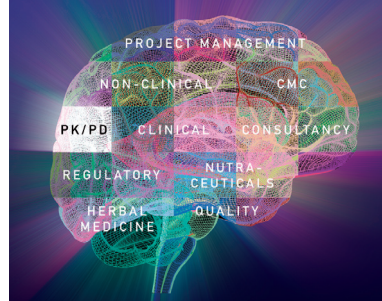


One partner, all the brains you need



PK/PD Modeling & Simulation

Providing in-depth insight in PK/PD data

During drug development, pharmacokinetic (PK) and pharmacodynamic (PD) Modeling & Simulation (M&S) is applied to facilitate selection of compounds to enter clinical development, to support optimization of drug formulations and CMC processes, and to optimize study designs (including dose selection). In addition, M&S is relevant for understanding the variability in treatment response, to bridge different study populations (e.g. from healthy volunteers to pediatrics) and to facilitate strategic project decisions (go - no go). M&S is widely applied in all stages of drug development and is an integral part of the regulatory dossier. Guidelines to perform such analysis have been released by the FDA and EMA.

At Kinesis Pharma, the M&S group has the expertise to assist sponsors with an in-depth analysis of PK and PD data through advanced PK/PD Modeling & Simulation.



What Kinesis offers

- **Exploratory analysis for instant decision-making**

To facilitate decision-making within the drug development program, Kinesis can perform exploratory analyses with short turn-around times. Based on interim data, models can be built to predict PK and/or PD for desired dose groups or for predictions to multiple dosing. In general this construction is used within early Phase I and Phase IIa studies, where the work contributes to a well-founded decision for subsequent dose groups and/or future study designs.

- **Pharmacokinetic meta-analysis including covariate analysis**

A PK meta-analysis can be performed by population PK analysis to characterize the PK of the candidate drug in the target population. The relationship between PK and covariates like age, weight and genotype, can be explored to explain parameter variability and to facilitate dose adjustment decisions. For future studies certain outcomes can be explained by the covariates indicated in the modeling exercise. Also simulations can be performed to explore the impact of the different covariates on the PK profile. Finally the model can be used to support label claims. Similar analysis can be done for PK/PD evaluations.

- **Bayesian analysis**

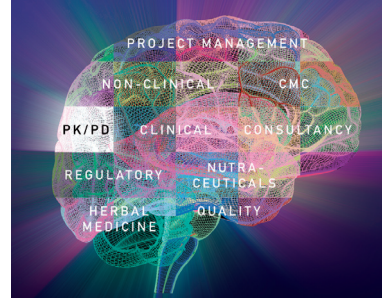
Bayesian type analysis can be performed in multiple stages of drug development. In case prior information is available, a Bayesian approach can be more appropriate for fitting of new datasets. Typical cases include determination of the next dose level in a dose escalation study, assessment of dose proportionality or extrapolations in pediatric studies.

- **Extrapolations to humans/pediatrics**

In case data of humans is not available, non-clinical data can be used to generate animal PK/PD models. Based on valid assumptions these models can be used to extrapolate to the human situation. Information from extrapolated data can be used as a base for the justification of a first dose in man study. In case human data in adults is available, models can be built to allow extrapolations to the pediatric population. Simulations can then predict a dose level that provides adequate exposure.



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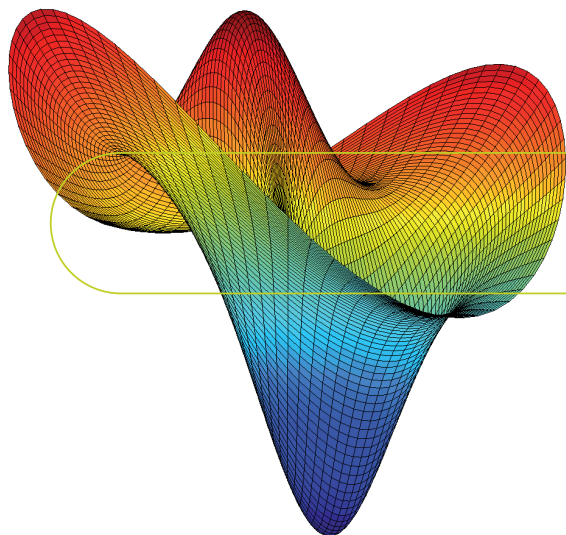
● Programming datasets

In many instances a company already has a team of modelers. However, these modelers do not always have the time or experience to program datasets for the analysis. Kinesis can help with its extensive experience and expertise in both modeling and programming. Datasets are programmed using SAS, where additional data checking can also be done (e.g. descriptive statistics, plotting and dry modeling run).

WinNonLin®, NONMEM®, S-PLUS® and R software are used for the different M&S projects. All work is performed following Standard Operating Procedures, thus ensuring integrity, traceability and reproducibility within the analysis.

Track record

Kinesis Pharma has been involved in many projects during different phases of drug development:



- Optimization of the release characteristics of a slow release fixed dose combination product by comparing *in vitro* dissolution profiles with dog and human *in vivo* release profiles (IVVC)
- Supporting the selection of the dose levels in a 3-month toxicology study using simulations of plasma concentrations after multiple dosing with non-linear PK
- Determination of relevant start doses or target concentrations for first-in-man studies by interspecies scaling
- Selection of the most optimal dosing schedule by estimates to predict the log drop in viral load after multiple dosing, to achieve the desired minimum decrease in viral load
- Optimization of the Phase III dosing schedule after characterization of the relationship between plasma concentrations and the *in vivo* receptor binding to a CNS target
- Bayesian probability estimation for an exposure to reach certain thresholds in Phase I tolerability studies

Why Kinesis Pharma?

- Experienced team of M&S consultants
- Surrounded by an in-house multi-disciplinary team
- Fast and well-founded decision making
- Broad experience in PK/PD analysis and modeling
- Committed to sponsor's projects and timelines
- Flexible approach

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'Nowadays M&S is widely applied in all stages of drug development and is an integral part of the regulatory dossier'



About Kinesis Pharma

Kinesis Pharma is an independent drug development organization with headquarters in Breda, the Netherlands. Kinesis Pharma aims to facilitate an efficient and high quality development and registration process for medicinal products and nutraceuticals through consultancy and contract research services. Kinesis Pharma's service offering includes CMC, non-clinical, clinical, regulatory, quality and project management activities for pharmaceutical, nutraceutical and biotech companies.

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