

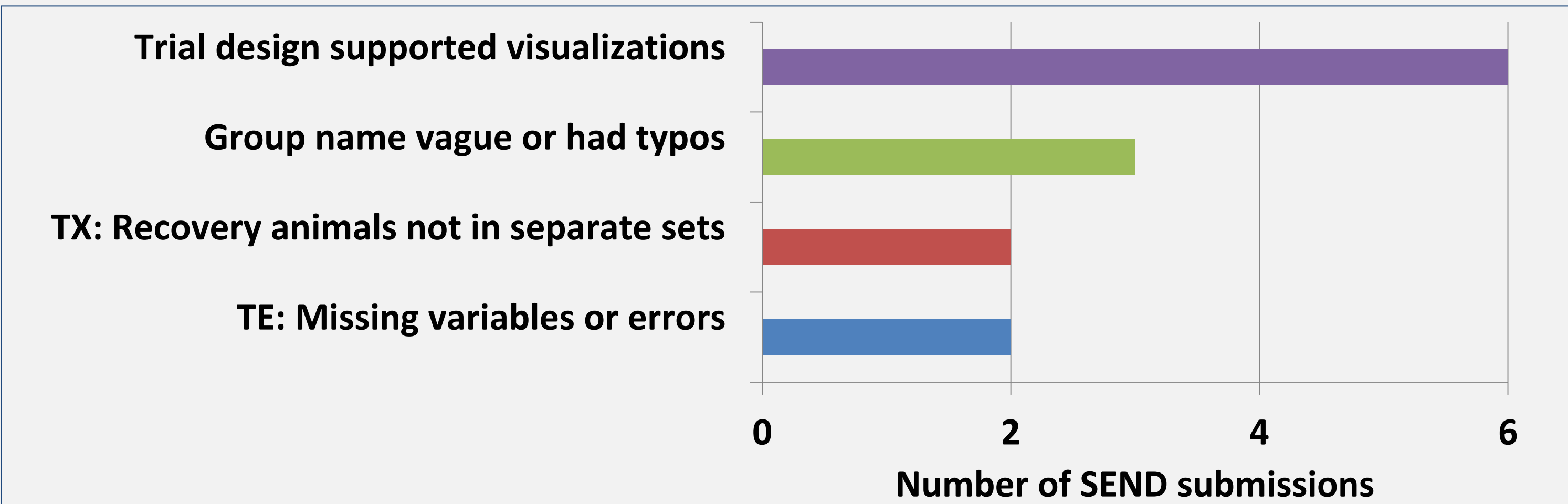
Elaine Thompson, Ph.D., Paul Brown, Ph.D., Patricia Brundage, Ph.D., Robert Dorsam, Ph.D., David Epstein, Jessica Hawes, Ph.D., Belinda Hayes, Ph.D., John Ho, Imran Khan, Ph.D., Stephanie Leuenroth-Quinn, Ph.D., Timothy McGovern, Ph.D., Matthew Whittaker, Ph.D., Lilliam Rosario, Ph.D.

