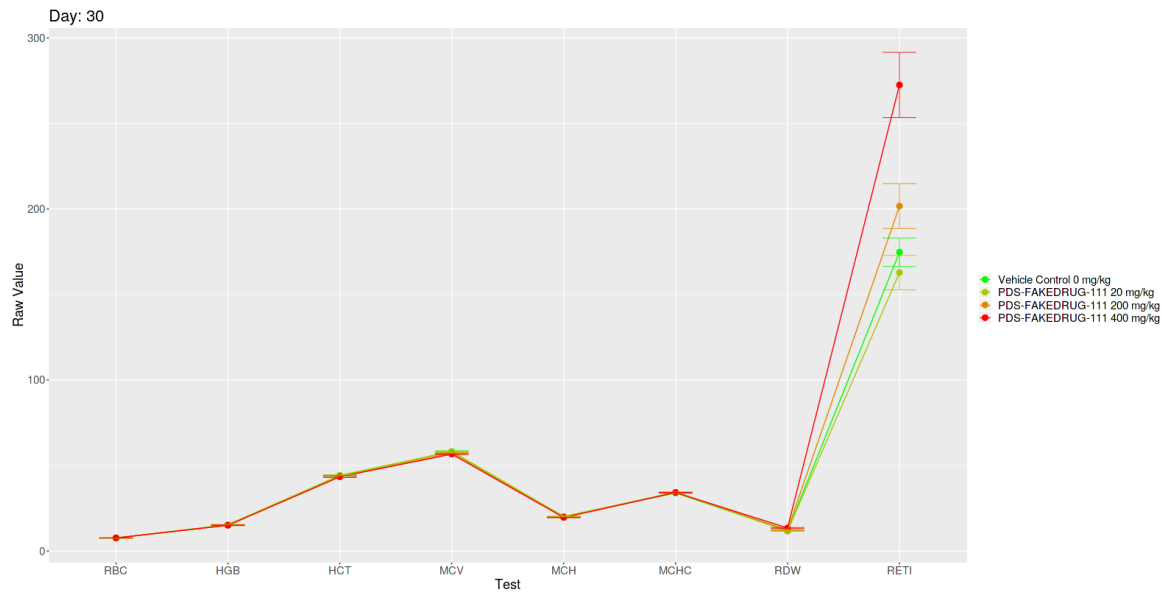


Advantages of SEND-Formatted Clinical Pathology Data



- Data can be transformed (e.g. z-score) to simultaneously assess treatment effects across several tests with vastly different scales.

