

ACoP Programming Proposal Example #1

1. Session Title:

Knowing the Odds: Translational Pharmacology, Pharmacometrics and Probability of Success in Drug Development.

2. Proposed Session Format: Symposium

3. Chairperson(s)'s name, title, affiliation, contact Information, and ISoP Membership Status

Chairs: Daniele Ouellet and Richard Lalonde

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4. Description of the session, Background and Scientific Importance

The attrition rate in clinical drug development is very high, with the majority of failures related to lack of efficacy. Key papers have been published on understanding drivers of survival of new molecular entity (see References section). As suggested by these retrospective analyses, an integrated understanding of the relationship between drug exposure, target engagement, and translation into clinical efficacy/safety endpoints is required for efficient drug development. By implementing the systematic application of translational modeling from new candidate selection, to proof of mechanism and proof of concept, probability of success can be provided to ensure that studies are optimized to adequately test the mechanism of action and successfully progressed beyond Phase II. Key decisions about progression in Phase 3 and in the post-approval stages can similarly be informed by the probability of success of proposed trials using pharmacometrics principles. Different pharmacometrics/modeling approaches can be used depending on the stages of development, mechanism of action, clinical/preclinical data, types of biomarkers, availability of disease models, etc. This session is proposed to provide an overview of efficient

drug development based on data driven decisions, determination of probability of success, and different case studies applying pharmacometric approaches in drug development.

References:

- Cook D, et al. Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework. *Nature Rev Drug Discov* 2014; doi 10.1038/nrd4309
- Morgan P, Van Der Graaf PH et al. Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival. *Drug Discovery Today* 2012; 17: 419-424.
- Owens PK et al. A decade of innovation in pharmaceutical R&D: the Chorus model *Nature Rev Drug Discov* 2015; 1: 17-28.
- Paul SM et al, How to improve R&D productivity:the pharmaceutical industry's grand challenge *Nature Rev Drug Discov* 2010; 9: 203-214.
- Wehling M. Assessing the translatability of drug projects: what needs to be scored to predict success? *Nature Reviews; Drug Discover* 2009; 8: 541-6

5. Learning objectives (100 words max.)

- 1) Understand how decisions are made and the use of pharmacometric approaches to better inform probability of success and guide drug development strategies;
- 2) Review translational modeling approach using different examples based on preclinical data;
- 3) Provide perspectives on the use of system's pharmacology to improve our confidence that a drug with a new mechanism of action will result in efficacy success;
- 4) Understand the use of Bayesian framework to help decision making and define probability of success in early development.

6. Speakers (4):

1) Richard L. Lalonde, Vice-President Global Clinical Pharmacology, Pfizer Research & Development, Groton, CT, Richard.lalonde@pfizer.com (ISoP member)

Presentation: Probability of Success and Drug Development Decision-Making: An Opportunity for Pharmacometrics

This presentation will provide an overview of how decisions are influenced by common individual/institutional biases and how to implement data-driven approaches to improve decision-making in drug development. Lessons learned from the application of probability of success to risk decisions across a portfolio will be shared along with institutional challenges.

2) Nahor Haddish-Berhane, Associate Scientific Director, Clinical Pharmacology & Pharmacometrics, Janssen Research & Development, nhaddish@its.jnj.com (ISoP member)

Presentation: Application of Translational Modeling to Inform Probability of Success

The proposed presentation would provide an overview of application of translational modeling to determine likelihood of success and understanding of risk. Based on preclinical in vitro and in vivo data and an understanding of the mechanism of action, translational models are developed to predict therapeutic doses and uncertainty around these predictions. Several case examples would be provided to understand the different sources of uncertainty and measures of success.

3) Piet van der Graaf, PhD, Director of Research for the Academic Center for Drug Research (LACDR) at the Leiden University (p.vandergraaf@lacdr.leidenuniv.nl) (ISoP member)

Presentation: Bridging Proof of Mechanism to Efficacy: A Systems Pharmacology Approach

This presentation would illustrate attributes of survival in Phase 2, focusing on how a system's pharmacology approach can provide insights for compounds who have demonstrated proof of mechanism yet lack bridging to efficacy endpoints.

