

THE A² PHARMACOMETRICS GROUP

Business Services
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Background

THE A² PHARMACOMETRICS GROUP (A2PG) was founded to specifically address Pharma's needs to reduce costly late-stage clinical trial failures. The US Food and Drug Administration (FDA) in March of 2004 posted a white paper, which discusses industry stagnation in the drug development pipeline¹. In particular, the costs of drug development continue to increase while the number of new drug applications (NDAs) submitted to the FDA has declined over recent years. The FDA concluded that the applied sciences for drug development have not kept pace with the basic sciences for drug research. Specifically, the medical advances in drug discovery have not resulted in lower failure rates in late stage clinical development. The high failure rate in late stage clinical development continues to drive up costs for new medicines.

Some of the reasons for the high failure rate in late stage clinical trials include:

- Incomplete or inadequately characterized exposure-response relationships.
- Smaller observed effect sizes than expected (planned effect sizes may not have been supported by careful evaluation of historical data).
- Failure to incorporate interim analyses when the knowledge of dose-response or treatment-effect was not available at the design stage.

The staff of THE A2PG has expertise in creating new approaches to fundamentally improve how safety and effectiveness of drug products can be demonstrated faster, with more certainty, and at lower costs. '*Model-based drug development*' is generally recognized as an essential component to address the high late-stage failure rates. A2PG is innovative and skilled at implementing this approach through the application of integrated analyses (models) of available data (i.e., internal and external sources) to inform strategy, trial design and decision-making in drug development.

A2PG's guiding principles for a quantitative, model-based drug development approach include:

- Adopt comprehensively quantitative approaches to enhance design, analysis and interpretation of programs and protocols.
- Establish a more complete quantification of the exposure-response relationships prior to Phase 3.
- Characterize and articulate clearly the inherent risk of a given program strategy or protocol design.
- Pursue aggressively alternative and resource-efficient trial design methodologies, the pursuit of which may require a strategy to influence the external environment.
- Design studies using the most current and complete knowledge about the given compound and compounds sharing a similar mechanism and/or indication.

The employees of A2PG have focused on these issues and concepts delineated above and have designed services, unique to the industry, around these Pharma needs. Currently,

¹ Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products. Food and Drug Administration (2004). www.fda.gov/oc/initiatives/criticalpath/whitepaper.html.

A2PG is unaware of any other out-sourcing based company that can deliver this comprehensive set of services to address Pharma's need for model-based drug development.

THE A² PHARMACOMETRICS GROUP the Company

The planned inception date of A2PG is September 1, 2007. A2PG is composed of a core group of Pharma leaders and talented, highly-trained individuals. Numbering 7-12 employees, A2PG will house a collective expertise and experience in pharmacometrics with few if any peers in the industry. This experience is exemplified by the active roles the group has taken in the scientific community. The roles include numerous publications in peer-reviewed journals, invited presentations at scientific meetings, and involvement in scientific organizations such as American Society of Clinical Pharmacology and Therapeutics (ASCPT), the American Association of Pharmaceutical Scientists (AAPS), and the American Statistical Association (ASA). Several members are currently developing and training students at the University of Michigan through lectures on modeling and simulation.

The staff of A2PG has the depth and breadth of skills and expertise in applying model-based drug development to overcome the challenges articulated in the Critical Path initiative. As former Pfizer colleagues located in Ann Arbor, Michigan, the A2PG staff has accumulated significant examples where these model-based drug development applications have added significant value to Pfizer:

- Model-based analyses and reports supporting favorable dosing regimen labeling following approval of the NDA, despite limited treatment-level data for the proposed (commercially desired) dosing regimen.
- Model-based analyses and clinical trial simulations, which supported a change in a compound's development strategy to focus on differentiating it with respect to a salient competitor – yielding a significant increase to the net present value of the franchise program.
- Proposed development strategies in which single Phase 3 registration trials would be conducted as proof of evidence and model-based (dose-response or regression) analyses of Phase 2 data provided supportive evidence. This proposed strategy has been favorably reviewed by the FDA.
- Model-based analyses and clinical trial simulations were performed to support the decision to discontinue development of an in-licensed compound, saving Pfizer from making a large milestone payment to the partner company.
- Model-based arguments have been used to persuade the FDA that a pediatric formulation was not necessary, thereby achieving exclusivity and the pediatric indication. Substantial development costs and delays in marketing, which would have been incurred, were avoided.

Mission/Vision

THE A² PHARMACOMETRICS GROUP's mission is to provide state-of-the-art model-based drug development services; to promote innovative, quantitative thinking on shaping and scrutinizing compound development strategies; and to facilitate integration of the clinical, statistical and clinical pharmacology disciplines through pharmacometric consultation, mentoring, and training.

