Talking Tox When Others Don't "Speak the Language"

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This presentation represents my personal views and not necessarily those of my employer.

When You Don’t Speak “Tox”

Executive Summary

- Toxicologists are key members of program teams (PTs)
  - PTs drive the strategy and operations of a drug development program; the toxicology package is relevant to major program decisions and deliverables
- Remember that on cross-functional teams not everyone speaks “tox”!
  - Keep terms clear and simple to make the material easier to understand
  - Assume your audience has limited subject matter knowledge – limit acronyms and welcome “silly” questions
- When preparing data presentations, limit content to the key data needed to make a decision and your interpretation of the results
  - Include an executive summary slide, key take aways/conclusions, and next steps
  - Include context about why the study was run
  - Use your program manager (PM) as a resource!

What is a Program Team?

- A program team (PT) is a cross-functional team made up of Subject Matter Experts from different departments working together to advance the program
- The PT is responsible for the development and execution of operational program plans
  - Generates an integrated timeline across the functions to track milestones such as Investigational New Drug (IND) submission
- The toxicologists' contributions to the PT vary by program stage
  - For pre-clinical programs, toxicologists help drive safety studies to determine initial dosing for pivotal tox and work closely with discovery groups and Chemistry, Manufacturing and Controls (CMC)
  - For clinical stage programs, toxicologists work closely with clinical development, clinical pharmacology, and regulatory and contribute to the briefing books and investigational brochures
- Clear communication is essential regardless of the program stage
  - Keep the PM in the loop as they can help bridge communication gaps and help with any follow up

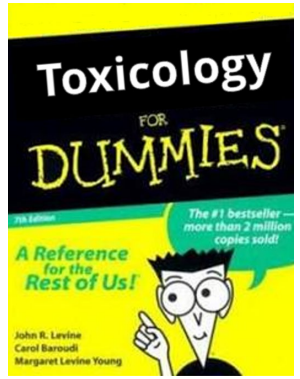
The PM Helps Facilitate Communication

What is the role of a program manager (PM)?

- The PM's role is to support the program lead and the overall operations of the program team
- The PM is an integral member of the program team that helps facilitate communication and ensures all cross-functional team members are on the same page
  - The PM can help document decisions and follow up on action items to ensure all members are working together toward the next timeline milestone

Cross-Functional Teams Require Clear and Simple Communication

- Program teams are cross functional so not everyone speaks “tox”
- Team members view toxicology content as complex and difficult to understand
- Communication is more effective when toxicologists follow some best practices:
  - Use simple terms
  - Explain the background – why is data this important? Why should PT members care?
  - Be receptive to answering even “silly” questions – make it approachable
  - Ask for help from your program manager/program leader to facilitate the conversation



Data Presentations are More Impactful When Designed with a Cross-Functional Audience in Mind

- **Include an "executive summary" slide**
  - Include the objectives of the discussion – why do team members need this information?
  - If feedback is needed, include the key questions here
- **Explain the study objective and design as simply as possible**
  - Why did we conduct the study? What will this inform?
  - Is this a standard study design?
- **Summarize the data – the team does not need to know everything just what affects key decisions**
  - Are the results what you expected – why or why not?
  - Encourage questions (even "silly" ones!) to engage the audience

Data Presentations are More Impactful When Designed with a Cross-Functional Audience in Mind

- **Provide key take aways and conclusions**
  - What do these conclusions mean to the team and why do they need to know them?
  - How does this impact program strategy and timelines?
- **Provide any next steps**
  - Does this inform subsequent studies? Does anything need to be repeated?
  - Do the next steps require cross-functional input (e.g., regulatory help submitting a special protocol assessment)?
- **Don’ts**
  - Do not use too many acronyms (but spell out the words when you do)
  - Do not have too many data slides – can add them to appendix/back-up for support

Provide Objective and Study Design
Example: DRF Study

Why do we need to do this study?
To get a general sense of adverse events and help determine the doses for our 28D IND enabling tox study

Objective:

- Dose range finding (DRF) to determine the potential toxicity of drug-x when administered once daily by oral gavage to rats for 14 days. In addition, the toxicokinetics (TK) will be determined

Spell out acronym

- **Table can be used to show study design**

Summarize Results at a High Level and Include Conclusion Statement

- Summarize results at high level in a table

Parameter	Low Dose	Mid Dose	High Dose
Moribundity/Mortality	**Note differences vs control so team can get a general sense of adverse events to narrow the dose level for the IND enabling tox study.** **If there is no difference, then note no change.**		
Clinical Observations			
Body Weight			
Food Consumption			
Hematology			
Coagulation			
Serum Chemistry			
Urinalysis			
Gross Pathology			
Organ Weights			