FDA/CDER
Silver Spring, MD

Abstract

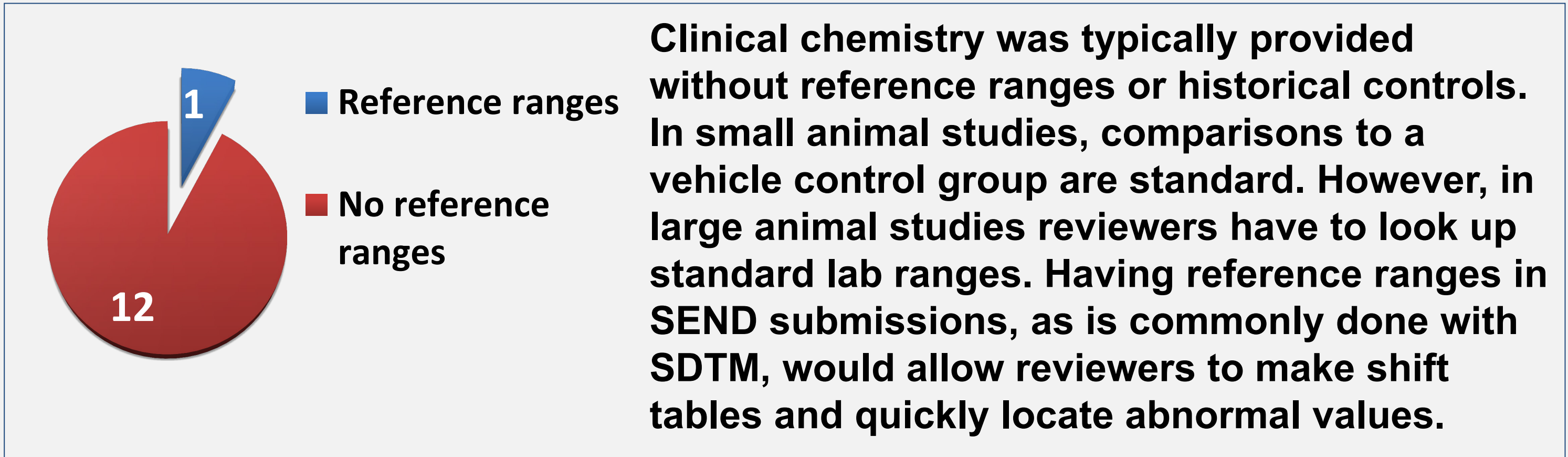
To evaluate readiness to receive nonclinical toxicology data in the SEND 3.0 standard, FDA/CDER initiated a community pilot. Thirteen stakeholders submitted studies in SEND, and FDA provided data fitness assessments and examined the suitability of tables, graphs, and visualizations for review. The quality and integrity of the trial design datasets, study findings, nonclinical Study Data Reviewer’s Guide (nSDRG), and define.xml were assessed. Most submissions had sufficient data integrity. It was usually straightforward to reproduce sponsor tables from numeric findings, but qualitative data like histopathology and clinical observations could benefit from further refinement in both standards and implementation. All but one data set lacked reference ranges for clinical chemistry (LB), and extracting and using data from the plasma concentration (PC) domain was difficult in many of the data sets. The quality and utility of the nSDRGs was high. Overall, we have established that SEND 3.0 can successfully support FDA regulatory submissions.

