Sensitivity Analysis of Attrition in Pharmacokinetic Samples in Rapid Acting Psychedelics: A Simulation-Based Study

Presenter

Nathan Patrick Burns, PhD

Co-authors

Pau Aceves Baldo, MPharm, MSc
Rachael MacIsaac, PhD

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Background & Rationale

- Psychedelics are a class of psychoactive compounds that produce rapid and profound alterations in perception, cognition, and consciousness. Often characterised by a fast onset of action and a short T_{max}, usually occurring within minutes of administration.

- Clinical trials include a comprehensive schedule of post-dose assessments, including collection of blood serum samples to characterise the pharmacokinetics (PK) of the investigational product.

- Missing collection samples can occur in any trial despite industry standard mitigation procedures. **However, sample missingness in rapid-acting compounds such as, but not limited to, Psychedelics is an under-studied methodological challenge that warrants formal evaluation.**

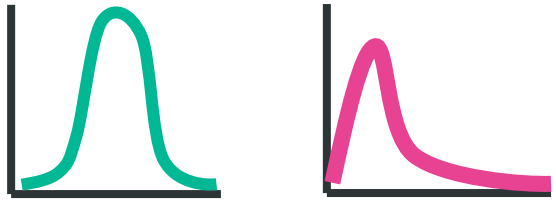
- Given the regulatory importance of accurately calculating PK parameters, a formal statistical evaluation is warranted **to quantify the potential impact of any missing collection sample** as well as **classify whether some missing collection timepoints are more sensitive to estimation errors.**

Abbreviations: PK = Pharmacokinetic; NCA = Non-compartmental Analysis; T_{max} = Time of occurrence of max concentration..

Aims

1. Simulate PK profiles for two Rapid-Acting Compounds

Achieved by sampling 10,000 subjects from following PopPK distributions:



Compound A
T_{max} = 5 min

Compound B
T_{max} = 2 min

2. Quantify PK Errors When Collection Samples Are Missing

Achieved by removing collection samples, re-estimating PK parameters using NCA, and calculating resultant error.

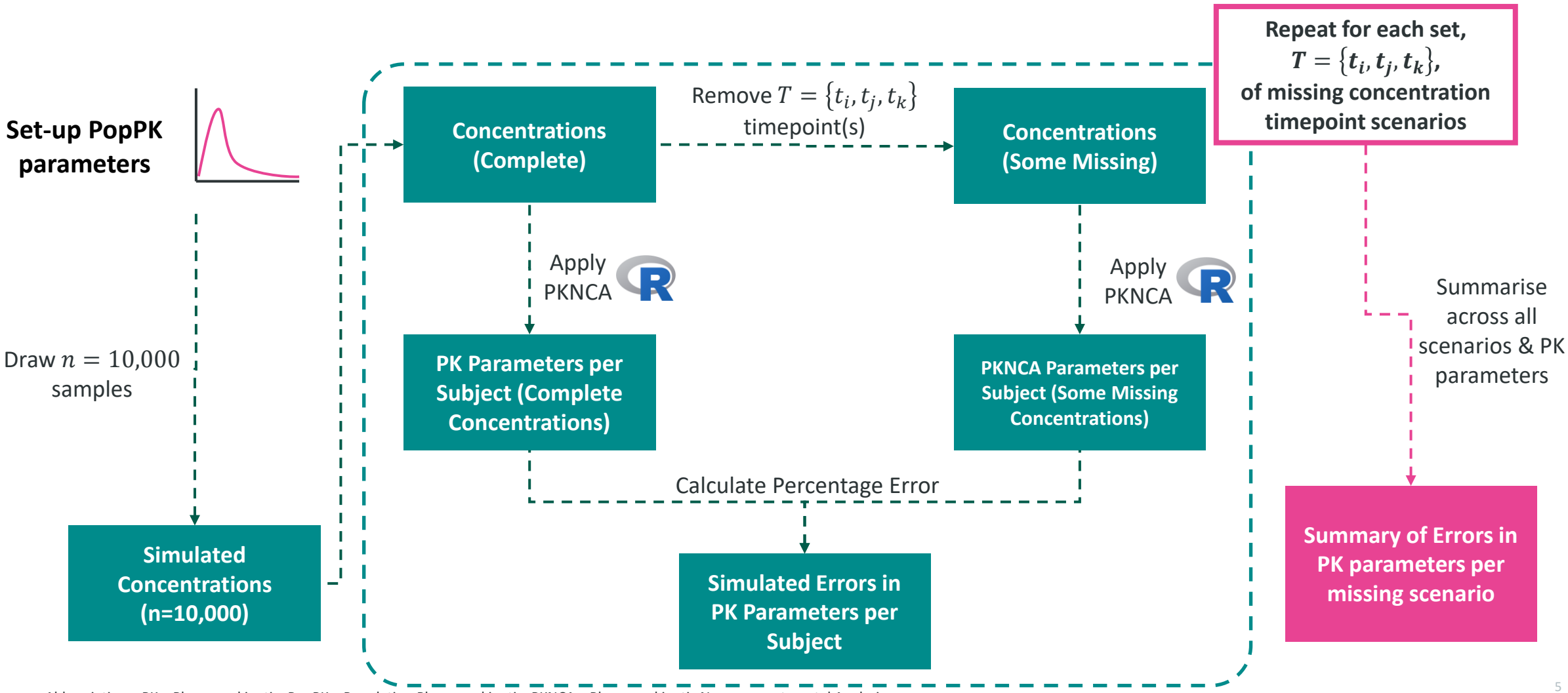
3. Classify Collection Windows Which Are Sensitive to Errors

