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Cross-Study Analyses of SEND Data: Toxicity Profile Classification

M. Carfagna[1] (carfagna.m.a@lilly.com), Cm Sabbir Ahmed[2,3], Md Yousuf Ali[2,3], J. Anderson[2], S. Butler[2,3], T. Fukushima[5], H. Hanafusa[5], W. Houser[6], N. Jensen[7], S. Leuenroth-Quinn[2], B. Paisley[1], K. Snyder[2], R. Thompson[8], S. Vispute[4], W. Wang[6]

[1]Eli Lilly & Co., Indianapolis, IN; [2]US Food & Drug Administration*, Silver Spring, MD*; [3]Oak Ridge Institute for Science and Education, Oak Ridge, TN; [4]Pfizer Inc., Groton, CT; [5]Shionogi & Co., Ltd., Osaka, Japan; [6]Bristol Myers Squibb, New Brunswick, NJ, [7]NovoNordisk, Copenhagen, Denmark; [8]Janssen, Spring House, PA.

Introduction

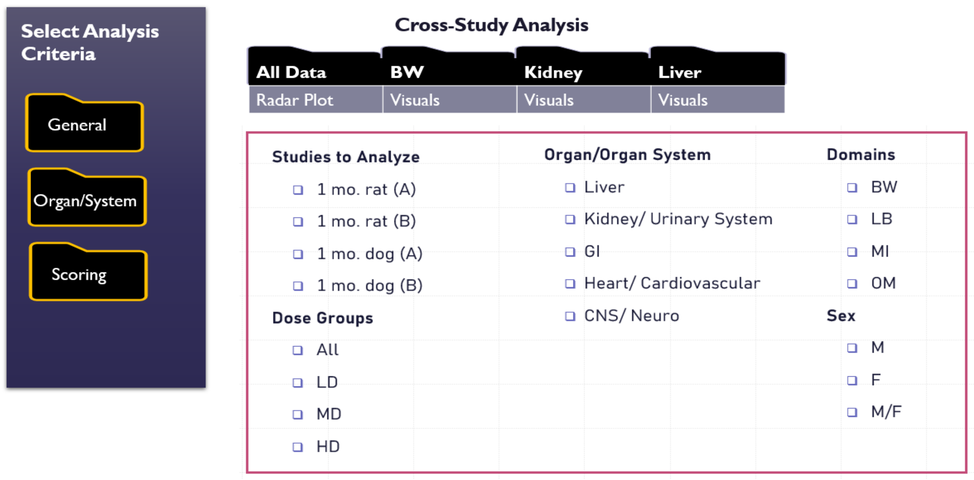
A collaboration between BioCelerate and US FDA CDER is developing analytic techniques to compare the toxicological findings of two or more studies using their SEND datasets for purposes such as: 1) understanding a single compound's toxicity profile across multiple studies, 2) evaluating on-target versus off-target toxicity for multiple compounds intended for the same pharmacological target. Toxicity profiles for key organ systems (liver, kidney, brain/neuro, GI tract, lungs) are presented as radar plots based on user-defined scoring and weighting of data from the body weight (BW), organ weight (OW), microscopic (MI), and laboratory (LB) domains. An example analysis using de-identified studies from the BioCelerate Toxicology Data Sharing (TDS) database contributed by different companies on separate compounds intended for the same pharmacological target, are proposed in the poster. Cross-study comparisons tools using SEND data are expected to improve the identification of unique findings related to the intended target, species and duration of dosing.

BioCelerate Member Companies

Bristol Myers Squibb
Boehringer-Ingelheim
Eli Lilly
Janssen
NovoNordisk
Shionogi
Pfizer

Methodology

Figure 1. Simulated Cross-Study Visualization Application Dashboard



Key Organ System Grouping: Toxicologically important target systems were identified and data relevant to the system were structured to perform focused analyses. Domains used for data analysis were BW, LB, MI and OM.

Data were normalized and transformed to enable cross-study comparisons by calculating Z-scores.

Scoring: SEND datasets were loaded into R and scored relative to the control animals of their respective studies in the LB, MI, and BW domains. MI is scored through a combination of incidence and severity where low severity findings occurring in 50% or more of animals results in a top score of 3. LB, and BW domains are scored through their relative zscore per column where a zscore between -1 and 1 is 0, and an absolute value zscore change of 3 or greater is 3.

A Rshiny app is being developed to display the visualizations of domain per group as highlighted below. This app will allow the user to control aspects of the scoring algorithm and visualizations.