THE A² PHARMACOMETRICS GROUP recognizes that client training is a key cornerstone to successful implementation of the model-based drug development strategy. The philosophy is to work with the client company in order to develop internal pharmacometric expertise and enhance the quantitative thinking of the project team. As internal expertise expands, project teams will be able to marshal efficiently these strategies and impact critical decision making – such as terminating non-viable compounds early or flagging compounds capable of commercial success.

The employees of A2PG have focused on the issues and concepts delineated above and have designed services, unique to the industry, around these Pharma needs. A list of services targeting these needs is provided in the next section.

Service Overview

A2PG services, centered on quantitative, model-based drug development are congruent with the Critical Path initiative of the FDA. These services are targeted to support pharmaceutical development spanning from pre-clinical translation to First-in-Human to Life Cycle Management (post-registration). The services can be classified into two categories, Projects and Consultation. Descriptions of these services are provided below. Additionally, a table is provided in the appendix, which details representative (yet not exhaustive) activities of these. The development milestones typically associated with the activities are also included for reference.

Projects

The project category accounts for activities that require well-recognized (tangible) deliverables. The three primary project sub-categories are Analyses and Reports (AR), Clinical Trial Simulations (CTS), and Knowledge Management (KM).

Analyses and Reports (AR)

Examples of Analyses and Reports activities include:

- Performing single and pooled (e.g., integrated summary) population PK analyses and negotiating PK label wording.
- Formulating efficacy (PK/PD), safety, and adherence (drop-out and compliance) models; time-to-event analyses; fitting exposure-response models to biomarker and clinical endpoint data.

- Quantifying benefit/risk as a function of dose regimen using clinical utility indices.
- Benchmarking the competitive landscape using meta-analyses (related to Knowledge Management – see below).
- Writing research or study (regulatory submission) reports; and composing manuscripts for product visibility.
- Additionally, cross-line integrated due diligence reports could be included.

Clinical Trial Simulation (CTS)

The Clinical Trial Simulation area focuses on testing and assessing the operating characteristics of hypothetical, competing, potentially adaptive designs with respect to relevant decision rules. Some typical activities, quantities, and decision criteria evaluated are:

- Selecting doses achieving a targeted efficacy level; the demarcation of a minimum dose that achieves an unacceptable adverse event profile.
- Identifying doses achieving a specified commercial profile; calculation of the probability of achieving a specified commercial profile relative to a competitor.
- Estimating the probability of technical success as a function of sample size (such as superiority or non-inferiority to a reference).
- Establishing the probability of making a correct decision (such as Go/No-Go or dose regimen) as a function of design characteristics.
- Powering to detect subpopulation differences in drug clearance in sparse population PK designs (juvenile or phase 2/3 PK settings) for labeling.

The projects described herein are interrelated, track drug development, and are integral to quantitative, model-based drug development, and are critical to the future of drug development as highlighted in the Critical Path initiative. The employees of A2PG have considerable experience in implementing these concepts and services and have experienced savings (eliminating sufficient samples sizes across projects or planned elimination of actual trials) on the order of phase 3 trial expenditures.

Consultation

The Consultation rubric operates as a flexible and technical resource for client project teams and/or pharmacometricians. Consultation generally has no fixed milestones for deliverables (in contrast to Projects) and is contracted in increments of time.

Strategic Consulting (SC) service activities include: technical review of projects and analyses; negotiation, formulation, and translation of decision rules and trial performance measures used in clinical trial design (e.g., calculating the dose required to achieve the commercial profile and estimating probability of making a correct decision for a design); determining designs and analyses for early termination of a compound for non-viability; and strategizing on adaptive or regression-based designs. Delineation of processes and outlining internal client re-organization to industrialize modeling and simulation are also provided. Development of initiatives for implementing quantitative, model-based drug

development and authorship of modeling and simulation best practices are available. These activities would be considered under Consultation, unless A2PG were specifically contracted to provide a tangible deliverable (see Projects above).

Drug Development (DD) consulting focuses on compound and therapeutic area development strategies and activities which include: project team involvement, such as management and/or membership; project, protocol, and tactical reviews; protocol co-authorship; appraisal of viability for in-licensing compound candidate; discussion of labeling issues; dosing strategies based on biomarkers; representation on the client's behalf with the FDA and interaction strategies therewith; and developing quantitative drug program strategies. Development and therapeutic area consultations stretching over phases might benefit from longer time increments of contracted obligation to ensure project continuity.

