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QPS White Paper

Pharmacokinetic Studies in Patients

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Studies in Patients versus Healthy Volunteers

Sometimes practical or ethical considerations dictate whether healthy volunteers or patients should be recruited for a particular study. But there are usually sound scientific arguments for collecting Pharmacokinetic (PK) data from actual patients, to supplement or substitute for PK data obtained from human healthy volunteers during the first phases of drug development. Knowing to what extent the results obtained in healthy volunteers – if available - can be extrapolated to the intended treatment population is critical. The US FDA has recognized the importance of PK studies for determining drug concentration-time profiles in target patient populations.

Pharmacokinetic Studies in Patients

There are occasions in which drugs behave differently in distinct subpopulations, the general population, or patients. A key rationale for performing PK studies in patients is to detect these subgroups prospectively. Examples of such studies are:

- Patients with renal insufficiency
- Patients with hepatic insufficiency
- Critically ill patients
- Poor versus extensive metabolizers
- Pediatric or elderly populations

PK studies in patients may also be used for the retrospective detection of those distinct subpopulations in which drugs behave different from the average patient. This end is usually achieved by correlating PK data with other covariate information such as smoking status, age, gender, body weight, renal function, or disease state and/or genetic/genomics data. Examples of such studies are:

- Patients with rheumatoid arthritis
- Patients with arrhythmias
- Patients with postoperative pain
- Patients with type 2 diabetes mellitus

Finally, a third reason to perform PK studies in patients is to test a drug already in the first phases of development, when the adverse event profile of the substance and/or its metabolites carries too serious a safety risk to justify administering it to healthy volunteers.

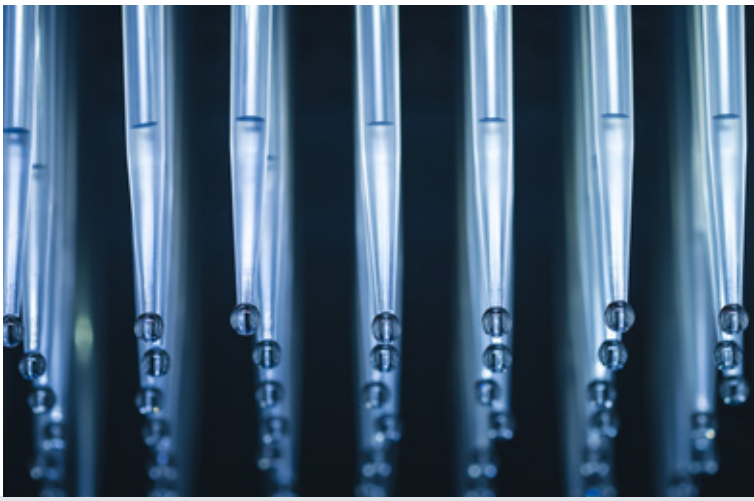
These studies are conducted in patients suffering from the disease the drug is intended to treat. Examples of such studies are:

- PK studies of cytostatics in oncology patients
- PK studies of immunomodulators in cardiac transplant patients
- PK studies of antipsychotics in schizophrenic patients

Data from all of the above PK studies can either be obtained by extensive blood sampling or sparse sampling. Interpretation of the results of these data will guide prescription decisions and optimal dosage calculations for individual patients.

Bioanalysis

Over the past two decades the introduction of liquid chromatography mass spectrometry has revolutionized drug analysis. This technique enables highly sensitive assays with low limits of quantification, even on very small samples. This advance in bioanalysis has significantly alleviated one of the practical constraints of sampling patient populations: the maximum number of



blood samples per patient that can be collected over a given period of time.

PK studies in patients have recently been made even more practical by the introduction of sensitive assays of dried capillary whole blood spots on filter paper. These assays simplify sampling by removing such constraints as: the timing of clinic visits; maximum number of patients that can be recruited in a study; minimum time allowed between consecutive samples for an individual; constrained times for the collection of blood samples; logistical constraints at investigational sites; and cost limitations.

Obviously, bioanalytical requirements will still sometimes mandate particular sampling schedules - for instance, a drug that decomposes in the presence of iron(II) must still be analyzed in plasma, not in dried blood samples. However, the days of suboptimal sampling designs as a consequence of bioanalytical constraints are largely over.

