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PK/TK Strategy in Drug Development: Optimizing Design, Execution, and Data Integrity

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Ryan Schmich, Associate Pharmacokineticist

- PK/TK strategy and execution supporting IND-enabling and clinical development programs
- Background in bioanalytical execution, informing sampling strategy and data quality risk mitigation
- Supports GxP-compliant studies with emphasis on data integrity and submission-ready deliverables

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Session Overview

- Align PK/TK study design with **IND-enabling decisions** and regulatory expectations
- Identify and mitigate **execution-driven variability** that undermines PK/TK interpretability
- Improve efficiency with CRO partnerships to **protect data quality**, maintain timelines, and regulatory readiness

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Strategic Design and Execution of IND-Enabling PK/TK Programs

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Where PK/TK Strategy Shapes IND Readiness

Study Design

- Dose selection and sampling define what can be learned

Execution

- Sample fidelity and bioanalysis determine data quality

PK/TK Analysis

- Interpretability depends on upstream decisions

Regulatory Narrative

- Defensible conclusions require traceability

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Execution Gaps Impacting PK Interpretability

Dose selection misalignment

- **Dose too low**: Exposure range insufficient to support PK characterization
- **Dose too high**: Saturation effects introduced unintentionally, confounding interpretation

Sampling design limitations

- Inadequate sampling density around C_{max}
- Sampling window too short to characterize elimination
- Pre-dose trough samples collected too early impacts steady state assessment

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The Domino Effect

- Early PK/TK design misalignment propagates uncertainty across development
- PK/TK parameters become unreliable, limiting confidence in safety margins
- Data lose translational value, undermining human dose projections
- PK models built on this data carry forward that uncertainty

Designing PK/TK protocols within a regulatory framework helps prevent these downstream effects.

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Regulatory Expectations for IND-Enabling PK/TK Data

- Nonclinical safety programs are structured by **ICH M3(R2)**, with TK expectations defined in **ICH S3A**
- Preclinical PK/TK data are reviewed to **assess the scientific justification for safety margins and human dose selection**
- Data must be **traceable, interpretable, and internally consistent** to support regulatory confidence

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The Role of GLPs in PK/TK Data Integrity

- GLPs establish the **quality system** that ensures nonclinical PK/TK data are reliable and traceable
- Pivotal safety and TK studies conducted under GLP support **defensible exposure-safety conclusions**
- Documentation, audit trails, and accountability enable **study reconstruction and regulatory confidence**

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Practical Study Design Starts with the Right Questions

- What decisions does the data need to support?
  - Comparing formulations
  - Justifying a clinical starting dose
  - Supporting species translation
  - Predicting exposure in a target patient population
- Build a framework to answer the questions before animals are dosed

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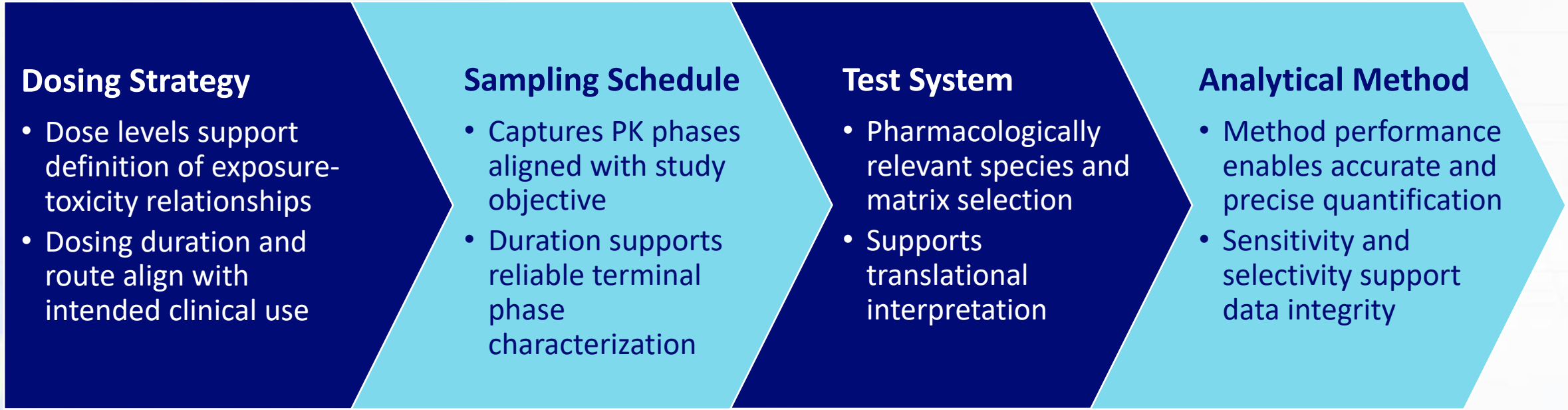
GLP PK/TK Study Protocol: Design Steps