Achieved by specifying an error threshold to classify acceptable/undesirable errors when particular collection samples are missing.

Abbreviations: PK = Pharmacokinetic; PopPK = Population Pharmacokinetic;NCA = Non-compartmental Analysis; T_{max} = Time of occurrence of max concentration..

Simulating Missing Collection Timepoints and Quantifying Errors

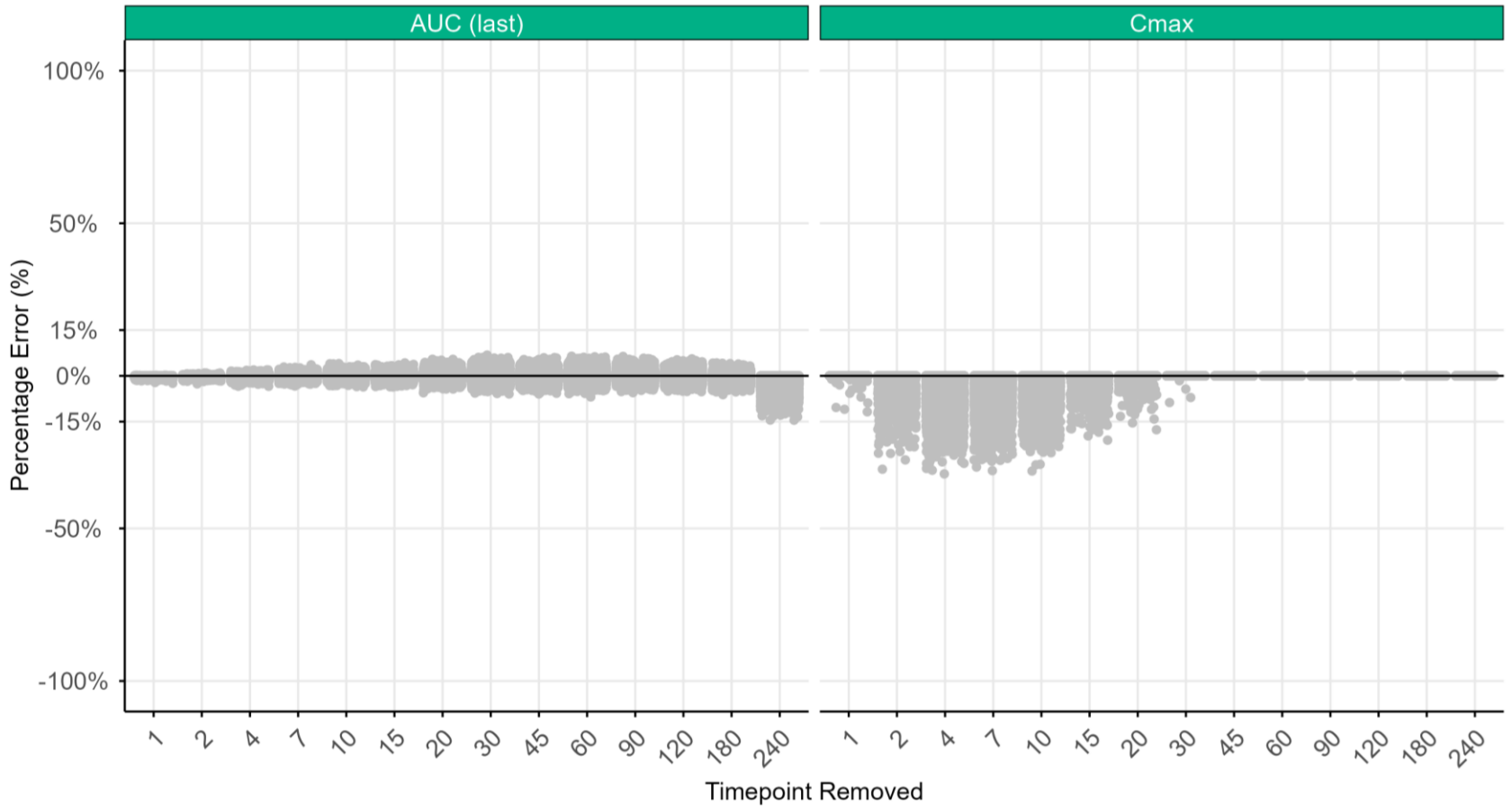
The results shown today are an illustrative example using samples drawn from two artificial PopPK distributions.



Abbreviations: PK = Pharmacokinetic; PopPK = Population Pharmacokinetic; PKNCA = Pharmacokinetic Non-compartmental Analysis.

Timepoint location drives the magnitude of PK estimation Error

Rapid Acting Compound A – T_{max} = 5 min, Duration 240 mins



- Each point represents the percentage error in a simulated subject's C_{max} or AUC_{last} when given timepoint was removed.
- There are 10,000 simulated subjects (i.e. 10,000 simulations per removed timepoint).
- Larger simulated errors in C_{max} when timepoint removed is around T_{max}.
- Larger simulated errors in AUC_{last} when last timepoint is removed.

Figure 1: Rapid Compound A – Percentage error in AUC_{last} and AUC_{last} when single timepoint is removed across n=10,000 simulated subjects.

Abbreviations: PK = Pharmacokinetic; PopPK = Population Pharmacokinetic; AUC = Area Under Curve (of concentrations); C_{max} = Max Concentration; T_{max} = Time of occurrence of max concentration.

Newly proposed classification framework – The “95/15” Rule

95/15 Rule: If, for a given PK parameter and missing sample scenario, there >5% chance that the percentage error exceeds ±15%, deemed undesirable. Otherwise, could be accepted.

- The ±15% threshold is anchored in regulatory bioanalytical guidance[1]. Sits below the bioequivalence acceptance boundary of 80–125% for the 90% CI of the GMR of Cmax and AUC[2-4]. **However, further quality control required to determine if this threshold is appropriate.**