A2PG also offers training and mentoring to client colleagues or designees interested in furthering their skills in quantitative drug development. As part of A2PG vision, internal building of pharmacometric expertise is fundamental to the overall implementation of the strategy.

Fee Structure

A2PG GROUP proposes a fee structure similar to and competitive with other industry pharmacometric consultants. This includes a fee structure for both projects (milestone-type payments) and consultancies (per diem billed).

Milestone

A2PG proposes the creation of a menu of services with cost ranges, where the actual cost will be determined by the scope of the project.

Per Diem

For per diem projects, A2PG proposes a rate of US \$2,900 per day.

Pass-through Costs

Travel Expenses

Travel will be reimbursed according to the client's policy for Travel and Entertainment.

Appendix A: Table of Primary Services with Development Milestone Timing

Service	Category	Type	Typical Activities	Development Stage
Population PK	Project	AR	Phase 1: Estimation of clearance, accumulation, half-life, dose escalation considering toxicology limits. Integrated analyses: Overall PK summary and covariate analysis. Phase 2/3 sparse design: PK summary and covariate analysis in target patient population, label relevance.	FIH – Registration

Exposure-Response	Project	AR	<p>Phase 1: Establishing concentration-biomarker relationship, dose-selection for proof-of-concept (POC), integrating preclinical models if necessary, and establishing the maximum tolerated dose.</p> <p>Phase 2: Establish relationships between exposure and clinical endpoints (such as QT), adverse events, time-to-event, and adherence (dropout) – essentially establishing the therapeutic index. Prerequisite for clinical trial simulation.</p> <p>Phase 3: Supportive evidence and eventual dose justification.</p> <p>Post-registration: Refinement of models for life-cycle management (useful for clinical trial simulation of head-to-head studies)</p>	FIH – Post-registration
Clinical utility index modeling	Project	AR	Establishing relevant exposure-response models, negotiating with project team/key opinion leaders for utilities values, formulating utility functions.	Phase 2
Competitor meta-analyses	Project	AR	Perform meta-analyses to assess competitive landscape and inform commercial profile (interlinked with Knowledge Management and often used in conjunction with exposure-response analyses and clinical trial simulation). Operates at the compound and mechanism level throughout an indication.	FIH – Registration

Translational modeling and prediction	Project	AR	Combination of exposure-response and preclinical or in vitro data to provide predictions to back-up compounds.	FIH-POC
Report and manuscript writing	Project	AR	Compose research or study reports for the client for any of the above analyses (either client or A2PG completed) including regulatory submission formats. Manuscript composition for product visibility.	FIH – Registration
Sparse population PK design	Project	CTS	Design clinically feasible and optimal designs for sparse phase 2/3 or juvenile studies. Negotiate with FDA on appropriateness of the design.	Phase 2/3
Regression or adaptive clinical trial design	Project	CTS	Work with project teams to achieve quantitative goals for a study, compile exposure response and adherence models, competitor meta-analytic models, and disease progression models to generate realistic trial data. Formulate clinical endpoint models and/or longitudinal models and decision criteria. Tabulate metrics such as probability of technical success, probability of achieving commercial profile, and probability of correct decision (establishing the operating characteristics of a design).	Phase 2/3
Technical review	Consulting	SC	Ad hoc modeling and simulation council membership, review of complex analytical modeling constructs and implementation, report review.	FIH – Registration

Trial design	Consulting	SC	Negotiation, formulation, and translation of decision rules and trial performance measures; technical aspects of calculating operating characteristics of regression and adaptive designs (e.g., commercial success, technical success, dose-selection criteria, probability of correct decision).	Phase 2/3
Training and Mentoring	Consulting	SC	Resources for training and mentoring inexperienced client staff in quantitative model-based drug development best practices and general pharmacometric methods. Includes secondment of client employees or designees as well as key personnel associated any client-internal initiative.	--
Industrialization of modeling and simulation	Consulting	SC	Delineating processes and concepts required for industrializing modeling and simulation throughout drug development. Includes processes particular to large scale training of quantitative model-based drug development.	--
In-licensing Review	Consulting	DD/SC	Independent review of compounds with potential for in-licensing.	--
Developing quantitative program strategies	Consulting	DD/SC	Triage compound information and provide guidance on strategies to implement quantitative, model-based initiatives target at the Critical Path.	FIH – Registration

Transitional project team membership.	Consulting	DD	Contribute to compound development as Clinical Pharmacology representative to project team.	FIH – Registration
Tactical compound review	Consulting	DD	Project, protocol, cycle time reviews, protocol co-authorship, discussion of labeling issues, dosing strategies based on preclinical information and biomarker relationships, translational modeling approaches.	FIH – Registration