4) Matt Hutmacher, MSc, Vice President, A2PG (Ann Arbor Pharmacometrics Group), Ann Arbor, MI (ISoP member)

Presentation: Use of a Probabilistic Framework to Enable Early Clinical Development
Quantitative Decision Making

This proposed presentation would provide an understanding of the use of a Bayesian approach to make decision based on early clinical data. Targets for PK, PD, or safety endpoints are selected based on modeling output, clinical relevance, benchmarks from competitors or commercial value. A Bayesian framework using posterior probability distribution to make decision and determine probability of success based on observed data in relation to a proposed target will be described using case examples.

7. Special AV requirements, Speaker Fees, etc

NA

ACoP Programming Proposal Example #2

1. Session Title: Novel Tools and Technologies: Is This Sustainable? Balancing Capability, Efficiency, Costs and Regulatory Acceptance

2. Proposed Session Format: Symposium

3. Session Co-Chairs: Navin Goyal and April Barbour

4. Description of the session, Background and Scientific Importance

Model-based analyses have become critical to answer key questions during drug-development helping to identify the target patient population and ensuring the optimal dose. Recently, there has been noticeable increase in development of software tools and technologies - commercial and free/open-source, adding to the pharmacometrician's toolkit arsenal. This has contributed to improved efficiency in the day-job with faster and relatively easier implementation of analyses with increasing level of complexities ranging from POPPK/PD, PBPK, QSP, Platform models to MBMA. The newer software tool(s) aim to provide "distinct features, capabilities, user-friendliness and efficiencies" when compared to some of the existing tools. While some of this is true, there is also considerable overlap in some of these characteristics.

There are tangible resource requirements with budget constraints as organizations try to rein in costs, namely licensing expenses, cost of training workforce, validation and implementation of new software. End-users also need to continuously seek to update themselves with these developments in parallel to their day-jobs. In addition, there is lack of clarity on regulatory acceptability of analyses conducted with approaches utilizing such novel tools and algorithms. A cost-benefit analysis evaluating the opportunities and challenges would best facilitate current and future industry-wide adoption of such novel software tools. Last but not the least, consideration should also be given to how these aspects interact with the academic training of future pharmacometricians and/or quantitative clinical pharmacologists. This session will provide perspective from regulatory, industry, and academia about adoption, application and future development of novel tools for pharmacometric analyses.

5. Learning Objectives

1. Examine the efficiencies of novel or emerging tools and technologies but also the challenges that accompany implementation of new software.
2. Discuss the current application of novel tools and whether there is any risk, regulatory or other, of using novel tools compared to those which are considered the "gold-standard".

3. Understand where the field of quantitative pharmacology is going over the next 5-10 years with regard to which tools may become more or less applied.
4. Examine if any and what changes may be needed to academic training programs in light of these developments.

6. Speakers (4)

Balancing capability while balancing budgets in a diversifying field.

Daniele Ouellet

The presentation will highlight balancing resource and budgets in light of varying skills among individuals (e.g experts in PBPK, QSP, traditional PopPK, CTS) within a quantitative pharmacology organization. Other considerations for adoption of new commercial and/or open source tools in the industry setting such as workforce training, validation and organization level implementation will also be discussed.

A Regulatory Perspective on Conducting and Reviewing Analyses that Utilize Emerging Technologies

Yaning Wang

This talk will focus on the regulatory perspective with regard to acceptability or challenges when reviewing analyses conducted with alternatives to most common software. Current tools utilized and process for adopting novel tools within the regulatory organization will be discussed.

Considerations for the development of free, open-source pharmacometric software.

Marc Gastonguay

This presentation will present considerations from the perspective of the software developer, specifically free, open-source software, with regard to development such as capabilities and functionality, qualification, training, and adoption. The motivation behind development of a new tool will also be discussed.

Training the future quantitative pharmacologist- Casting a wide net or choosing an area of expertise.

Joga Gobburu

This talk will explain current practice when training quantitative pharmacologists including software utilized in the curriculum versus software used for a specific project. The strategy with regard to focusing on a few specific software programs, having an introductory understanding of many tools, or a hybrid will be discussed.

7. Special AV requirements : NA

8. Budget: All listed speakers are ISoP members and no travel assistance is needed.