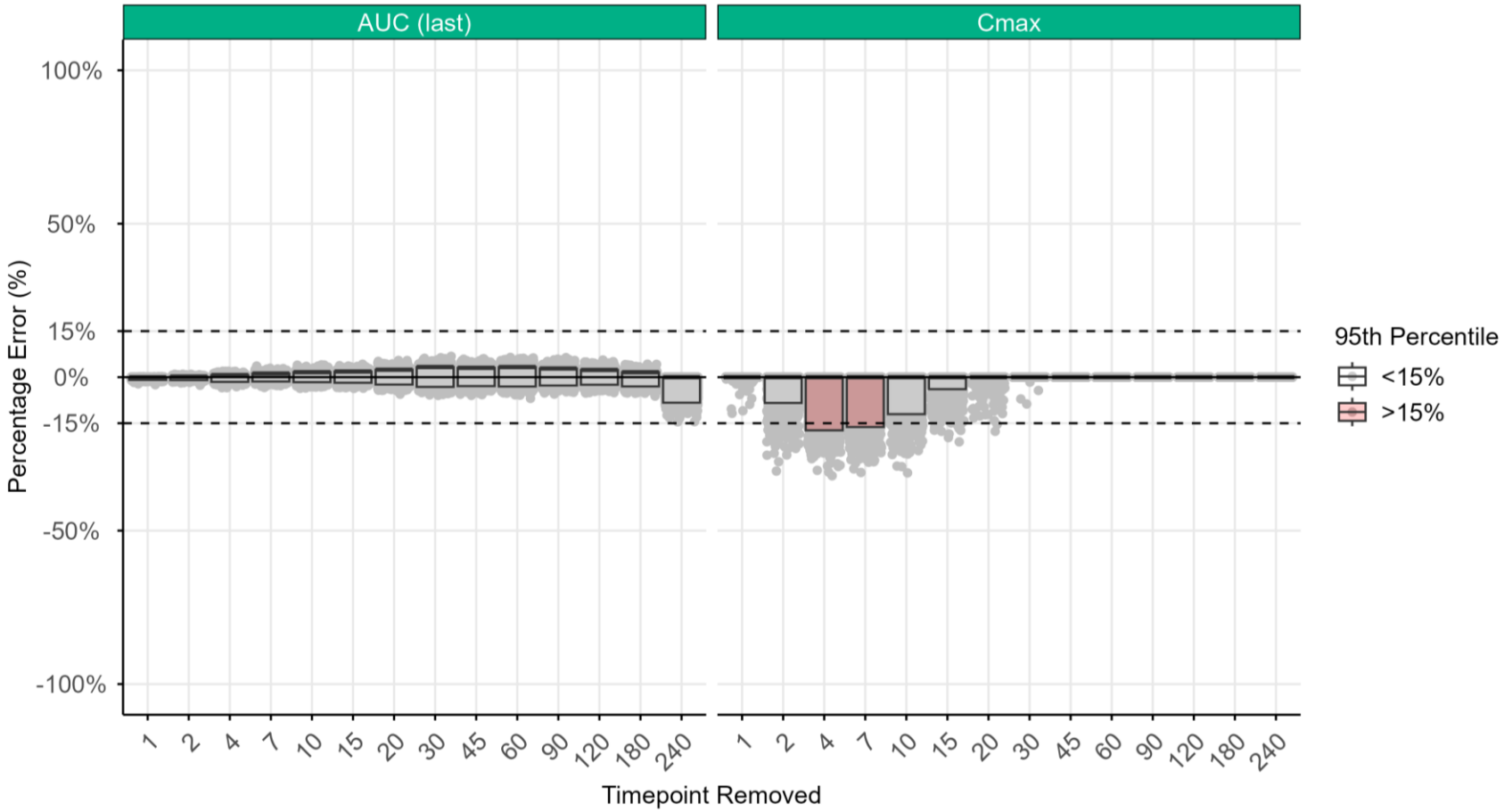
- The 95/15 rule is a novel concept intended as a quantitative framework for impact of missing samples, not as a decision rule. Its intended use is to support scientific judgement of PK Analysts in future clinical trials, for example:
  - Classification of protocol deviations,
  - Retention/exclusion of subject profiles in Non-compartmental Analyses,
  - Design of future PK clinical trials.

Abbreviations: PK = Pharmacokinetic, CI = Confidence Interval, GMR = Geometric Mean Ratio.

