2019 NCB Nonclinical Biostatistics Conference

RUTGERS THE STATE UNIVERSITY OF NEW JERSEY

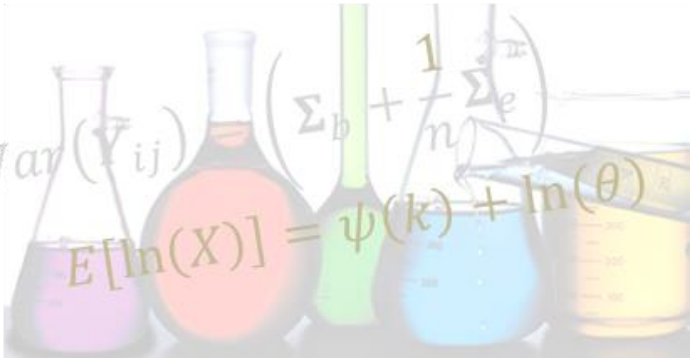
June 17-19, 2019

BIOPHARMACEUTICAL SECTION

ASA Biopharmaceutical Section
Nonclinical Biostatistics Conference

June 17-19, Rutgers University

Advancing drug development from discovery to commercialization



College Avenue Student Center
126 College Ave, New Brunswick, NJ 08901

Acknowledgements

The Organizing Committee would like to thank the following organizations for their support:

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Special thanks also to the *Department of Statistics* at *Rutgers University* for hosting the event and to the *American Statistical Association* for registration services.

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	Binbing Yu	AstraZeneca	*Shuguang Huang*	Stat4Ward
	Rick Burdick	Burdick Stat Consulting		

Monday, June 17			
Time	**Abstract #**	**Title**	**Presenter**
8:00 – 8:30		Breakfast	
8:30 - NOON	Short Courses	R Shiny with real-data example (Room A) Analysis of Composition Data with CMC applications (Room B)	Max Kuhn Juan José Egozcue, Maribel Ortega, and Tony Lonardo
NOON – 1:00		Lunch	
1:00 – 1:10		Welcome	John Kolassa (Rutgers)
1:10 – 1:20		NCB and ASA Biopharm	Mandy Bergquist (GSK)
1:20 – 1:30		Graduate Student/Young Professional Outreach	Phillip Yates (BMS)
1:30 – 2:15	C1	Statistical methods for comparative assessment of quality attributes	Richard Burdick (Burdick Statistical Consulting)
2:15 – 3:00	V1	Use of R in a regulated environment	Xiao Ni (Novartis)
3:00 – 3:15		Break	
3:15 – 4:00	S1	Harness the Power of Real World Evidence and Artificial Intelligence in Drug Development	Harry Yang (MedImmune)
4:00 – 4:45	D1	Transfer Learning in Single Cell Transcriptomics	Divyansh Agarwal (U. of Pennsylvania)
4:45 – 5:00		Break	
5:00 – 6:00		**ASA Presidential Presentation**	Karen Kafadar (UVA)
6:00 – 7:15		Reception	

Key: CX = CMC, DX = Discovery/Biomarkers, SX = Safety/Pharmacology, VX = Statistical Computing and Visualization

Tuesday Common Schedule, June 18			
Time	**Abstract #**	**Title**	**Presenter**
8:00 – 8:30		Breakfast	
8:30 – 9:15	V2	Bayesian Analysis using Stan	Daniel Lee (Generable)
9:15 – 10:00	C2	Population bioequivalence, in-vitro bioequivalence and CMC or analytical equivalence	Yi Tsong (CDER, FDA)
10:00 – 10:15		Break	
10:15 – 11:00	D2	Applications of Deep Learning in Pharmaceutical Development	Xin Huang (AbbVie)
11:00 – 11:45	Poster	Poster Session	
11:45 – 12:45		Lunch	
12:45 – 2:00		Parallel sessions	See break-out tables
2:00 – 2:20		Break	
2:20 – 3:35		Parallel sessions	
3:35 – 3:55		Break	
3:55 – 4:45		Parallel sessions	
4:45 – 5:00		Break	
5:00 – 5:15		Best Nonclinical paper award and Student Poster awards	
5:15 – 6:00		**Keynote Speaker Presentation**	José Pinheiro (J&J)
6:00 – 7:15		Reception	

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Tuesday Afternoon Students, June 18			
Time	**Abstract #**	**Title**	**Presenter**
11:45 – 12:45		Lunch Roundtable Discussion	
1:35 – 2:00		Career Opportunities	

Tuesday Afternoon CMC parallel sessions (room A), June 18			
Time	**Abstract #**	**Title**	**Presenter**
12:45 – 1:10	C4	An Empirical Comparison of Methods for the Statistical Design and Analysis of Accelerated Stability Experiments	Bill Porter (Peak Process Performance Partners)
1:10 – 1:35	C5	Equivalence Margin Evaluations for Analytical Method Transfer	Oluyemi Oyeniran (J&J)
1:35 – 2:00	C6	Statistical approach to a Real Time Release (RTR) strategy for dissolution testing in a continuous manufacturing (CM) process	Dwaine Banton (Janssen)
2:00 – 2:20		Break	
2:20 – 2:45	C7	Near-Universal Equivalence Bounds for Similarity in Bioassay	David Lansky (Precision Bioassay)
2:45 – 3:10	C8	Estimating the Precision of Analytical Methods in Pharmaceutical Development and Manufacturing	Ranran Dong (Genentech)
3:10 – 3:35	C9	A fit-for-purpose perspective on Shelf-Life and Internal Release Limits determination: objectives and models	Angel Lu (Pharmalex)
3:35 – 3:55		Break	
3:55 – 4:20	C10	Process Monitoring in Pharmaceutical Industry - Challenges and Recommended Solution	Yiming Peng (Genentech)
4:20 – 4:45	C11	Linear Splines for Shelf Life Analysis of a Drug Product Stored in Hybrid Storage Conditions	John Oleynick (J&J)

Tuesday Afternoon Other parallel sessions (room B), June 18			
Time	**Abstract #**	**Title**	**Presenter**
12:45 – 1:10	D4	Design issues for dose-response studies	Shuguang Huang (Stat4Ward)
1:10 – 1:35	D5	Multivariable Association in Population-scale Meta'omic Surveys	Himel Mallick (Merck)
1:35 – 2:00	D6	Gauging Epigenetic Changes by Combining RNA Expression, DNA Methylation and Histone Acetylation Data	Davit Sargsyan (Rutgers/Janssen)
2:00 – 2:20		Break	
2:20 – 2:45	S3	New paradigm to derive and assess ADA cut points	Charles Tan (Pfizer)
2:45 – 3:10	S4	Assessing the Suitability of Immunoassay Cut Points from Validation for Use In-Study	Andrew Gehman (GSK)
3:10 – 3:35	S5	Design and analysis of a Reproductive Toxicology Auditory Startle Test	Kanaka Tatikola (J&J)
3:35 – 3:55		Break	
3:55 – 4:20	V4	Gaining Insights into lncRNA Function in IBD from Network Analysis via a Shiny Dashboard	Stefan Avey (Janssen)
4:20 – 4:45	V5	A unified framework for unconstrained and constrained ordination of microbiome read count data	Stijn Hawinkel (Ghent University)

Wednesday, June 19			
Time	**Abstract #**	**Title**	**Presenter**
8:00 – 8:30		Breakfast	
8:30 – 9:15	V3	Getting to know Python through examples	Dan Chen (Virginia Tech)
9:15 – 10:00	D3	Increased Collaboration and Reducing Risk Through Bayesian Insight into the Feasibility of an Evolving Animal Model in Discovery	Thomas Bradstreet (BMS)
10:00 – 10:15		Break	
10:15 – 11:00	S2	Infinite Parameter Estimates in Proportional Hazards Regression	John Kolassa (Rutgers Univ.)
11:00 – 11:45	C3	Design and Analysis of Computer Experiments for Continuous Manufacturing Processes	John Peterson (GSK)
11:45 – NOON		Concluding remarks	Steven Novick
12:00 – 1:30		Lunch / End of Conference	
1:30 – 2:15		Organizing Committee	

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Short Course Descriptions

Monday, June 17, 8:30 AM – 12 PM

Course Title: An R shiny tutorial with nonclinical applications
Instructors: Max Kuhn and Phil Bowsher, RStudio

Description: RStudio will be presenting an overview of Shiny, R Markdown and HTML Widgets. This is a great opportunity to learn and get inspired about new capabilities for creating compelling analyses with applications in drug development. No prior knowledge of R, RStudio or Shiny is needed. This short course will provide a hands-on introduction to flexible and powerful tools for statistical analysis, reproducible research, and interactive visualizations. For the workshop attendees, we will be providing a free RStudio training instance to use in case participants cannot install software on their laptops.