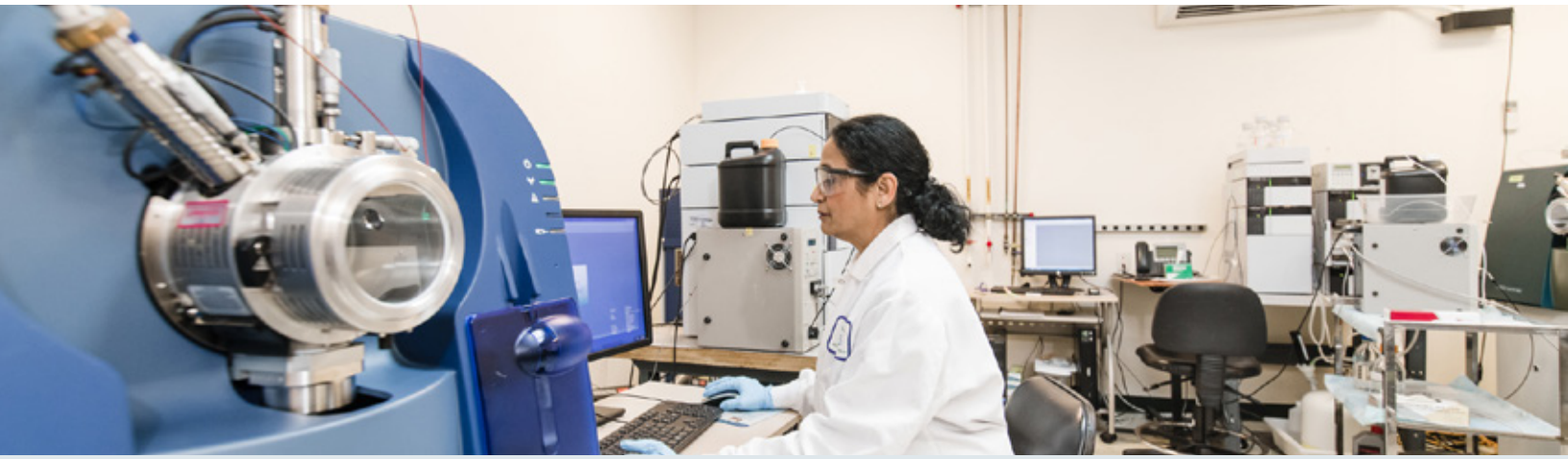
PK Modeling – Optimal Design

PK studies that determine a drug concentration-time profile in a target patient population, using patients who provide only sparse samples at random times, are known as “Population PK studies”. Data from all patients are modeled simultaneously using nonlinear mixed effects modeling. This method estimates the mean population PK parameters (e.g. clearance), the inter-individual variability, and the residual variability (which encompasses intra-individual variability, measurement errors and model misspecification).

Although there are now statistical methods to analyze sparse data from population PK studies, the design of these population PK studies is not straightforward. Many questions arise about how best to conduct these investigations. How many patients should be included? What sampling scheme should be used? How many different sampling schemes are required? How many patients need to be allocated to each sampling scheme, and how to adjust for covariates that may change over the course of the study? To answer these questions one needs to know the PK profile of the drug, the statistical methods used to analyze data from population PK studies, and also the practical constraints of sampling the patient population.

Conclusion

Currently, population PK study designs are based on logistical, financial and ethical constraints, as well as prior knowledge of the drug concentration-time profile. These factors are important, but may yet result in a study of “insufficient design” unable to determine the desired PK parameters. Such a study would be unable to resolve the fundamental questions the population PK model was created to answer; the study would be wasted. Thus, there is both a scientific and an ethical imperative to ensure PK studies are designed such that they provide useable results.



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QPS is Committed to Working with You

QPS has extensive experience in supporting PK studies in patient populations. We understand the complexities, particularly with respect to proper sample handling, sampling designs, bioanalysis, managing and conducting (global) clinical trials, and monitoring the pharmacokinetics of your new small or large molecule drug candidates. We are committed to working with you personally to advance your product for the benefit of patients worldwide.

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QPS provides clients with broad access to our nonclinical and clinical development capabilities. Clients also benefit from our experience in nonclinical and clinical development of a diverse portfolio of treatment modalities for a wide range of diseases. Our preferred vendor agreements also provide for the establishment of client-dedicated units within our organization.

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References

FDA: Guidance for Industry. Population Pharmacokinetics. [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegula toryInformation/Guidances/UCM072137.pdf]. 1999 Feb

Rajman I. PK/PD modelling and simulations: utility in drug development. Drug Discov Today. 2008 Apr; 13: 341-6

Kaila N, Straka R, Brundage R. Mixture models and subpopulation classification: a pharmacokinetic simulation study and application to metoprolol CYP2D6 phenotype. J Pharmacokin Pharmacodyn 2007; 34: 141-56

Rowland M, Sheiner L, Steimer J-L, Eds. Variability in Drug Therapy: Description, Estimation, and Control. New York: Raven Press 1985

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