Trial Design

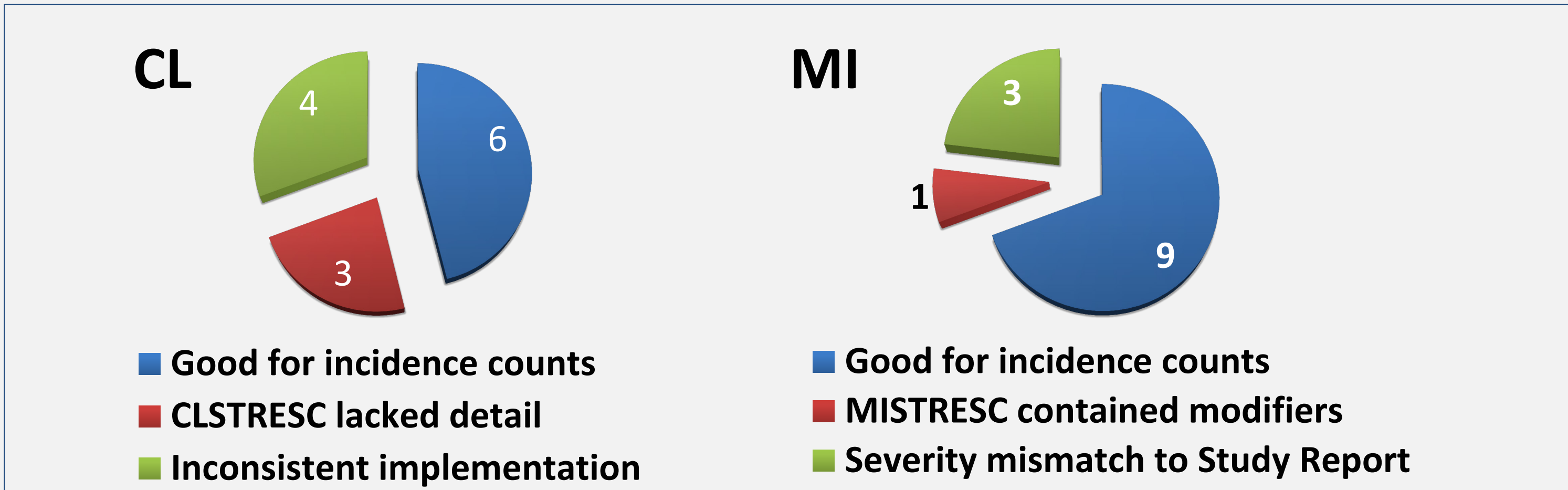


Close adherence to the trial design model provided in the SENDIG is important for visualization. Group names are displayed in software, so providing meaningful names like “5 mg/kg/day Recovery” rather than “Group 4” is helpful. Animals in recovery or toxicokinetic groups are easiest to identify for tables and charts when they are presented in separate trial sets.

Clinical Chemistry (LB)

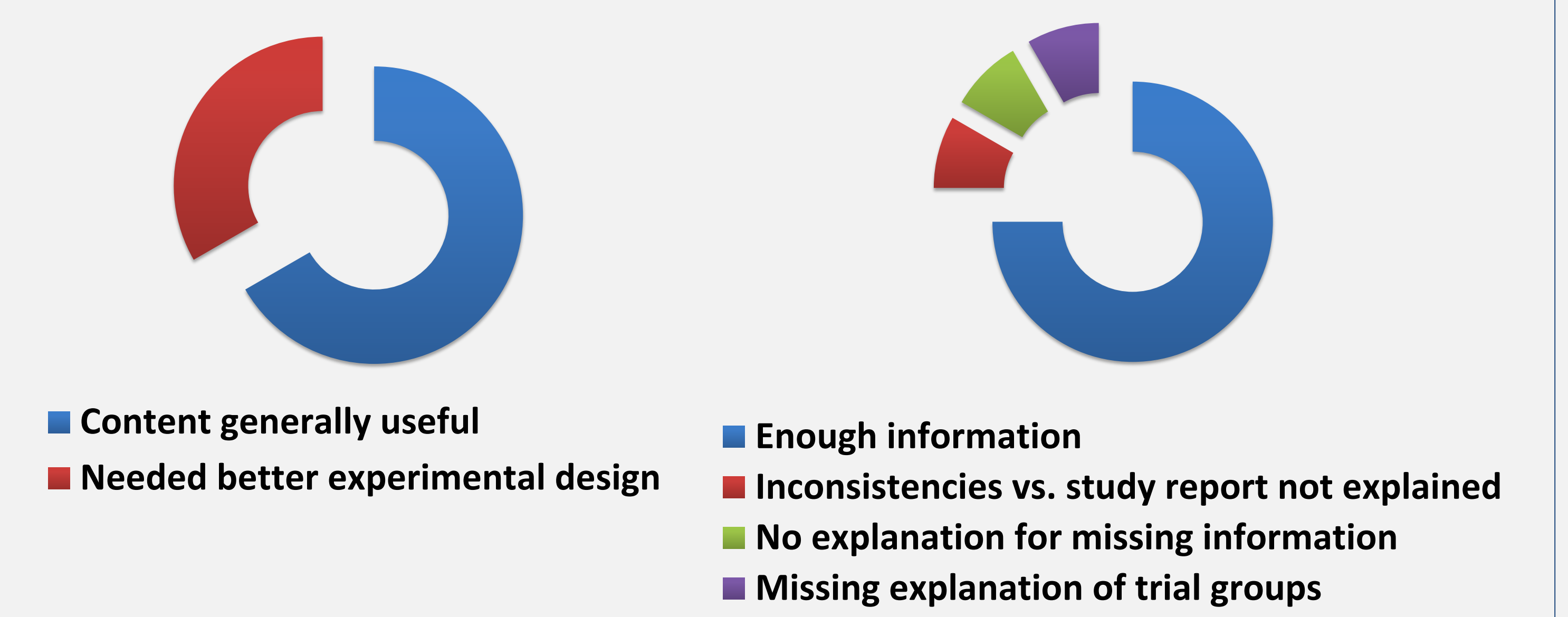


Qualitative Findings (CL, MI, MA)



Visualizations of histopathology (MI), gross pathology (MA), and clinical observations (CL) are typically made from incidence counts over --STRESC. Findings and severities must be converted to SEND carefully for incidence tables to accurately reflect study findings. SEND 3.1 will improve MI with controlled terminology, but MA, MI, and CL could all benefit from implementation improvements.