Course Title: Getting it right: Compositional analysis of biological measurements
Instructors: Anthony Lonardo (Lonardo StatReg Associates) and Juan José Egozcue and Maribel Ortego (Dept. Civil and Environmental Engineering, Universitat Politecnica de Catalunya in Barcelona, Spain)

Description: In biological systems like those encountered in the Pharmaceutical industry, critical chemical and biological measures are developed to accelerate discovery and development and ensure process control and product quality. Many of these measures have the characteristic of being elements of a whole and their measures frequently add to a constant. For example, a drug substance may contain a combination of 3 species which add to 100% (y1+y2+y3=100%). Systems of measurements such as these are called Compositional Data (CoDa). Unfortunately, analysis of compositional data is often performed implicitly assuming that these data comply with a standard Euclidean distance and geometry. These assumptions are considered inconsistent. Using conventional methods could lead to incoherent inference and estimation of tolerance or multivariate regions which are not scientifically possible. This problem had long been known and first identified by Karl Pearson (1896). It took 100 years, but a strategy was developed by Aitchison (1986), and new and exciting innovations have, and are being developed since then (for instance see contributions to CoDaWork conferences). This problem has been addressed for a number of disciplines, but only recently (Lonardo, 2017) applied to critical pharmaceutical compositional problems.

This course will provide a brief introduction to the topics and will lay out modern strategies and methods for dealing with the challenges of Compositional Data Analysis. This will be taught by leading experts (JJ Egozcue, MI Ortego) in this quickly developing field.

ASA Presidential Address. *Speaker*: Karen Kafadar (Department of Statistics, Univ. of Virginia)

Title: To Screen or Not to Screen? Evaluating benefits & biases in cancer screening trials

Abstract: On the surface, it seems obvious that cancer screening should reduce mortality. But do regular cancer screenings really save lives, or extend lifetimes? If cancer screening is useful, it should both detect the cancer earlier when less aggressive treatment options are available and also extend lifetimes. But suppose all it does is enable earlier detection; the date of death remains the same. That may not be a very useful outcome for the patient. As with any medical treatment, a randomized trial is the most effective method for evaluating cancer. Neither the design nor the analysis of results from cancer screening trials is as straightforward as that for clinical trials. In addition to the effect of "lead time" (earlier diagnosis) just mentioned, screening trials involve cases that are not all "comparable": slower-growing cancers are more likely to be screen-detected than those that grow so fast that screening never had a chance to detect them ("length biased sampling"). Screening trials involve these and other biases; estimating the "benefit" of cancer screening requires that we take them into consideration. In this presentation, I will discuss four of these effects, as well as methods to account for them. A model for evaluating length-biased sampling shows that these biases can have a substantial impact, whereby screening looks "beneficial" even in the absence of a real screening benefit. Finally, I will discuss the 2019 ASA President's Initiatives, one of which incorporates statisticians' role in addressing problems like the one discussed in this presentation.

Keynote Address. *Speaker*: José Pinheiro (Johnson & Johnson)

Title: Extensions of MCP-Mod beyond dose finding in drug development: Model-based methods under model uncertainty in CMC and Discovery

Abstract: The MCP-Mod approach was developed in the context of dose selection in clinical drug development, with the goal of providing a well-principled method for model-based target dose estimation under model uncertainty. The central idea of the methodology is the use of a set of candidate models to represent the unknown dose-response profile, using a multiple comparison procedure (MCP) to account for model uncertainty in combination with modeling (Mod) of the dose response relationship. MCP-Mod has received widespread interest and application in the pharmaceutical industry since it received a positive qualification opinion from the CHMP/EMA and a fit-for-purpose denomination from the U.S. FDA.

Although originally developed with a specific application in mind, the key principle of model-based inference under model uncertainty that underpins MCP-Mod may be employed in other areas of drug development. In this talk we'll explore some of such potential extensions, namely in the areas of CMC and Drug Discovery. A review of MCP-Mod in its original context will also be presented and illustrated, so no prior knowledge of the methodology will be assumed.

Invited Speaker Abstracts

NCB

Presenter: John Kolassa (Rutgers)

A welcome to the conference.

Presenter: Mandy Bergquist (GSK)

A brief overview of the NCB working group as part of Biopharmaceutical Section of the ASA. Benefits of participating in NCB activities.

Presenter: Phillip Yates (BMS)

A quick summary of the NCB conference graduate student program.

CMC

C1. *Speaker*: Richard K. Burdick (Burdick Statistical Consulting)

Title: Statistical methods for comparative assessment of quality attributes

Abstract: There has been much recent interest from regulatory agencies concerning the comparative assessment of quality attributes. Evidence is the EMA workshop held in May 2018 to review their draft reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development, a September 2018 PDA workshop on the topic, and the June 2018 withdrawal of the FDA draft guidance "Statistical Approaches to Evaluate Analytical Similarity" to consider changes that will "promote a more efficient pathway for the development of biosimilar products". Many competing statistical approaches have been proposed to demonstrate comparability, and this presentation will review several of them citing advantages and disadvantages. The presentation considers both statistical tests and heuristic rules, and describes the necessity of controlling risks for both patients and sponsors.

C2. *Speaker*: Yi Tsong (CDER, FDA)

Title: Population bioequivalence, in-vitro bioequivalence and CMC or analytical equivalence

Abstract: In a traditional assessment of bioequivalence of two formulations of a drug, one compares the average bioavailability form the two formulations. In early 1990s, statisticians and clinical pharmacologists pointed out in some situations, it is not sufficient to demonstrate average bioequivalence, and they proposed to compare the individual responses to the two drug formulations within the subjects. This method is called individual bioequivalence (IBE). At the same time, population bioequivalence (PBE) was also proposed to compare the marginal or population distributions of bioavailability. The new approaches overcome the main weakness of ABE by considering the variability of the bioavailabilities in addition to their means. PBE, defined as $(\mu_T - \mu_R)^2 + (\sigma_T^2 - \sigma_R^2)$ which is the difference of the square of the difference in means, and the difference between the variances. It is compared to $\theta_{PBE} \cdot \max(\sigma_0^2, \sigma_R^2)$ for equivalence, where $\theta_{PBE} = \frac{(\ln(1.25)^2 + \epsilon_P)}{\sigma_0^2}$, $\sigma_0 = 0.2$ and $\epsilon_P = 0.02$. For application as in-vitro BE, FDA Guidance recommends to use ln(1.11) for small variability. In another word, PBE is determined by a function of ABE margin. In this presentation, we discuss the weakness of using PBE to assess in-vitro, CMC and analytical equivalence.