Too much detail for the audience

Dose group	Vehicle	Low Dose	Mid Dose	High Dose
Males-Dose Levels	0 mg eq./kg/day	5 mg eq./kg/day	15 mg eq./kg/day	30 mg eq./kg/day
No. of animals	15	10	10	15
Thymus	0.403 ± 0.118	0.295 ± 0.077 *	0.159 ± 0.063 **	-
Spleen	0.730 ± 0.324	0.07	0.564 ± 0.105	-
Testes	3.23 ± 0.27		2.76 ± 0.52 *	-
Prostate	0.856 ± 0.173		0.629 ± 0.120 **	-
Females-Dose Levels	0 mg eq./kg/day		5 mg eq./kg/day	10 mg eq./kg/day
No. of animals	15	10	10	15
Thymus	0.396 ± 0.118	0.301 ± 0.075 *	0.190 ± 0.070 **	-
Spleen	0.483 ± 0.051	0.433 ± 0.046	0.405 ± 0.056 **	-

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

https://doi.org/10.1371/journal.pntd.0007026.t008

Lachau-Durand S, Lammens L, van der Leede BJ, Van Gompel J, Bailey G, Engelen M, Lampo A. Preclinical toxicity and pharmacokinetics of a new orally bioavailable flubendazole formulation and the impact for clinical trials and risk/benefit to patients. PLoS Negl Trop Dis. 2019 Jan 16;13(1):e0007026. doi: 10.1371/journal.pntd.0007026. PMID: 30650076; PMCID: PMC6334931.

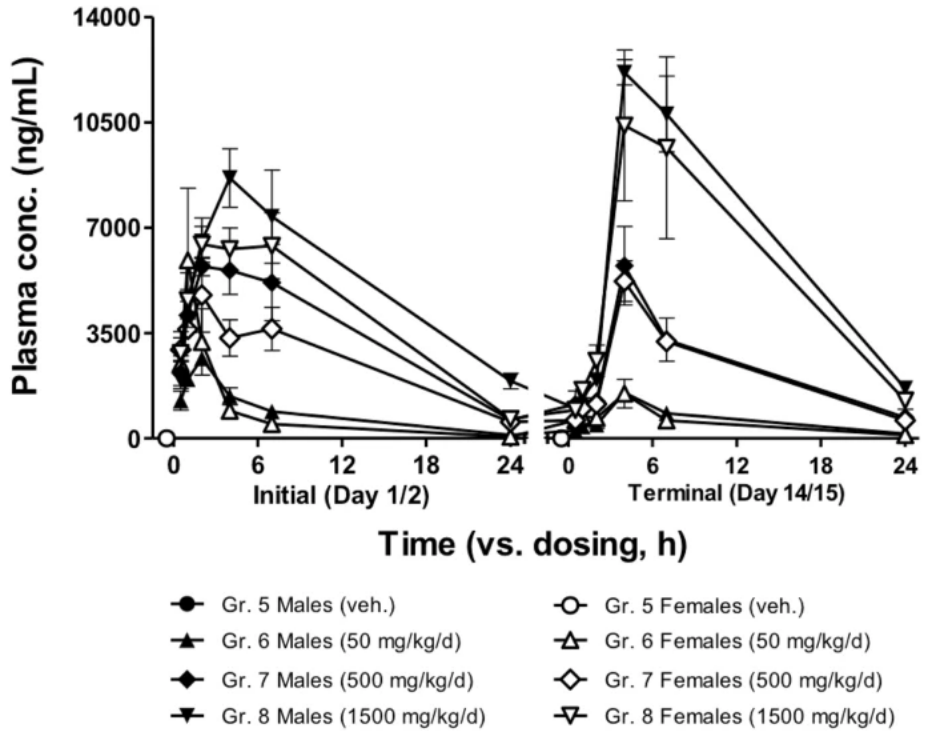
- Add a conclusion statement – what do these results mean to the team?

Summarize Results at a High Level and Include Conclusion Statement

- Include high-level summary graph

Speak to the graphs.
What are we looking at?
Acute toxicity and determine whether dose accumulation occurs by performing toxicokinetic (TK) analysis on the first and last days of dosing

Figure 1



Bioanalytical results from satellite animals.

Sibley, K., Chen, J., Koetzner, L. *et al.* A 14-day repeat dose oral gavage range-finding study of a first-in-class CDI investigational antibiotic, in rats. *Sci Rep* **9**, 158 (2019). https://doi.org/10.1038/s41598-018-36690-9

- Add a conclusion statement – what do these results mean to the team?