Nonclinical Study Data Reviewers Guide

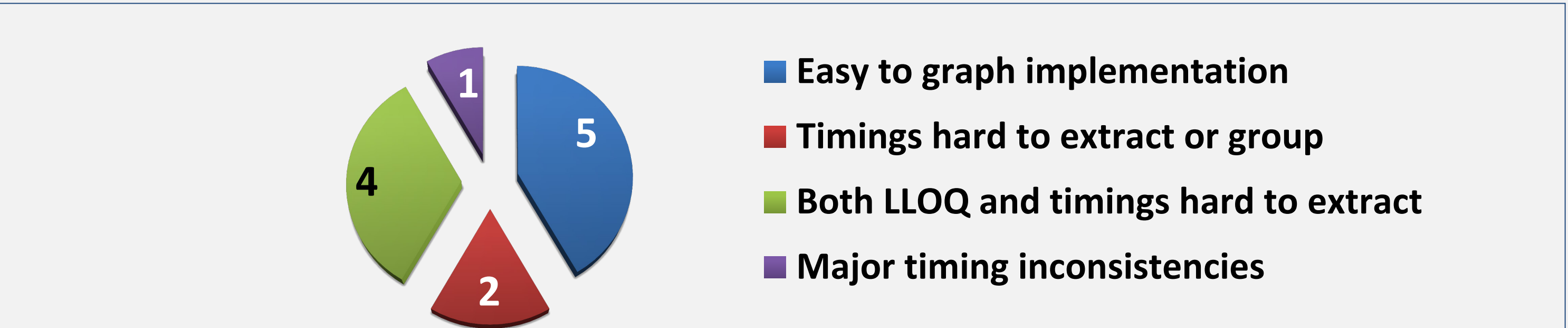


Overall, reviewers thought the information in the nSDRG was useful and valuable to understanding the SEND data, particularly in several sections:

- Experimental design information in Section 2.1
- Trail design domain table/diagram in Section 2.2
- Explanation of nonstandard terminology in Section 3.3
- Dataset summary in Section 4.1
- Differences between the SEND dataset and study report in Section 6.2

Although the information in some sections may not be immediately applicable to review, it is useful to data managers when troubleshooting a SEND submission is necessary. (e.g., Section 3.1 and Section 5).

Pharmacokinetics (PC)



The PC domain proved to be the most challenging numeric domain to visualize. Graphing and calculating pharmacokinetic parameters requires

- Nominal timings in numbers or ISO 8601 times with no nulls
- Clear timing of each time series relative to the dose
- Unambiguous grouping of each time series

Many of the pilot PC domains required human intervention to graph or calculate pharmacokinetic parameters. More work is needed on the standard.

Conclusions

The Fit for Use pilot was very valuable. FDA was able to test our software and KickStart service, improve the Technical Conformance Guide and increase our readiness for SEND submissions. Findings from the pilot are being used to charter efforts at CDISC and PhUSE to improve the MI, MA, PC, and CL domains in SEND, and to provide feedback to the NSDRG PhUSE workstream.

Detailed findings from Fit for Use are publically available on the CDISC website. <http://wiki.cdisc.org/display/NSFFUW/Nonclinical+%28SEND%29+Fit+for+Use+Workstream+Home>

Acknowledgements

Thank you to all the participants who provided data sets: AbbVie, Bristol-Meyers Squibb, Celgene, Eisai, Genentech, GlaxoSmithKline, Janssen, Eli Lilly, Merck & Co., MPI Research, Novartis, Pfizer, and Sanofi; and to CDISC and PhUSE.

Disclaimer

The information in these materials is not a formal dissemination of information by FDA and does not represent agency position or policy.