C3. *Speaker*: John Peterson (GSK)

Title: Design and Analysis of Computer Experiments for Continuous Manufacturing Processes

Abstract: Continuous manufacturing processes are an important and upcoming technology for the pharmaceutical industry. For such processes, it is often natural and helpful to develop mechanistic models for each stage of the continuous manufacturing process. These models are then linked together to form one complex, nonlinear model, typically having at least several input factors. The exploration and understanding of the response surface associated with such a model can be greatly aided with the methodology of "computer experiments". This area has been in development and utilization for a couple of decades in other industries, but is new to pharmaceutical development. Our talk will show how the design and analysis of computer experiments can be used to aide in the understanding and to provide support complex mechanistic models for continuous pharmaceutical manufacturing. We will also point to the use of R packages and JMP for the design and analysis of computer experiments using a real continuous pharmaceutical manufacturing example.

Discovery/Biomarkers

D1. *Speaker*: Divyansh Agarwal/Nancy Zhang (University of Pennsylvania)

Title: Transfer Learning in Single Cell Transcriptomics

Abstract: Cells are the basic biological units of multicellular organisms. The development of single-cell RNA sequencing (scRNA-seq) technologies have enabled us to study the diversity of cell types in tissue and to elucidate the roles of individual cell types in disease. Yet, scRNA-seq data are noisy and sparse, with only a small proportion of the transcripts that are present in each cell represented in the final data matrix. We propose a transfer learning framework to borrow information across related single cell data sets for de-noising and expression recovery. Our goal is to leverage the expanding resources of publicly available scRNA-seq data, for example, the Human Cell Atlas which aims to be a comprehensive map of cell types in the human body. Our method is based on a Bayesian hierarchical model coupled to a deep autoencoder, the latter trained to extract transferable gene expression features across studies coming from different labs, generated by different technologies, and/or obtained from different species. Through this framework, we explore the limits of data sharing: How much can be learned across cell types, tissues, and species? How useful are data from other technologies and labs in improving the estimates from your own study? If time allows, I will also discuss the implications of technical batch artifacts in the joint analysis of multiple data sets, and propose strategies for alignment of data across batch.

D2. Xin Huang (AbbVie)

Title: Deep Learning Opportunities and Challenges in Drug Discovery and Biomarker Development

Abstract: Deep Learning has gained extreme popularity in recent years as the advancement of computing power makes it possible to optimize a multi-layer artificial neural network within a short period of time. Deep Learning has proven its superiority in handling unstructured data relative to other machine learning techniques and has been widely used for image classification and natural language processing. While deep learning has the power to make sense of unstructured data, such as images or physician notes, its uptake by nonclinical statisticians is slowed due to several challenges, including the methodologies themselves and the required tool boxes and computation infrastructure. Statisticians are considered the data experts, so we should play an active role whether the data are structured or unstructured.

In this talk, we will discuss the methods and applications of deep learning in pharmaceutical development, including transfer learning for lung cancer subtyping, applications in natural language processing of free text for drug development and scientific communication, and deep learning-based image analysis for biomarker discovery. These successful case studies and latest methodology development can further raise the awareness, expand knowledge base, share best practice and facilitate wider applications of deep learning for a more efficient drug development and generate additional insights to communicate the value of innovative medical intervention.

D3. Thomas Bradstreet (BMS)

Title: Increased Collaboration and Reducing Risk Through Bayesian Insight into the Feasibility of an Evolving Animal Model in Discovery

Abstract: A proposal was presented for a three-treatment, randomized, parallel, longitudinal translational medicine study of hyperlipidemia in monkeys. Animals were to enter the study and during the Run-In Period they were to receive a special diet to drive up their lipid levels to a specified target level to qualify to enter the randomized Treatment Period. It was suggested that it would take 30 animals to enter the Run-In period to qualify at least 24 animals to enter the Treatment Period. Based upon data from 3 previous studies, it was determined that the predicted probability of success (PPOS) in the Run-In Period based upon the initial proposal was unacceptable. Indeed, it might take as many as 65 animals to enter the Run-In Period to achieve an acceptable PPOS to qualify 24 animals. Armed with this information, a collaborative critical reassessment of the study and evolving animal model included, but was not limited to: hyperlipidemia target levels, entrance criteria, monitoring procedures, innovative experimental designs, decision rules, lab space, and fiscal constraints.

Safety/Pharmacology

S1. *Speaker*: Harry Yang (AstraZeneca)

Title: Harness the Power of Real World Evidence and Artificial Intelligence in Drug Development

Abstract: Real-world data (RWD) are healthcare data that are collected outside the constraints of conventionally-controlled randomized trials (CRTs) and real-world evidence (RWE) is the knowledge derived from aggregation and analysis of RWD. Traditionally, RWE was either utilized in the design stage of CRTs to define endpoints, study populations, treatment effect size or collected as post-marketing commitments. In recent years, however, the rapid increase in the volume, variety, and accessibility of digitized RWD, coupled with artificial intelligence (AI), has presented unprecedented opportunities for harnessing RWE in support of drug development throughout its lifecycle. This presentation discusses how advances in technologies have changed the drug development paradigm including drug safety evaluations. Such changes entail the need for statisticians to acquire knowledge and skills in cloud-based systems capable of generating evidence from big data using artificial intelligence (AI) and machine learning. Case examples are presented, showcasing the impact and power of RWE and AI in drug development.

S2. Presenter: John Kolassa (Rutgers University)

Title: Infinite Parameter Estimates in Proportional Hazards Regression

Proportional hazards regression shares the possibility of infinite parameter estimation with logistic and multinomial regression. In this talk, I demonstrate how to perform approximate conditional inference on finite components of the proportional hazards regression model in the presence of infinite estimates for nuisance parameters, by employing optimization techniques to reduce the data set to one yielding conditional inference approximating that of the desired regression model.

Statistical Computing/Visualizations

V1. *Speaker*: Xiao Ni (Novartis)

Title: Use of R in a regulated environment

Abstract: R as an open source statistical language and the ever-growing R ecosystem have gained popularity among statisticians, including those in the pharmaceutical industry and the FDA. The R tool chain including tidyverse, Shiny and Rmarkdown etc. empowers statisticians to process high-throughput and messy data, perform exploratory analysis through visualizations and modeling, and build dynamic web applications / reports to facilitate collaborative data interpretation and communication.

On the other hand, there are challenges associated with using R or any other open-source tools in a regulated environment, e.g. “validation” of R packages, “validation” of a dynamic interactive Shiny application, or even in understanding of different terminology such as “validation” or “qualification”. Although FDA stated in its statistical software clarifying statement that “FDA does not require use of any specific software for statistical analyses...”, there has been no consensus or practical guidance on how to address these challenges.

In this talk, I will shed light on these issues, using information from the 2018 R/Pharma validation workshop as well as the subsequent cross-industry collaborative R Validation Hub project. I will present some concepts/principles such as fit-for-purpose, as well as techniques in Shiny app development such as using meta-data and Shiny modules, bookmark states, exporting to reports with annotation/code etc. These may help towards achieving reproducibility, traceability and transparency, and could be also be useful for non-GxP applications.

V2. Speaker: Daniel Lee (Generable)

Title: Bayesian Analysis using Stan

Abstract: Stan is a state-of-the-art platform for statistical modeling and high-performance statistical computation. Thousands of users rely on Stan for statistical modeling, data analysis, and prediction in the biological, social, and physical sciences, engineering, and business. Users specify log density functions in Stan's probabilistic programming language and invoke the following inference algorithms: 1) full Bayesian statistical inference with MCMC sampling (NUTS, HMC); 2) approximate Bayesian inference with variational inference (ADVI); 3) penalized maximum likelihood estimation with optimization (L-BFGS).