[1] ICH. (2022). *Bioanalytical Method Validation and Study Sample Analysis.* Accessed 05/04/2026. **[2] ICH. (2024).** *Bioequivalence for Immediate-Release Solid Oral Dosage Forms.* Accessed 05/04/2026. **[3] European Medicines Agency (EMA). (2010).** *Guideline on the Investigation of Bioequivalence.* Accessed 06/05/2026. **[4] U.S. Food and Drug Administration (FDA). (2022).** *Statistical Approaches to Establishing Bioequivalence.* Accessed 05/04/2026.

The 95/15 Rule Identifies Sensitive Collection Timepoints

Rapid Acting Compound A – T_{max} = 5 min, Duration 240 mins.



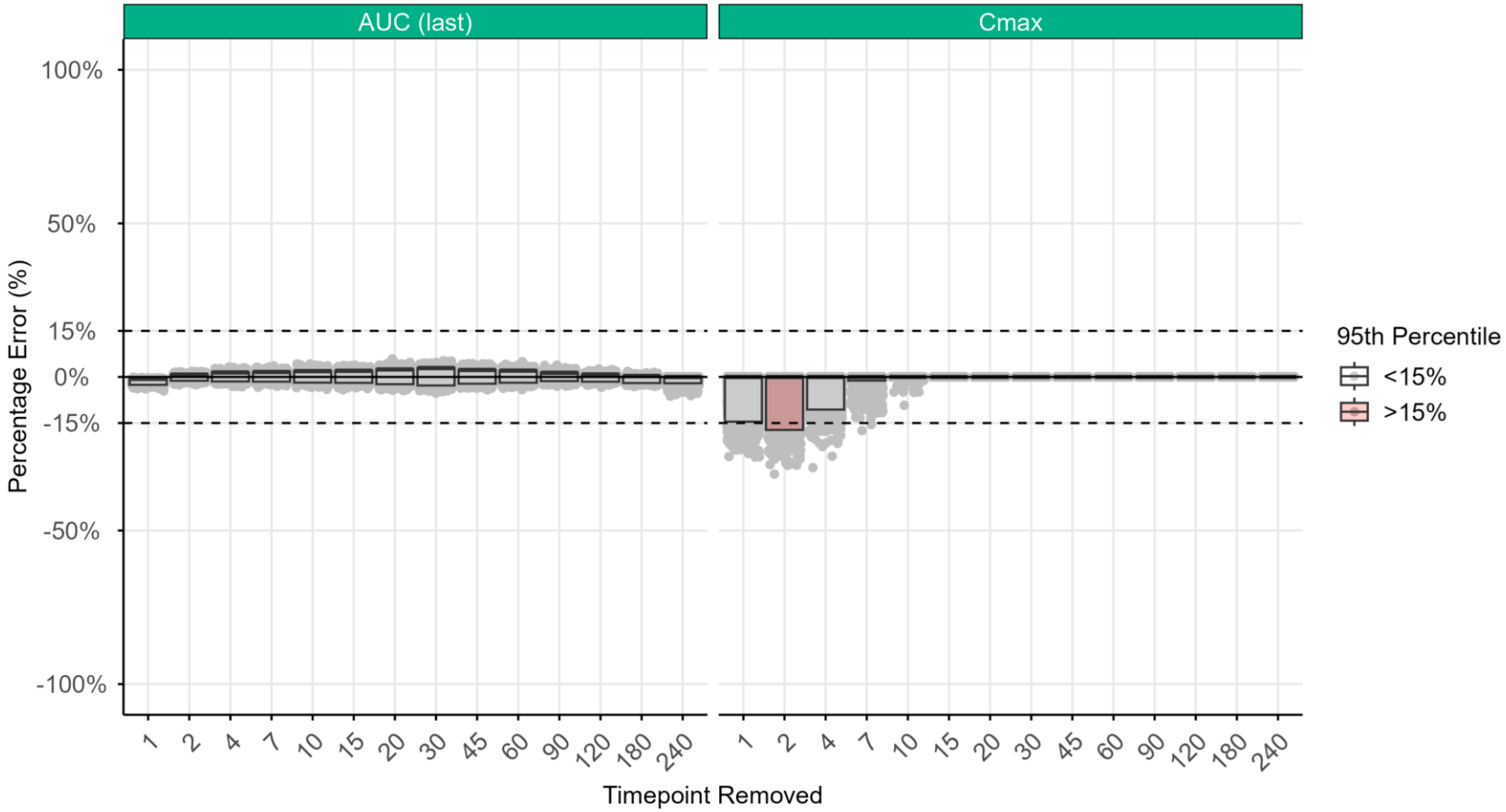
- Undesirable errors in **Cmax** when **T = 4 or 7 mins** removed (Tmax = 5 mins).
- No undesirable scenarios for **AUC (last)** when single timepoint removed.

