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

Daniele Ouellet, PhD (ISoP member)
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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

Quantitative Applications in Biopharmaceutics: Development and Use of Quantitative Mechanistic Modeling and In Vitro In Vivo Correlations for Formulation Screening and Selection, and Setting Clinically Relevant Dissolution Specifications

Symposia

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Richard Bertz, Bristol-Myers Squibb, PO Box 5400, richard.bertz@bms.com

Session Description

The use of modeling and simulation in biopharmaceutics for the selection of optimal clinical formulations in both early and late stage of development, and the translation of in vitro and preclinical in vivo characteristics into human bioavailability is gaining increasing importance. More importantly, the application of quantitative methods for assuring quality of a new product has become central to the Quality-by-Design (QbD) expectation from regulatory agencies that have been widely adopted by the industry. Currently risk-based approaches are used to control product quality with insufficient or no consideration of clinical relevance. The integration of biopharmaceutics tools into QbD implementation for drug product development is key for setting clinically relevant drug product specifications (CRDPS) as they provide the link between product chemistry and manufacturing controls (CMC) and its clinical performance.

This symposium will focus on use of mechanistic modeling such as physiologically-based pharmacokinetic modeling (PBPK) in development of formulations, and empirical models correlating in vitro dissolution and drug manufacturing process parameters with human in vivo data to assess product quality. The first two presentations will highlight the tools and strategies used for translating observed clinical behavior and in vitro characterization of formulations into quantitative physiological based models for understanding the mechanisms of drug absorption and bioavailability. The subsequent presentations will demonstrate the use of in vitro in vivo correlation (IVIVC) and in silico PBPK modeling and simulation for defining CRDPS, and for identifying critical process parameters to define the manufacturing design space (i.e., QbD).

Learning Objectives

- Use of mechanistic modeling of in vitro data from physicochemical characterization and dissolution studies to inform decisions early in the formulations development process
- Describe the techniques and requirements for development and evaluation of robust In Vitro-In Vivo Extrapolation (IVIVE) and In Vitro-In Vivo Correlation (IVIVC) models and their application in formulation selection and optimization
- Describe the role of IVIVC and PBPK modeling in setting clinically meaningful dissolution specifications and assuring the quality of a new drug product

Potential Speakers

1. **Shriram M Pathak**, PhD Research Scientist, SimCYP
   Shriram.Pathak@certara.com
   Presentation: Physiologically based modeling of preclinical in vitro and in vivo data for selection of optimal formulations for development
2. **David Good**, PhD Senior Research Investigator II, Drug Product Science and Technology , Bristol-Myers Squibb David.Good2@bms.com
   Presentation: Quantitative predictions that combine in vitro biopharmaceutics characterization and early clinical data to identify commercially viable formulations
3. **Patrick Marroum**, PhD Clinical Pharmacology and Pharmacometrics, AbbVie
   Patrick.Marroum@Abbvie.com
   Presentation: The role of IVIVC in setting clinically meaningful dissolution specifications and assuring the quality of a new drug product
4. **Sandra Suarez Sharp**, PhD Division of Biopharmaceutics, Office of New Drug Products, CDER FDA Sandra.Suarez@fda.hhs.gov
   Presentation: The role of modeling and simulation in setting clinically relevant drug product specifications

Additional AV Needs: None