The most exciting of the above algorithms is HMC with NUTS which, due to its self-tuning properties, brought HMC and full Bayesian inference to wider statistical and machine learning communities. With NUTS, users routinely fit models with thousands and even hundreds of thousands of unknowns jointly, a task that was completely out of reach for the Gibbs Sampler which was the state of the art in MCMC before Stan. In this talk, I will describe the basic structure of the Stan language, talk about how Stan works under the hood, and point out its strengths and weaknesses.

V3. Speaker: Dan Chen (VA Tech, graduate student)

Title: Getting to know Python through examples

Abstract: Python and R are among the most popular languages in data science. Depending on your background, you will either start your journey in one language or the other, e.g., statisticians typically come from the R world and computer scientists come from Python. In practice, people eventually learn the other language, regardless of background. We will begin this transition into Python and learn how it is used to process and model data by example. Let's see out how to install it, run it, load data, tidy it up, make a few plots here and there, and fit some models, using Pandas, Seaborn, Scikit-learn, and statsmodels. By the end of this you should be able to see the similarities of Python and your data analysis language of choice, and be able to tackle those blog posts and tutorials you've been skipping all this time.

Contributed Speaker Abstracts

CMC

C4. Presenter: Bill Porter (Peak Process Performance Partners LLC)

Title: An Empirical Comparison of Methods for the Statistical Design and Analysis of Accelerated Stability Experiments

Abstract: Risk-based assessment of drug product shelf life based on accelerated degradation studies can frequently be performed if an expanded Arrhenius kinetic model relating the rate of degradant formation to exposure to elevated temperature and relative humidity can be fitted to experimental measurements of the fraction of parent drug substance that is converted to a stability-limiting degradant collected under these stress conditions after varying exposure times. Historically, such modeling efforts date from the mid-twentieth century. After several decades of shelf life estimation based on accelerated conditions using simple temperature-based Arrhenius models, attention became focused on real time stability studies, resulting in formal guidelines issued by regulatory authorities. However, recently the pendulum has swung back, and there is renewed interest in using more complex Arrhenius-like models incorporating both thermal and moisture stress to obtain a prediction of shelf life under normal storage conditions as a means to accelerate drug development and reduce development costs. We discuss various experimental designs that have been used historically and demonstrate that efficient modeling can be performed using designs in which degradation is allowed to continue until failure to meet shelf life specifications under all stress conditions tested. A method for generating artificial (simulated) data with realistic uncertainty is described. Several different approaches to statistical modeling are described, including a method based on using just the estimated shelf life at each stress condition, a holistic nonlinear regression approach based on the direct shelf life estimation using the approach developed by King, Kung and Fung, and different two-stage methods based firstly upon estimation of the degradation rates themselves followed by a second stage fitting an Arrhenius model to the rates estimated in the first stage using ordinary least squares, weighted least squares or generalized least squares multiple linear regression methods. By using simulated data generated using known model parameters, the relative accuracy and precision of these different modeling procedures could be compared.

C5. Presenter: Oluyemi Oyeniran (J&J)

Title: Equivalence Margin Evaluations for Analytical Method Transfer

Abstract: In pharmaceutical development, Analytical Method Transfers (AMT) are essential components, in which a validated analytical test procedure in one laboratory is adopted by one/more recipients laboratories. Typically, an equivalence test is performed to assess the similarity of laboratory performances in the analytical procedure. The intent of equivalence testing is to demonstrate that the laboratory performances in the analytical procedure of a receiving lab is within an acceptable range of the transfer lab. Statistical equivalence testing is a statistical tool for method transfer which includes both, a practically relevant acceptance limit and a direct control of the statistical risks. To assure an efficient and sustainable transfer of analytical procedures, a practically relevant and scientifically meaningful evaluation with corresponding equivalence margin is crucial. Deciding what constitutes an important and acceptable equivalence margin between results is rather challenging. The success criterion is not statistical significance, but rather analytical relevance. In this presentation, we will discuss the use of historical data, statistical designs and the application of statistical tools as a guidance for the scientist/analyst in the determination of equivalence margin. In the course of our discussion, we will point out some limitations, which can lead to misuse, as well as the utility of applying appropriate testing designs.

C6. Presenter: Dwaine Banton (Janssen)

Title: Statistical approach to a Real Time Release (RTR) strategy for dissolution testing in a continuous manufacturing (CM) process

Abstract: The pharmaceutical industry is undergoing a revolution in how pharmaceutical products are manufactured from batch processing to continuous manufacturing (CM). The advantages include higher quality, less environmental impact, flexibility in meeting market demand and faster to market through an RTR strategy. To meet the promise of faster release, critical quality attributes (CQA) such as content can be characterized through Near Infrared (NIR) technology. In vitro dissolution testing is one of the critical quality control tests of solid oral dosage forms required for releasing drug product into commercial distribution. The laboratory based analytical method for determining in vitro release is time consuming and expensive, so there is ample incentive to develop a surrogate measurement method as part of a comprehensive real time release (RTR) strategy. This talk will outline the essential steps in moving from: 1. a comprehensive DoE leading to a multivariate hierarchical model of content by NIR and dissolution rate at 30 minutes (Q30) vs critical process factors, to 2. a linear estimator relating mean content by NIR and process effects to mean Q30, to 3. a validation design and confirmation of the predictive surrogate model. Finally, a Bayesian posterior predictive approach was used to characterize the method's analytical performance.

C7. Presenter: David Lansky (Precision Bioassay)

Title: Near-Universal Equivalence Bounds for Similarity in Bioassay

Abstract: A major goal of bioassay development, validation, and monitoring is to minimize bias of potency. Testing for similarity via equivalence tests has become an essential part of modern bioassay analyses. Sensitivity analyses, reported here, show that scaled shifts in parameters measure non-similarity in ways that are assay-independent. We show that well-chosen similarity equivalence bounds limit bias in potency due to non-similarity. Hence, equivalence bounds for non-similarity can be informed by bias limits based on product specifications and the analytic target profile.

C8. Presenter: Ranran Dong (Genentech)

Title: Estimating the Precision of Analytical Methods in Pharmaceutical Development and Manufacturing

Abstract: The precision of an analytical method expresses the closeness of agreement between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be considered at three levels: repeatability, intermediate precision and reproducibility. In this talk, we will focus on estimating the intermediate precision of analytical method from three aspects: 1) analytical method validation during development; 2) analytical method monitoring during commercial manufacturing; 3) stability study across development and manufacturing. We will discuss case studies, share lessons learned, and demonstrate that the analytical method is suitable for its intended use throughout the lifecycle.

C9. Angel Lu (Pharmalex)

Title: A fit-for-purpose perspective on Shelf-Life and Internal Release Limits determination: objectives and models

Abstract: This talk proposes to use a Bayesian approach to better estimate shelf-life and internal release limits in mixed model settings. It starts by explaining the general concepts, regulatory expectations, and the flaws in the current methods. This talk also includes illustrations of the Bayesian approach in two applications that use a linear mixed model and a non-linear mixed model respectively.

C10. Yiming Peng (Genentech)

Title: Process Monitoring in Pharmaceutical Industry - Challenges and Recommended Solution

Abstract: In recent years, many pharmaceutical companies have been developing systematic approaches to monitor manufacturing processes, and provide the opportunity to influence the evolving regulatory oversight. In this talk we will give an overview of the fundamental concepts and assumptions of the standard Statistical Process Control (SPC) approach. We will explain the challenges of applying the standard SPC approach in pharmaceutical industry, and discuss our journey in implementing the alternative SPC approach to enhance process understanding and drive process improvement. We will also discuss the connection between process monitoring and process capability analysis to support the evaluation of state of control.

