

## Analysis and Reporting for New Drug Approval

Pharsight® Reporting and Analysis Services (RAS) is a highly skilled team of pharmaceutical scientists, biostatisticians, and technical experts committed to providing high-quality, regulatory-compliant PK/PD analysis, biostatistics, and reporting for new drug approval. All RAS work is executed to the highest professional standards, in minimum time, at competitive rates.

### About RAS

- **Leveraging Pharsight Software:** RAS scientists make use of Pharsight's industry-leading software tools in a validated environment – including [WinNonlin®](#), [IVIVC Toolkit™ for WinNonlin](#), [WinNonlin AutoPilot™](#) and [Pharsight Knowledgebase Server™ \(PKS™\)](#) – to provide timely, high-quality analyses, data management and report writing for preclinical and clinical studies supporting sponsor's new drug approval submissions under Module 4 (Non-Clinical Study Reports) and Module 5 (Clinical Study Reports) of ICH's Common Technical Document for Regulatory Filing. The PKS system that RAS uses is compliant with 21CFR Part 11 for the management of electronic records and electronic signatures. RAS also makes use of other industry standard tools, such as SAS®, S-PLUS® and NONMEM®.
- **Expert Staff, Global Reach:** On the clinical side, the Pharsight RAS group is led by Jean-Francois Marier, PhD, FCP. Mark L.J. Reimer, PhD, leads the preclinical development team. Jean-Sebastien Brunet, M.S., leads the statistics and data management group. RAS comprises a team of PhD/MD/PharmD scientists with expertise in pharmacokinetics (PK), bioanalytics, pharmacodynamics (PD), biostatistics, regulatory strategy and report writing. The RAS team is experienced in all major disease indications and development phases, and serves all major drug development geographies. RAS scientists bring experience to Pharsight representing more than 400 client engagements in the past several years.
- **Delivery Approach:** RAS conducts its business according to four key principles: (1) uncompromising scientific integrity; (2) teamwork; (3) technical innovation; (4) commitment to customer service in all aspects of project execution.

### RAS Capabilities

- **Preclinical PK Analysis:** RAS offers the following unique combination of PK analysis services to support your preclinical drug development needs:
  - **Toxicokinetic and PK analysis**
    - Noncompartmental PK/PD analysis using [WinNonlin®](#) and [WinNonlin AutoPilot™](#) (TK and PK analysis in animals, based on sparse or rich data, and delivery of preclinical PK report)
    - Compartmental analysis and simulations (semi-physiological)
  - **Allometric Scaling**
    - FDA approach (conversion factors from Guidance based on BSA)
    - Scaling of NCA parameters (scaling of clearance according to body weight)
    - Scaling of compartmental parameters (all PK parameters, plus mechanistic approach that allows time-concentration simulation after single/multiple dose)
    - These approaches offer particular advantages for biologics and for boosting the confidence of scaling adult parameters and predictions to pediatric population.

- **PBPK Modeling**
  - Physiologically-based PK modeling (predict drug exposure in tissues and organs, mechanistic extrapolation of dose-to-dose, route-to-route, animal-to-human)
  - PBPK modeling and reporting for chemical risk assessment and analysis of environmental compounds, leveraging [Pharsight Trial Simulator™](#).
- **Bioanalytical and DMPK Consulting Services**
  - Bioanalysis (bioassay selection of small and large molecules, quantitative and qualitative LC-MS/MS approaches, cross-validation studies)
  - Drug metabolism/pharmacokinetics (in vivo and in vitro metabolite identification/profiling, preclinical strategies and planning, recommendations for preferred partnerships)
  - IND Applications (comprehensive documentation including: tox results, TK/PK results in all species, allometry, dosing recommendations for FIH study and Phase I protocol)
- **Clinical PK Study Analysis:** RAS scientists use the latest, validated versions of [WinNonlin®](#), [WinNonlin AutoPilot™](#) and [PKS™](#) for efficient PK/PD analysis, data management and reporting:
  - **Phase I Studies (healthy subjects in general)**
    - Maximum tolerated dose (MTD) Studies
    - Single Ascending Dose (SAD) studies
    - Multiple Ascending Dose (MAD) studies
    - Bioequivalence/bioavailability
    - Food effect studies
    - Drug-drug interaction studies
    - Studies in special populations (e.g., renally and hepatically impaired)
    - QT prolongation studies
  - **Phase II Studies for dosing requirements (Phase IIa) and efficacy (Phase IIb)**
    - Designs and workplans are specific to your drug indication
  - **RAS methods are simple, efficient and robust**, leading to protocols optimized for:
    - Number of samples (a key cost driver )
    - Sampling schedule (to improve your picture of PK)
    - Dose and Population
- **Biostatistics and Data Management:** RAS offers broad biostatistical expertise to support optimal trial design decisions, build the right dataset to achieve your target product profile, and perform critical analyses and reporting for your submission.
  - **Statistical Plan Development**
    - Protocol and CRF development
    - Statistical analysis plans to increase probability of success and optimize design of subsequent trials
    - Development of randomization schedules
  - **Dataset Construction**
    - Database design and integration
    - SAS® and S-PLUS® programming
    - Modeling and simulation analysis plan development, including *a priori* sets of rules on model build-up and how missing data will be handled