Robust protocols are built on a foundation of:

- Clear objectives
- Scientifically justified design elements
- A deep understanding of regulatory expectations (GLPs)

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Recipe for Success: Nonclinical Safety Program

Ingredients that matter to regulators:

- Clear exposure objectives
  - What exposure supports safety margin and dose selection?
- Sampling that defines exposure
  - Absorption *and* elimination under tox conditions
- Validated analytical methods
  - Robust, Accurate, Precise, Sensitive, and Selective methods
- Traceability across design, execution, and reporting
  - Decisions are explainable, methods reproducible

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Managing and Mitigating Variability in Nonclinical Studies

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Anticipating and Mitigating Variability: A Practical Approach

- The **quality of the PK/TK dataset** is directly dependent on the **integrity of the collected samples**
- Variability is introduced at multiple stages: **pre-analytical, analytical, and biological**
- The greatest opportunity for mitigation occurs **before samples reach the bioanalytical lab**
- Once samples are collected and stored, **many sources of variability are irreversible**
- Proactive alignment between study design, sample handling, and bioanalysis protects PK/TK interpretability

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Taxonomy of Variability

- Pre-analytical – most controllable source of error
  - Dosing conditions, fed vs fasted state, procedural stress, sample collection and handling

- Analytical – inherent to the bioanalytical method itself
  - Instrument/assay performance, internal standard behavior, matrix effects, solubility

- Biological – true inherent differences in how animals handle a drug
  - Genetic differences, sex, age, health status, microbiome

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Maximizing Program Success

- Controlling variability requires consistent execution across dosing, sampling, processing, and analysis
- IND-enabling PK/TK programs require specialized expertise, infrastructure, and regulatory rigor
- Strategic CRO partnerships help mitigate execution risk while protecting data integrity and timelines

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The CRO as a Strategic Partner

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Beyond Cost and Capacity

- CRO selection extends beyond **price lists and facility size**
- Effective assessments include on-site visits and in-depth discussions with scientific and QA teams

  - Technical expertise and experience
  - Regulatory track record
  - Quality systems

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Strategic CRO Alignment: From Execution to Insight

- CRO engagement models range from **transactional execution** to **strategic alliance**
- Strategic alignment requires trust, transparency, and active communication

Best practices include:

- Joint data reviews and early discussion of unexpected findings
- Clear roles, decision authority, and success metrics
- Leveraging CRO experience to produce submission-ready deliverables

Strong alignment directly improves:

- Data integrity
- Timeline adherence
- Regulatory review readiness

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Conclusion: Building a Successful IND-Submission

- IND-enabling PK/TK programs are complex, multidisciplinary efforts
- Success depends on three core principles:
  - **Strategic study design** grounded in regulatory expectations (e.g., ICH M3(R2)), S3A)
  - **Proactive control of variability** through thoughtful protocol design and execution
  - **Strong CRO alignment** to ensure execution quality, interpretability, and submission readiness
- The goal is a **clear, defensible safety narrative** supporting first-in-human dosing

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Acknowledgments

Sara Underwood, BS

Slide development and conceptual framework

Erik Burns, PhD

Content development and conference coordination

Cody Hawkins, BS

Visual design support

Alturas Analytics PK/TK & Bioanalytical Teams

The DVDMDG Organizing Committee

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