C11. John Oleynick (J&J)

Title: Linear Splines for Shelf Life Analysis of a Drug Product Stored in Hybrid Storage Conditions

Abstract: Large-molecule pharmaceutical products frequently require storage in refrigerated conditions, typically 2-8C. For some patients, this may restrict them from certain activities, such as a travel, and it would be helpful to the patient if the product could be stored at room temperature, such as 25C, for a short duration prior to use. To accommodate this, stability studies can be conducted to ensure that the product remains safe and effective for the duration of its shelf life, when it is stored at the recommended temperature for most of the duration of the shelf life, and then stored at a controlled room temperature for a short period before the end of the shelf life, such as 1-4 weeks. These conditions may be referred to as hybrid storage conditions. A typical statistical analysis of a stability study assumes the product will have a consistent degradation for the duration of its shelf life, frequently a linear or log-linear rate, or a higher order kinetic model. But this may not be appropriate if the storage conditions are changed in the middle of the study, and the product may change or degrade at one rate during the recommended temperature portion of the study and a faster rate during the room temperature portion. We propose using linear splines in a regression model to accommodate this change in storage temperature, and show that the product remains safe and effective for the duration of the hybrid storage stability study.

Discovery/Biomarkers

D4. Presenter: Shuguang Huang (Stat4Ward)

Title: Design issues for dose-response studies

Abstract: For probit regression used for estimating assay LOD, CLSI EP17 gives the suggestion that “The dilution series should be made so that at least three dilutions yield hit rates within the range of 0.10 to 0.90 and at least one dilution yields a hit rate exceeding 0.95” (so > 5 concentrations). EP17 also comments that “It is not desirable to have more than one dilution at either extreme (ie, < 0.10 and/or > 0.95), as this could unduly impact the quality of the probit model fit and resulting LoD estimate.”
What is the statistical rationale for choosing a particular design? Is it true that having extreme concentrations would unduly impact the model fit? For a given resource and budget, say 100 assays, which design is better: 5 concentrations with 20 replicates for each concentration; 10 concentrations with 10 replicates each; or 20 concentrations with 5 replicates each? This presentation investigates this very basic yet unaddressed question that is constantly faced by the lab scientists.

D5. Presenter: Himel Mallick (Merck)

Title: Multivariable Association in Population-scale Meta'omic Surveys

Abstract: It is challenging to associate features such as human health outcomes, diet, environmental conditions, or other metadata to microbial community measurements, due in part to their quantitative properties. Microbiome multi'omics are typically noisy, sparse (zero-inflated), high-dimensional, and extremely non-normal, often in the form of count or compositional measurements. Here, we introduce an optimal combination of novel and established methodology to assess multivariable association of microbial community features with complex metadata in population-scale observational studies. Our approach, MaAsLin2 (Multivariable Association with Linear Models), relies on linear models to accommodate a wide variety of modern epidemiological study designs including cross-sectional and longitudinal. To construct this method, we conducted a large-scale evaluation of a broad range of scenarios under which straightforward identification of meta'omic associations can be challenging. These simulation studies reveal that MaAsLin2's linear model preserves statistical power in the presence of repeated measures and multiple covariates while accounting for the nuances of meta'omic features and controlling false discovery. We also applied MaAsLin2 to a microbial multi'omic dataset from the Integrative Human Microbiome Project (HMP2) which, in addition to reproducing established results, revealed a unique, integrated landscape of inflammatory bowel disease (IBD) across multiple time points and 'omics profiles.

D6. Davit Sargsyan (Rutgers/Janssen)

Title: Gauging Epigenetic Changes by Combining RNA Expression, DNA Methylation and Histone Acetylation Data

Abstract: Epigenetic changes are caused by modification of gene expression rather than gene mutation. There are various levels at which these changes can be measured, starting with histone modifications that allow gene transcription by relaxing chromatin structure, to DNA methylation, especially in the promoter region, that can prevent binding of transcriptional proteins to the gene, to amount of messenger RNA (mRNA) in cytoplasm. We therefore combined the three measurements from a single experiment to find genes that exhibited specific patterns, e.g. decreased histone acetylation and/or increased DNA methylation while decreasing mRNA expression. In the study conducted by Dr. Kong's lab, cancer-preventive effect of curcumin (a natural compound found in turmeric) was tested in azoxymethane+dextran sulfate sodium (AOM+DSS) mouse model. The mice were randomly assigned to one of the three experimental groups: control, AOM+DSS or AOM+DSS+Curcumin. During the study colon tissue samples were collected at weeks 8 and 18, genetic material extracted from the samples' epithelial cells and processed using massive parallel sequencing (also known as next-generation sequencing, or NGS). By combining RNA and DNA data our team has already shown that methylation of the promoter region of Tnf gene was inversely correlated with RNA expression levels at week 18. This finding was subsequently validated by qPCR (Guo 2018). However, no attempt has been made until now to examine all three measurements together. Here we took a step-wise approach by first separating genes with differentially expressed RNA, then examining how CpG methylation of DNA promoter region and histone acetylation of these genes was altered. Since a single gene can have multiple CpG clusters and more than one peak in histone acetylation readouts, unique solutions were developed and applied for analysis and visualization of the data that helped explore the relationships and the underlying mechanisms affecting these markers. This study also enhanced our understanding of the nature of the relationship between histone modification and DNA methylation as they might be both, directly affecting one another or complementary impacting the downstream RNA expressions.

Safety/Pharmacology

S3. Presenter: Charles Tan (Pfizer)

Title: New paradigm to derive and assess ADA cut points

Abstract: Immune responses to therapeutic protein products have the potential to affect product pharmacokinetics, pharmacodynamics, safety, and efficacy. Detection and analysis of Anti-Drug Antibody (ADA) formation is a helpful tool in understanding potential immune responses. In January 2019, FDA published guidance on the development and validation of ADA assay. This talk will present the newly developed Pfizer-wide best practice for the cut points determination for the screening and confirmatory steps in the multi-tier ADA detection assays. Three innovations incorporated in this new paradigm will be described and justified. Several real case studies will be used to illustrate the approach and its benefits. This new paradigm also enables more meaningful decisions on whether populations are sufficiently similar to allow common cut points.

S4. Presenter: Andrew Gehman (GSK)

Title: Assessing the Suitability of Immunoassay Cut Points from Validation for Use In-Study

Abstract: Ensuring patient safety is a crucial component of developing new medicines. Both pre-clinically and clinically, immunoassays evaluate the immunogenicity of biotherapeutics by screening for and confirming anti-drug antibody (ADA) response based on response thresholds or cut points. These cut points are calculated statistically on responses from drug-naïve subjects during assay validation and are designed to control the rate of false positives. During in-study testing, the assay cut points are then applied to responses from treated subjects. This approach assumes that samples used in validation are representative of those in-study; however, the two stages may be substantially separated in time or the samples from each stage may be from different patient populations. Therefore, assessing the appropriateness of pre-study validation cut points for in-study use is essential for ensuring control of the false positive rate and for having confidence that the assay can detect ADA. This work examines case studies to compare in-study baseline responses to those from validation and to evaluate recommended approaches for determining when to calculate study-specific cut points for in-study use.

S5. Presenter: Kanaka Tatikola (J&J)

Title: Design and analysis of a Reproductive Toxicology Auditory Startle Test

Abstract: Reproductive toxicology studies are part of the battery of preclinical safety screens necessary to permit a NCE to pass into human studies. One such screening test is the acoustic startle test. The acoustic startle test generates a burst of sound at a specific pressure level. The response in the test animal is a jerk-like motor reflex and can be measured by movement-sensitive (startle) devices. The response is assessed with respect to latency, amplitude, and threshold as the key response measurements. A diminished acoustic startle response can indicate a brain-stem neurological deficit. This talk will present an innovative design and modeling strategy for the repeated application of the noise signals, exploiting earlier work in serially balanced designs, permitting a coherent estimate of carryover and treatment effects. We will present the rationale behind the experimental design, its construction and modeling strategy.