- **Statistical Analysis**
  - General ANOVA modeling
  - Generalized mixed-effects models, multiple linear and non-linear regression
  - ROC analysis to identify covariate(s) that maximize probability of response
  - Survival analysis
  - Prediction of dichotomous and polytomous outcomes
  - Interim data and/or blinded analysis
  - Post-approval statistical evaluations, including sub-group analyses
  - Meta-analysis across multiple phases
  - Exploratory PK/PD correlations and clinical outcome
- **Reporting, Regulatory Support and CDISC**
  - Biostatistical support at regulatory meetings
  - Data summarization of PK, safety and tolerability (Tables, Figures and Listings)
  - Integrated safety (ISS) and efficacy (ISE) summaries
  - Interpretation and preparation of safety tables and reports using SAS
  - Support for advisory panel and data monitoring committee meetings
  - CDISC consulting
  - Dataset construction (CDISC, eANDA, eCTD)
  - Publication and abstract preparation
- **Data Archiving and Real-Time Data Assembly**
  - Services to build and maintain the required database of data and reports for submission, as PK/PD studies are completed ("real-time data assembly").
  - [PKS™](#) serves as compliant data repository for PK/PD study archiving.
- **PK-Based Formulation Development Strategy**
  - RAS makes optimal use of information about your compound's PK profile to guide formulation and reformulation strategies from early-phase development to post-approval.
  - RAS scientists use the latest tools for efficient IVIVC analysis, featuring the [IVIVC Toolkit™ for WinNonlin](#). Specific IVIVC applications include:
    - Modified-release formulation & Super Generics [505(b)(2)]. RAS offers extensive experience in studies supporting 505(b)(2) submissions.
    - Fixed-Dose Combination (>2 products combined into 1 tablet formulation).
    - Drug delivery systems (e.g., transdermal, parenteral, pulmonary)
  - RAS also provides meta-data search and analysis for optimal formulation development and product positioning
- **Population PK Modeling:** In its Critical Path Initiative, FDA is increasingly advocating the use of pharmaco-statistical models to support improved drug development decision-making. RAS scientists offer expertise in all aspects of population PK modeling and simulation for specific studies:
  - PK/PD modeling of sparse and rich data
  - Model discrimination and validation together with Monte Carlo simulation
  - Sparse sampling strategies
  - Population PK/PD analyses
  - Parametric and nonparametric population PK/PD analyses



## Reporting and Analysis Services (RAS)

- **Protocol Writing, Regulatory and Scientific Writing:** RAS has medical writing capabilities to support protocol writing, individual study reports, and PK sections of integrated reports for regulatory submission.
  - Clinical Study Report (ICH E3)
  - Abbreviated Report
  - Population PK/PD Report

### Contact RAS

For more information about Pharsight Reporting and Analysis Services, please visit [www.pharsight.com](http://www.pharsight.com) or contact:

James Hayden  
Senior Vice President, Global Sales  
Email: [jhayden@pharsight.com](mailto:jhayden@pharsight.com)  
Telephone: +1-201-274-6373