Un-Transformed

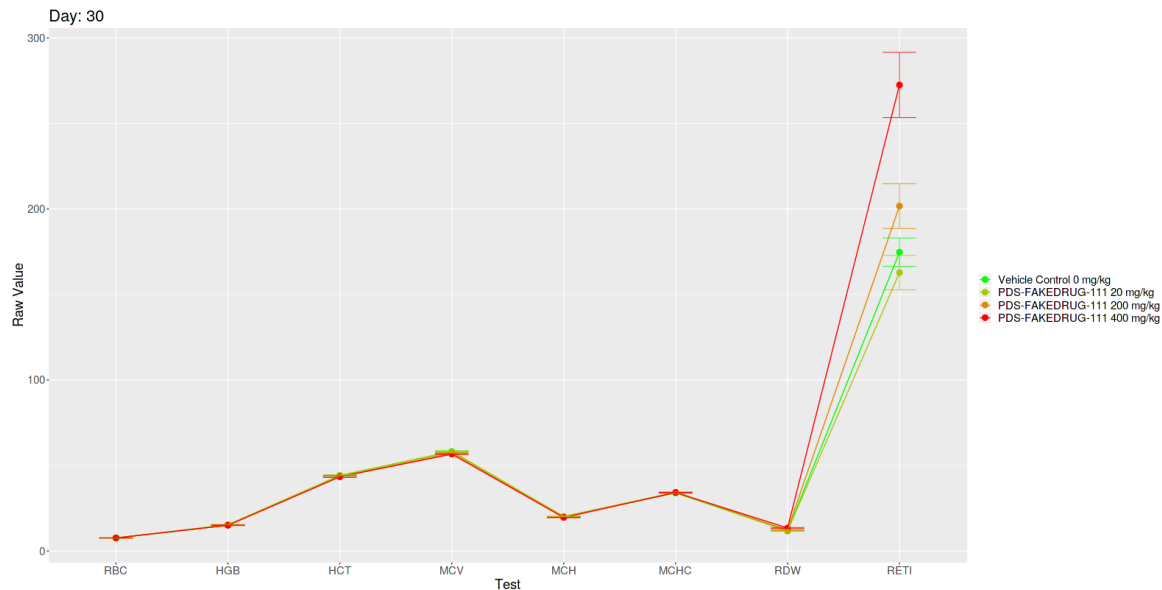


Advantages of SEND-Formatted Clinical Pathology Data

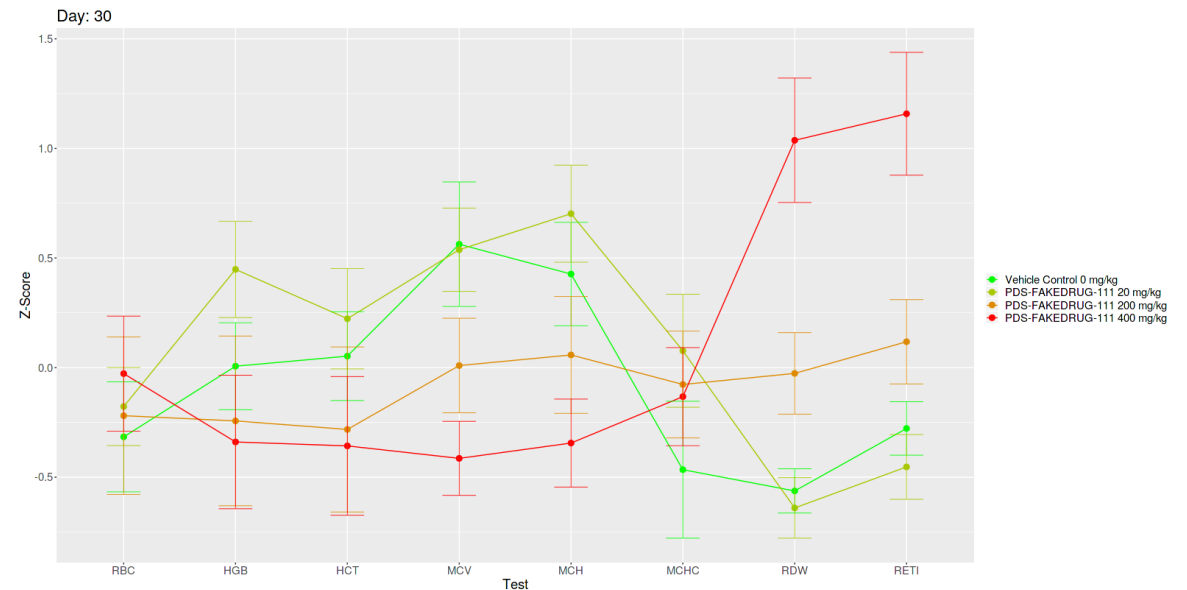


- Data can be transformed (e.g. z-score) to simultaneously assess treatment effects across several tests with vastly different scales.