Results

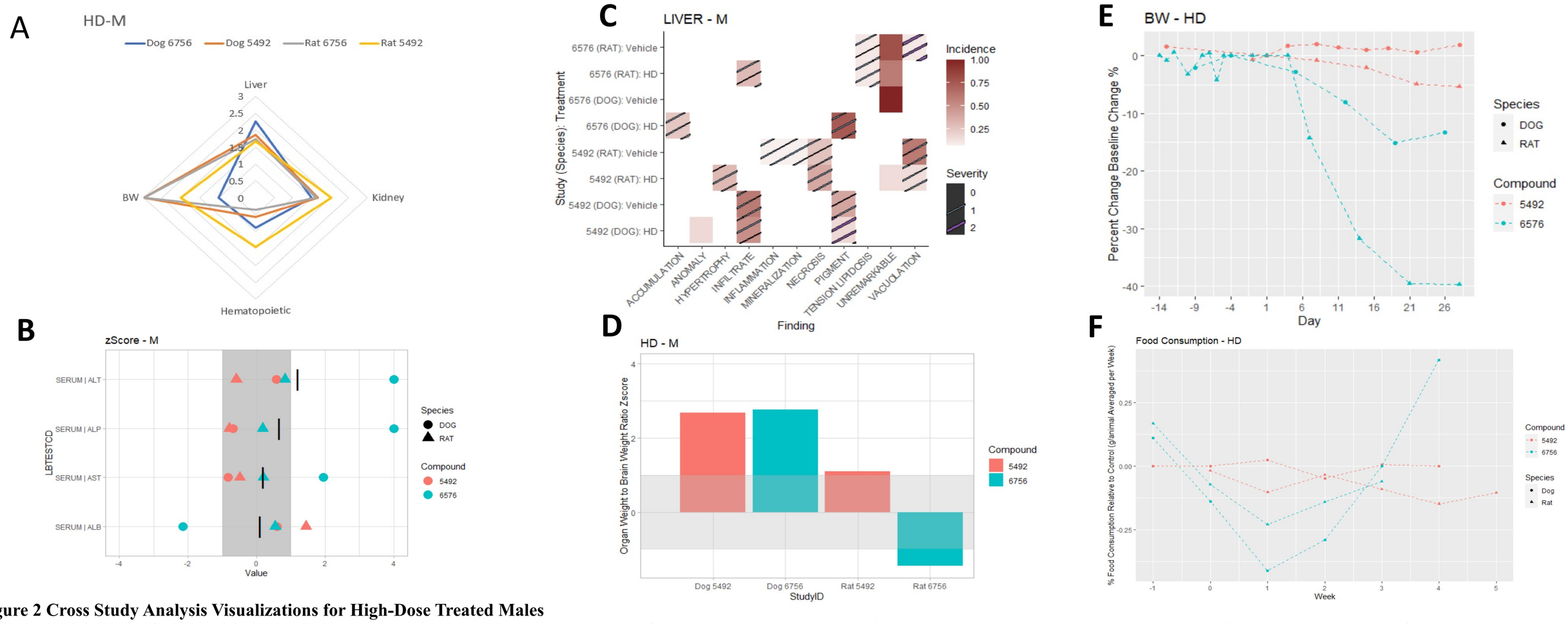


Figure 2 Cross Study Analysis Visualizations for High-Dose Treated Males

A) Displays high-level score for body weight (BW) and 3 key organ systems (Liver, Kidney, and Hematopoietic) for high-dose males in two paired dog/rat repeat-dose toxicity studies. Decreases in body-weight (BW) create high score values for animals treated with compound 6756 **B)** Clinical chemistry zscore of four studies with average across the values displayed as a black bar. The gray region in the back indicates zscore within -1 to 1 indicating a non-significant change**. C)** Heatmap visualization of incidence and severity of microscopic findings (MI) for liver. **D)** Liver organ weight ratio to brain zscore change relative to control. The gray region in the back indicates zscore within -1 to 1 indicating a non-significant change, showing that Rat 6756 had a significant decrease in liver organ weight. **E)** Paired plots of BW and food consumption over the duration of the study. Comparison allows for the acknowledgement that compound 6756 treated animals displayed a recovery in food consumption in the later weeks of the trial that corresponded with some weight recovery in dogs.

Summary and Conclusions

- Data transformation enabled cross study analysis by facilitating comparisons of domains between studies from different species
- A user defined scoring system was developed to visualize trends and differences between multiple studies
- These types of analyses extract additional information from SEND data beyond single study evaluations.
- This type of analysis can be used to detect target related effects and/or changes in toxicity profile with different dosing periods.

*This Poster reflects the views of the authors and should not be construed to represent FDA's views or policies.