Statistical Computing/Visualization

V4. Presenter: Stefan Avey (Janssen)

Title: Gaining Insights into lncRNA Function in IBD from Network Analysis via a Shiny Dashboard

Abstract: Long noncoding RNAs (lncRNAs) are effector RNAs that control virtually all cellular processes. Their roles in inflammatory bowel disease (IBD) are poorly defined. Over 80% of the risk alleles for IBD reside in non-coding regions of the genome. Understanding how lncRNAs impact disease pathogenesis could unveil the underlying mechanisms and potentially lead to novel therapeutic targets. Data reduction techniques and visualization platforms are needed to facilitate the use of large -omic datasets comprising lncRNA and mRNA expression. We developed an interactive dashboard using R Shiny for mining a network framework constructed on a large-scale IBD gene expression dataset to generate and validate lncRNA-IBD hypotheses. Methods: RNA sequencing was performed on 2,497 gut biopsy samples from 1,162 IBD and control subjects from the Mount Sinai Crohn's and Colitis Registry (MSCCR) generated in collaboration with the Icahn School of Medicine at Mount Sinai. Gene interactions and multi-scale modules were identified using Multiscale Embedded Gene Co-expression Network Analysis (MEGENA). The resulting gene modules were annotated with correlated lncRNAs, relevant IBD traits, and functional biology. A web application was built in the R Shiny framework as an interface to these analyses. Interactive visualizations allow a user to easily: 1. Identify lncRNA-associated gene modules; 2. Extract gene module members and their key driver (hub) genes; and 3. Retrieve annotations of gene modules with IBD clinical associations and biological insights via signature enrichments in the SaddleSum API. Results: By applying rigorous statistical methods and state-of-the-art data visualization tools, we have presented one of the largest IBD lncRNA expression databases in an easily accessible and interpretable format, providing a resource for understanding disease biology, target prioritization and potential biomarker identification. The utility of this approach has been confirmed with experimental data for a subset of lncRNAs.

V5. Presenter: Stijn Hawinkel (Ghent University)

Title: A unified framework for unconstrained and constrained ordination of microbiome read count data

Abstract: Explorative visualization techniques provide a first summary of microbiome read count datasets through dimension reduction. A plethora of dimension reduction methods exists, but many of them focus primarily on sample ordination, failing to elucidate the role of the bacterial species. Moreover, implicit but often unrealistic assumptions underlying these methods fail to account for overdispersion and differences in sequencing depth, which are two typical characteristics of sequencing data. We combine log-linear models with a dispersion estimation algorithm and flexible response function modelling into a framework for unconstrained and constrained ordination. The method is able to cope with differences in dispersion between taxa and varying sequencing depths, to yield meaningful biological patterns. Moreover, it can correct for observed technical confounders, whereas other methods are adversely affected by these artefacts. Unlike distance-based ordination methods, the assumptions underlying our method are stated explicitly and can be verified using simple diagnostics. The combination of unconstrained and constrained ordination in the same framework is unique in the field and facilitates microbiome data exploration. We illustrate the advantages of our method on simulated and real datasets, while pointing out flaws in existing methods. The algorithms for fitting and plotting are available in the R-package RCM.

Regular posters (alphabetical by area and presenter last name)

P1-C. Presenter: Nelson Afanador (Merck)

Title: Unsupervised Latent Variable Models for Improved Understanding of High-Dimensional Process Data in Early Bioprocess Development

Pharmaceutical bioprocess development has followed the evolution of computing power resulting in an increased availability of high-dimensional process data. Accordingly, interpretable models to describe highly non-linear bioprocess data have relied on unsupervised latent variable models (ULVMs) such as Principal Component Analysis (PCA), Independent Component Analysis (ICA), and Kernel PCA (KPCA). Unfortunately, these methods have several drawbacks. For instance, PCA has a sensitivity to scaling and outliers, and an inability to model higher order statistics in helping reveal important hidden information in the observed data, and an underlying linear approach. ICA ameliorates several shortcomings of PCA by reducing higher-order dependencies and decorrelating the observed data. Furthermore, ICA relies on the same eigenvalue decomposition method as PCA as a pre-processing 'whitening' step, thus potentially inheriting some of the shortcomings of PCA. KPCA offers a flexible option for modeling non-linear relationships, but the selection of an appropriate kernel can be a difficult task. Accordingly, the use of ULVMs to describe highly non-linear data continues to be an interesting challenge. This presents a great opportunity for the exploration and utility of Unsupervised Random Forest (URF). An immediate gain obtained from URF is its scale independence making the need for pre- processing of the data superfluous in order to improve its ability to model both linear and non-linear relationships. Additionally, URF provides a very intuitive interpretation of the data by allowing visualization on a low dimensional space via multidimensional scaling. This talk will explore the pros and cons in the use of URF versus other ULVMs in the research space of early bioprocess development.

P2-C. Presenter: Cristian Oliva Aviles (Genentech)

Title: Estimating error propagation as a novel alternative to a conservative end-to-end stability analysis approach

Degradation of Drug Substance and Drug Product may be experienced as part of processing requirements. A sequence of processing steps at allowed temperatures and storage times may be combined in an end-to-end stability analysis that estimates the total change of a critical quality attribute, which may be used to assess whether or not Drug Product will meet stability acceptance criteria at the end of shelf-life. We present an overview of an existing conservative approach that computes the total change of an attribute by adding up interval estimates of the change observed at each processing step. In addition, we introduce a novel and less conservative approach that focuses on the estimation of the error propagation through all processing steps.

P3-C. Presenter: Dwaine Banton (Janssen)

Title: Low pH Viral Inactivation Modular Claim via Bayesian Hierarchical Logistic Regression

Low pH inactivation of enveloped viruses has been shown to be effective in the viral inactivation step of the manufacturing of biologics. To date, most support for a modular inactivation claim – meaning once certain process parameters are set, there is no need to measure viral activity in terms of log10 reduction value (LRV), as inactivation is guaranteed – has been based on descriptive statistics from various experiments. Being able to make a statement about the probability of successful viral inactivation, based only on process settings, without doing any measurements, is clearly beneficial for a company. The use of descriptive statistics alone is not sufficient, as it does not allow for statistical inference, nor the proper assessments of the risk of such a decision. The main difficulty that arises when one tries to model these data is that there is usually a significant proportion of left censoring of the LRV values. In this presentation, we derive a binary response from the LRV data, and use a logistic regression to account for the various process factor settings that may affect the probability of success. We use a hierarchical model to account for the correlation structure that is induced due to the amalgamation of the data from various experiments. The analysis is done in a Bayesian framework to deal with the possibility of quasi-separation, and to make proper probability statements about the chances of success, given the data.

P4-C. Presenter: Plinio De Los Santos (Merck)

Title: Comparison of Count Modeling Techniques for Estimating Environmental Monitoring Limits in Clean Rooms

Pharmaceutical and biotechnology industries manufacture their products in clean rooms, which are designed to hold low levels of particulates (like microorganisms recovered from the air or from the clean room surfaces). Alert and action limits are employed to monitor and control the state of the room, keeping the level of particulates at appropriate levels. Particulate monitoring systems could generate count data with the following characteristics: are repeated counts subject to nested data structures, could be inflated at zero or at low counts, and on instances could exhibit long thin tails to the right with potential outliers. During the presentation we will compare multiple statistical modeling techniques for setting alert and action limits using environmental monitoring data, to better understand the strengths and limitations of these techniques.