Un-Transformed



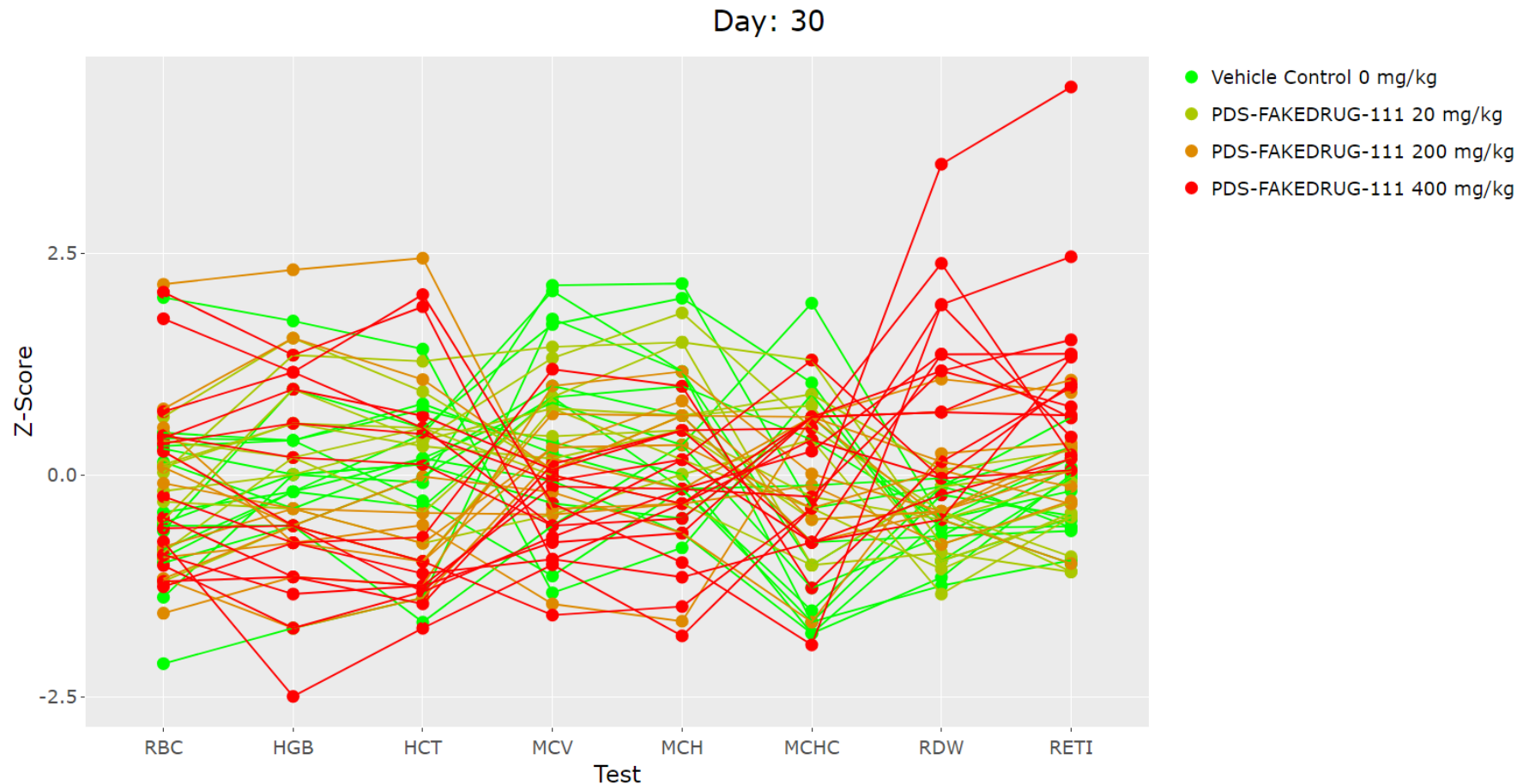
Transformed



Advantages of SEND-Formatted Clinical Pathology Data