Figure 2: Rapid Compound A – Percentage error in AUC_{last} and AUC_{last} when single timepoint is removed across n=10,000 simulated samples; with 95th Percentile Interval.

Abbreviations: PK = Pharmacokinetic; PopPK = Population Pharmacokinetic; AUC = Area Under Curve (of concentrations); C_{max} = Max Concentration; T_{max} = Time of occurrence of max concentration..

The 95/15 Rule Identifies Sensitive Collection Timepoints

Rapid Acting Compound B – T_{max} = 2 min, Duration 240 mins.



- Undesirable errors in **Cmax** when **T = 2 mins (Tmax)** removed.
- No undesirable scenarios for **AUC (last)** when single timepoint removed.

Figure 3: Rapid Compound B – Percentage error in AUC_{last} and AUC_{last} when single timepoint is removed across n=10,000 simulated samples; with 95th Percentile Interval.

Abbreviations: PK = Pharmacokinetic; PopPK = Population Pharmacokinetic; AUC = Area Under Curve (of concentrations); C_{max} = Max Concentration; T_{max} = Time of occurrence of max concentration..

Early Results – Simulated Data with Multiple Missing Timepoints

- **Difficulty summarising simulated errors involving multiple missing collection timepoint.** With 14 discrete collection timepoints, $T = \{1, 2, 4, \ldots 240\}$ mins, there are 91 possible missing timepoint scenarios involving two missing samples, e.g. $\{T_i, T_j\} = \{1,2\}, \{1,4\}, \ldots \{180, 240\}$. There are 364 for three missing samples, …etc.

- Early results suggest missing **two or more collection timepoints around T_{max}** *may* lead to *"undesirable"* errors (≥5% chance of error ≥15%) in C_{max} and AUC_{last}.

- Early results suggest missing between **two and three collection timepoints post-T_{max}** *may* lead to *"acceptable"* errors (<5% chance of error ≥15%) for AUC_{last}, further work required to confirm.

- Results may vary depending upon the PopPK parameters used; unacceptable scenarios for Rapid Compound A may not be the same for a Rapid Compound B.

Abbreviations: PK = Pharmacokinetic; PopPK = Population Pharmacokinetic; AUC = Area Under Curve (of concentrations); C_{max} = Max Concentration; T_{max} = Time of occurrence of max concentration..

Conclusion

- **The "95/15 Rule" is a novel quantitative framework** for evaluating the impact of missing PK samples, anchored in existing regulatory guidance.

- **Not all missing samples are equal.** Proximity to T_{max} is the critical factor, with a single missing sample near T_{max} driving undesirable errors in C_{max}.

- **Simulation at scale.** The 10,000 simulated samples deliver statistical robustness that impossible to achieve with real-world missing data alone.

- Further work required to determine the effect of multiple missing sample timepoints on estimation of C_{max} and AUC_{last}.

- Further work required to examine effect on other PK parameters, the effect of out-of-window or hemolysed samples, … and more.

Abbreviations: PK = Pharmacokinetic; AUC = Area Under Curve (of concentrations); C_{max} = Max Concentration; T_{max} = Time of occurrence of max concentration..