P5-C. Presenter: Buffy Hudson-Curtis (GSK)

Title: An overview of Bayesian approaches to content uniformity

Before a batch of a newly manufactured drug product is released to consumers, content uniformity testing is used to establish that the dosage units of a drug product consistently contain the specified amount of drug (active pharmaceutical ingredient). For dosage units from a batch to be of uniform content, the amount of active pharmaceutical ingredient in the dosage units of a batch must be reasonably close to the intended (target) dose, thus avoiding the patient risk of under/over dosing. Tests of content uniformity assess the assayed results of a sample of units from a batch against a predetermined set of criteria. The United States Pharmacopeia (USP) chapters provide testing standards for content uniformity that are used by more than 140 countries. The specifics of most modern USP content uniformity tests may be found in USP<905> for solid dosage units, USP<3> for topical and transdermal drug products, and USP<601> for aerosols, nasal sprays, metered-dose inhalers, and dry-powder inhalers. In addition, the approach discussed in ASTM E2810 (the CuDAL approach) and the PTI-TOST have been suggested as techniques for batch release.

Content uniformity tests by regulatory agencies are not Bayesian in nature. USP-recommended tests include the so-called zero-tolerance counting tests (how many units in the sample are acceptable) and ad-hoc mean-centered statistical intervals. As these test methods are not associated with exact hypotheses nor do they consider the test size, collected data from a manufactured batch either meet or do not meet USP-based acceptance criteria. The Bayesian content-uniformity methods, however, allow for statistical inference to be made based upon a test of two hypotheses through the probability that the units from within the tested batch meet the acceptance criteria. Further, a Bayesian approach to examine historical data provides a useful means to assess batch and process performance against any content-uniformity tests while addressing more complex data structures when applying these tests. A review of the Bayesian procedures in the literature, including a novel two-tier, two variance-components content uniformity test will be given in this presentation.

P6-C. Presenter: David Lansky (Precision Bioassay)

Title: Bioassays: big challenges yield interesting design and analysis methods

Bioassays bring practical and statistical challenges including complex designs, non-linear responses, multiple sources of variance, non-additive effects, and more. Designs that are practical in the laboratory, are amenable to adoption of laboratory robotics, and support randomization are useful, but statistically complex. While non-linear mixed models help address many issues, they are sensitive to outliers and come with a need (particularly for complex designs) to choose among many reasonable candidate random effect models. We report some success with strategies for fixed and random effect model selection as well as ways to report results (graphically and with variance components) that help bioassay analysts monitor sources of variation that are known to be important. We will also describe several promising areas for additional research.

P7-C. Presenter: Qianqiu Li (Janssen)

Title: Bayesian and Bootstrap Analysis of Truncated Data for Justification of Specification and Equivalence Testing

Truncation occurs when a value beyond a threshold is not detectable or measurable. For a nonnegligible proportion of left-truncations, the tasks for justification of specifications and determination of equivalence margins are tackled. In stability studies with different numbers of batches and lengths of time intervals, under multilevel models, Bayesian tolerance limits calculated via conditional and full likelihood functions are compared. In two-group comparability studies with different sample sizes and truncation probabilities, bootstrap predictive intervals of the 90% 2-sided confidence limits are used to evaluate the impact with and without incorporating truncation information. The comparison results suggest that the risk of out of specification and rejection of equivalence can be reduced based on historical data while accounting for truncation.

P8-C. Presenter: Fangfang Liu (Pfizer)

Title: Quantifying Uncertainty of Process Reliability Estimation Using Bayesian methodology

The seemingly unrelated regression model has been developed by Peterson (2008, 2009) to calculate process reliability using Bayesian methodologies for multiple response experiments. This method has been widely applicable to design space calibration and process optimization. In this poster, we provide a modification of Peterson's work in three directions. First, we utilize the direct Monte Carlo method developed by Zeller (2010) to generate the posterior samples instead of using the Monte Carlo Markov Chain (MCMC) method. Second, we obtain the posterior distribution for the reliability function under any operating condition within the design space and thus the uncertainty of process reliability estimation could be quantified. Third, a Bayesian multiple testing procedure is developed to solve the problem of simultaneously testing whether the process reliabilities at multiple operating conditions are above some specific level. Afterwards we illustrate our proposed method using one simulation study.

P9-C. Presenter: Timothy Schofield (Independent consultant)

Title: The Role of CMC Statisticians: Co-Practitioners of the Scientific Method

CMC Statisticians play a critical role in the development and lifecycle management of pharmaceuticals and vaccines. A key to this is an understanding of the scientific method. This presentation will follow the history of the scientific method, from the principle of inductive reasoning introduced by Plato and his contemporaries to Karl Popper's claim that "empirical falsifiability" is the distinguishing characteristic between science and non-science. Several traps and misconceptions will be explored which have hampered broad acceptance of statistical solutions in CMC. The presentation will end with an examination of the skills and behaviors which might favor healthy partnerships between statisticians and non-statisticians, in the pursuit of delivering worldwide value to patients in need.

P10-C. Presenter: Perceval Sondag (Merck)

Title: Optimal designs for similarity testing in and relative potency estimation

Relative potency assays are used to measure biological activity of a test batch relative to the one of a reference standard. It is calculated from the horizontal distance between the log(concentration)-response functions of both products. The curve shapes must be declared similar for the test batch to have constant relative potency with the reference standard. The most common model used in those potency assays is the four-parameter logistic model (4PL).

Some work has been done to build an optimal design for fitting 4PL models, but they are missing two important points. First, the reality in laboratories do not allow to choose the concentration points freely. Instead, one can only chose the maximum concentration and dilution factor. Second, those optimal designs are only built for one 4PL model, not for the comparison of two models. In this talk, we propose a weighted optimal design that take into account those particularities of potency assays, given prior distributions on the reference and test batch curve parameters.

P11-C. Presenter: Chi-Hse Teng (Novartis)

Title: In-silico evaluation of the impact of different LC-MS/MS acceptance criteria on PK parameters

We always try to follow regulatory guidance (e.g. FDA guidance and EMA guideline) for regulated bioanalyses (e.g. PK/PD/IG determinations especially in GLP and GCP related studies). There are two major categories of the acceptance criteria, one for a small molecule by a chromatographic assay and the other by macro molecule by a ligand binding assay.

Since protein quantification in a biological matrix by LC-MS/MS is relatively new area, there has been no clear definition for the acceptance criteria by health authorities. There are several white papers which stated that the 20/25% rule is appropriate. We have analyzed a monoclonal antibody in human serum by LC-MS/MS using wider acceptance criteria (i.e. 20/25% rule) mostly used in ligand binding assays instead of 15/20% rule mostly used in chromatographic assays. However, FDA rejected our proposal to use 20/25% rule and requested us to narrow the acceptance criteria down to 15/20%. In this presentation, I would like to show how we evaluate the impact of 15/20% vs. 20/25% acceptance criteria in silico.

P12-C. Presenter: Hong Tran (J&J)

Title: A weighted Bayesian tolerance interval

Bayesian statistics has been widely utilized as an approach that incorporates prior knowledge into statistical inference. In Pharmaceutical Manufacturing, Bayesian applications are still limited. Statistical tolerance intervals (TI) are the most common used for controlling product quality. There are two main Bayesian approaches for calculating statistical tolerance intervals: Hamada and Wolfinger. A simulation-based approach was implemented to compare Wolfinger, Hamada and frequentist tolerance intervals that control the probability content at a specified level of confidence. As sample sizes increase, compared to frequentist, Hamada TI become more conservative while Wolfinger TI are more liberal. To address this issue, we propose a weighted Bayesian TI that compromise Hamada and Wolfinger approaches. The proposed Bayesian TI results in narrower intervals in certain scenarios while the confidence content coverage remains comparable to frequentist.