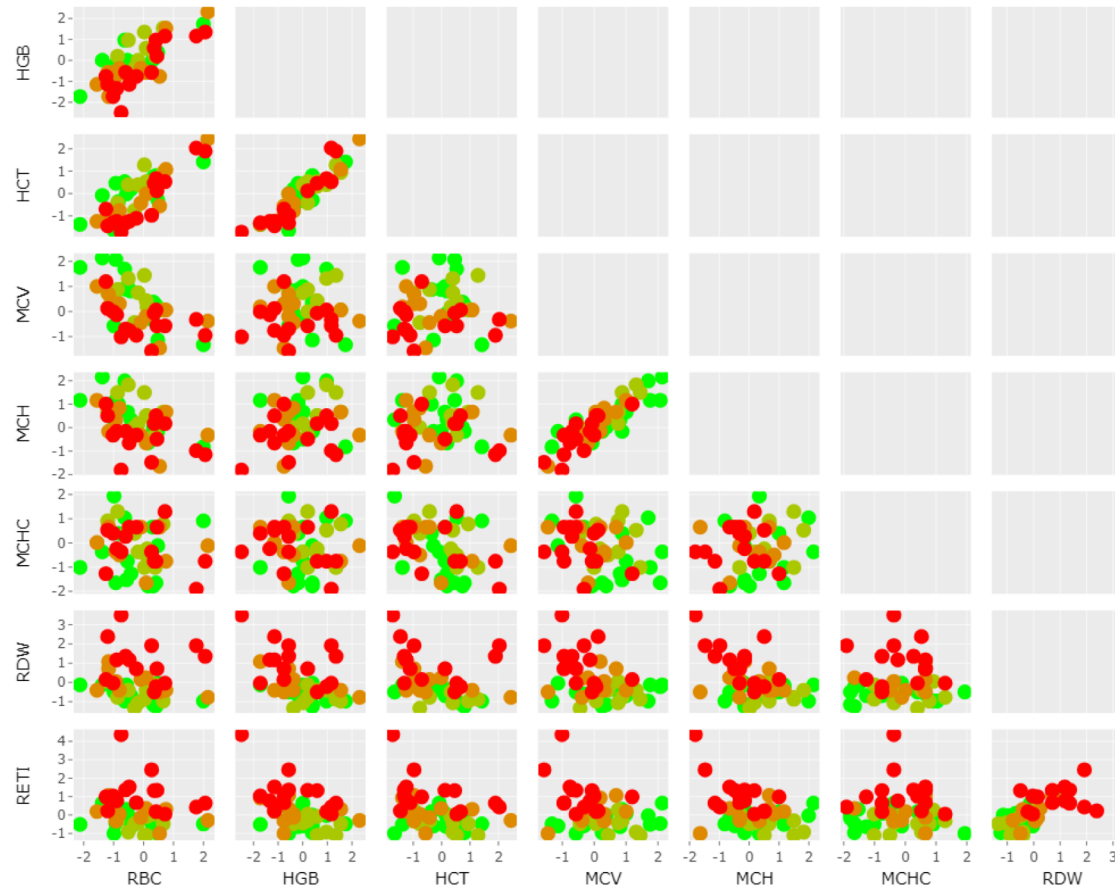
- Evaluate individual subject results simultaneously across tests:



Advantages of SEND-Formatted Clinical Pathology Data



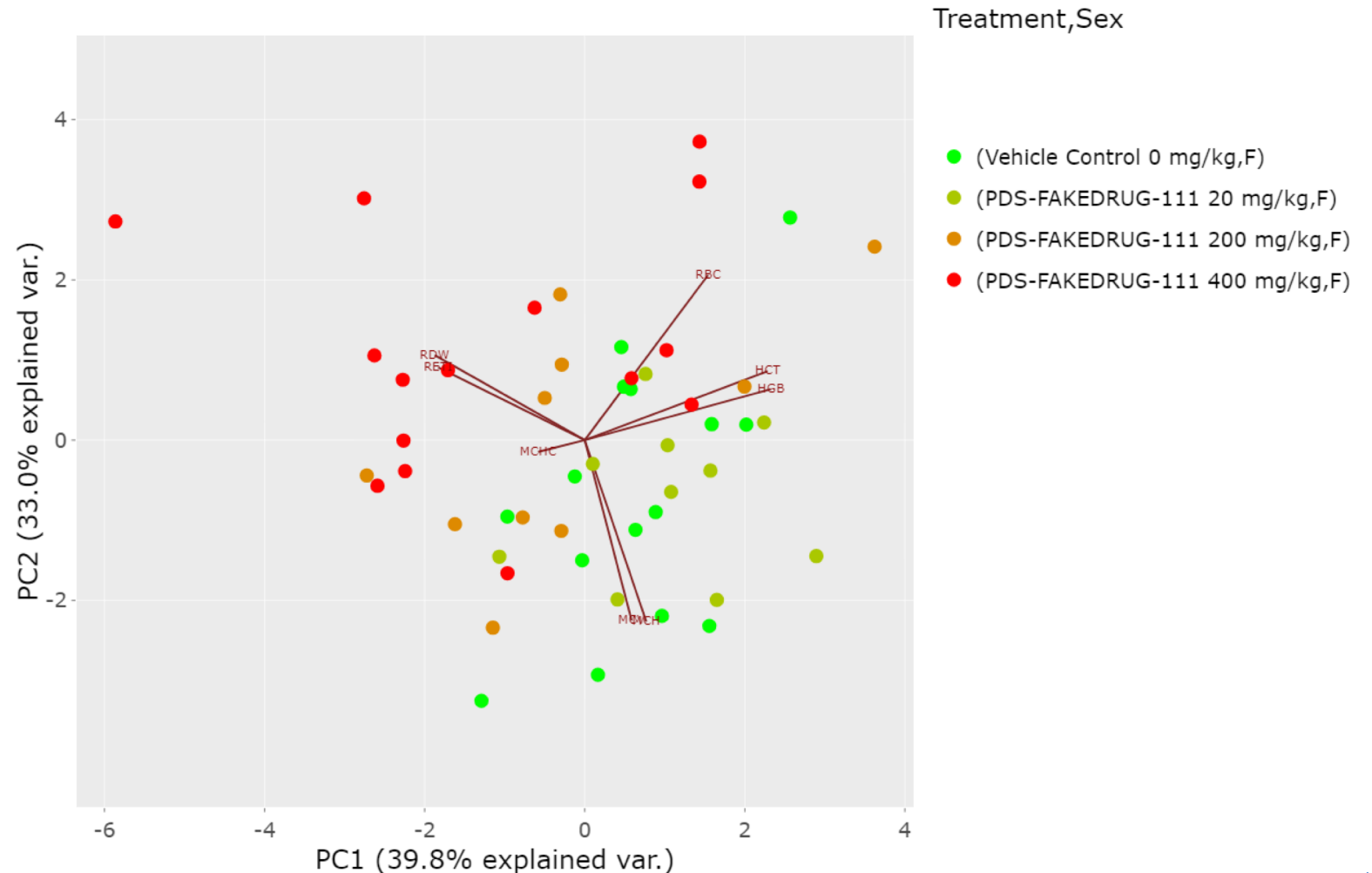
- Evaluate correlations among test results:



Advantages of SEND-Formatted Clinical Pathology Data

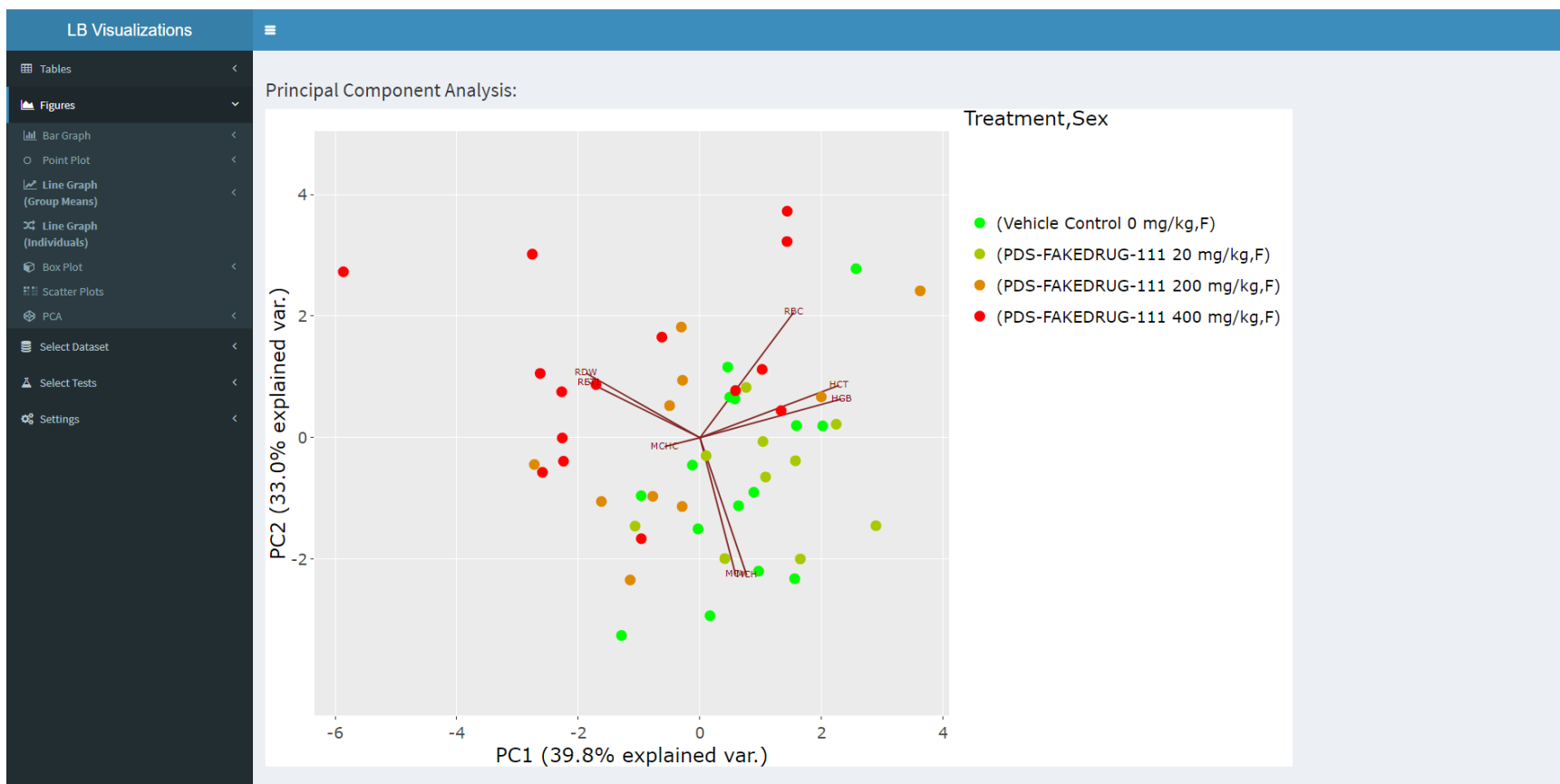


- Employ dimensionality reduction techniques, e.g., principal component analysis (PCA), to evaluate the differences in individuals across a set of test results.



Advantages of SEND-Formatted Clinical Pathology Data

- Open source software can be collaboratively developed via consortia such as PhUSE and used across organizations:



R Shiny Web Application

- R is a free software environment for statistical computing and graphics (<https://www.r-project.org>).
- Shiny is an R package developed by RStudio to enable R programmers to easily build interactive web applications (<https://shiny.rstudio.com>).
- The R Shiny web application is currently hosted on a public R Shiny server provided by RStudio (<https://www.shinyapps.io>).
 - <https://phuse-nonclinical-scripts.shinyapps.io/LBapp>

Application Details

- The application was developed in collaboration with the Pharmaceutical Users Software Exchange (PhUSE) Nonclinical Scripts Working Group.
- The source code for the R Shiny application is available on GitHub:
 - <https://github.com/phuse-org/phuse-scripts/tree/master/contributed/Nonclinical/R/LBapp>

Interested in Collaborating?

- Contact the co-leaders of the PhUSE Nonclinical Scripts Project:
 - Kevin Snyder: kevin.snyder@fda.hhs.gov
 - Bill Houser: william.houser@bms.com
- We are always looking to welcome new team members, and no coding experience is required to join!

Software Demonstration

<https://phuse-nonclinical-scripts.shinyapps.io/LBapp>