P13-C. Presenter: Chao Wang (FDA)

Title: Equivalence test of binary responses with covariate adjustment

Equivalence assessment of binary responses from test and reference treatments are frequently seen in medical studies. It has been shown that when confounding covariates may exist, it is necessary to adjust the treatment effect by the confounding covariates. However, it is unclear regarding how to test equivalence. In this study, we model the relationship between the binary response and treatment variable and confounding covariates by logistic regression and investigate several possible approaches to test equivalence. We consider tests based on Wald, score, and likelihood ratio tests and compare their performances regarding type I error and power through simulation studies.

P14-C. Presenter: Jing Xiao (Merck)

Title: Innovative Lyophilization Cycle Validation Strategy for Multiple Products Tech Transfers to Enable Increased Filling and Lyophilization Capacity

A new lyophilization cycle was proposed to enable increased filling and lyophilization capacity. The previous validation method requires much testing of products in the lab. The new product temperature and moisture mapping strategy can identify critical locations with chamber(s) and design a comprehensive map that can reduce about 60% testing products and is robust and repeatable across all intended cabinets. Additionally, this new statistical strategy employs equivalence testing for moisture and temperature of the lyophilization cycle to assess suitability of the proposed lyophilization for intended equipment and product matrix.

P1-D. Presenter: Ondrej Libiger (Janssen)

Title: Using non-linear longitudinal analysis to characterize the relationship between the concentration of a CK1d inhibitor and the elongation of a cell circadian cycle

Background: Recent clinical data highlighted the reciprocal link between circadian disruption and psychiatric disorders. Casein kinase 1 delta (CK1δ) is an enzyme that helps regulate the internal pacemaker of cells, and inhibiting its activity has the potential to restore circadian rhythms in patients with bipolar disorders, schizophrenia and depression. The goal of this work was to develop a statistical methodology to characterize the relationship between compound concentration and the elongation of the circadian cycle using real-time monitoring of photon production in U2OS cells transfected with the circadian transcription factor BMAL linked to luciferase ("Clock in a Dish").

Three independent time series measurements were taken at 700 five-minute increments for seven concentrations of a tool compound with documented potency and a vehicle, yielding ~17,000 data points. Observed data indicated the presence of circadian rhythms with longer cycle periods as the concentration of the compound increased. We fitted a nonlinear cyclical curve defined by an offset, amplitude, phase, frequency and a dampening constant to each of the 24 times series. We then fitted a three-parameter logistic curve to the estimates of cycle period as a function of the compound's concentration in order to model the concentration-response relationship. Using the proposed approach, we estimated the compound's half maximal effective concentration (EC50) at 0.2 ± 0.09 μM (mean ± SE). Combining the automated analysis with the "Clock in a Dish" model facilitated the decision-making process regarding whole cell permeability and potency of novel CK1δ inhibitors, and thus supported an active discovery program within the Neuroscience TA.

P2-D. Presenter: Mariusz Lubormirski (Janssen)

Title: A new method for performing power calculations for multinomial distribution alternatives and its applications to the design of a NASH study

Nonalcoholic Steatohepatitis (NASH) is a liver disease that has been associated with liver damage and constitutes an unmet medical need. The severity of the disease is measured by the Nash Activity Score (NAS). Any new treatment evaluation must demonstrate efficacy by reducing NAS activity marker. NAS is measured as a score (0-8) that is defined as the sum of three sub-scores which are Steatosis (S) (0-3), Ballooning (B) (0-2) and Lobular inflammation (LI) (0-3). A reduction in the NAS score by 2 or more points and a reduction of 1 or more points in two sub-scores is defined as a meaningful subject improvement in disease condition. The objective is to calculate adequate sample size for a set of Multinomial parameters (Steatosis, Ballooning, Inflammation) corresponding to realistic improvements with different parameters moving at different rates. We propose a novel way to define multinomial alternatives and to use it to construct statistical power curves. The objective was to assess how many non-human primates (NHP) were needed to demonstrate a change in the NAS score by assuming that different sub-scores changed magnitude at different rates across time.

P2-D (continued)

The distributions of the three sub-scores are each assumed to be multinomially distributed. We propose a representation of the Null and alternative hypotheses based on the quantiles of a standard normal distribution. The Null hypothesis is defined by $p_{S,0}$ $p_{B,0}$, and $p_{LI,0}$ and is obtained from existing baseline data. For the Steatosis parameter, and likewise for the other two, we find quantiles that divide the normal curve into k intervals with probabilities given by the vector $p_{S,0}$. To generate alternatives, we shift baseline quantiles by delta, which produces a shift in the probabilities of the NAS score distribution. We perform simulations in R to calculate power under various alternatives.

P3-D. Presenter: Wei Zhao (AstraZeneca)

Title: Detecting Bliss Synergy in in -vivo Combination Studies with a Tumor Kinetic Model

Linear models are reliable methods in general to analyze in-vivo tumor growth studies. The steepness of the regression slope represents the drug effectiveness; however, not all tumor growth under immunotherapy treatment follows a linear pattern, even after log transformation. Tumor kinetic models are mechanistic models, in which a set of differential equations are used to macroscopically describe the tumor proliferation and tumor killing. In drug combination studies, an additional drug-drug interaction term can be added to the tumor kinetic model; however, the drug interaction claimed by these types of models cannot be directly translated into synergistic effect. We developed a novel approach that simultaneously models tumor growth in the control, monotherapy, and combination therapy groups. The new approach makes it possible to test for synergistic effect directly and make comparisons of synergistic effect between different studies.

P1-S. Presenter: Dwaine Banton (Janssen)

Title: Defining biological significance: A cross-program analysis of lymphocyte redistribution in non-human primates after dosing with CD3 redirecting biotherapeutics

Clinical pathology data from 350 cynomolgus monkeys across 15 studies with 9 different CD3 redirecting molecules were compiled. We developed a tool, using Bayesian methodology, to define a biologically significant decrease in absolute counts of lymphocytes at 24 hours post-first dose. These data were analyzed to better understand the phenomenon of lymphocyte redistribution, a hallmark of CD3 redirector activity. Treated animals exhibited a bimodal distribution of lymphocyte values at 24 hours post-first dose, engendering the hypothesis that the treated group consists of two sub-groups: "responder" and "non-responder". These "responder" and "non-responder" probability distributions were characterized, and an acceptable boundary condition was defined to appropriately classify future measurements into either sub-group. These analyses provide valuable context for understanding lymphocyte redistribution, not only relative to control (such as when using traditional methods), but also relative to other treated animals across the CD3 platform. This is important for accurate identification of promising treatments. For the first time, we can look across a multitude of studies to identify global platform trends as well as changes unique to a given compound. pharmacological activity is generally considered by leading health authorities, e.g., in experimental mice, as supporting rationale to investigate novel anti-cancer treatment(s) in human trials. In taking into account rigorous statistical applications, we actually found significant improvements in several key parameters of efficacy associated with the immunotherapeutic combination in our case study, that were not realized from the rudimentary approach. We demonstrate with our case study how the commonly accepted reporting standards for mouse anti-tumor drug investigations followed in the literature can be improved upon to ascertain clearer and more insightful conclusions.

P2-S. Presenter: Olivier Thas (Hasselt University and Ghent University)

Title: A comprehensive comparative study of methods and models for synergy

The notion of synergy in drug combination studies is a concept under development for many years and statisticians have tried to address the data analysis aspects with statistical solutions. Several methods for testing for synergy have been developed over the past years, relying on different definitions of additive effects and on different models: E.g. BLISS independence (1), Loewe (2), Harbron (3), HSA (4) and BIGL (5). In this presentation we present results from an extensive simulation study designed to compare these methods with respect to type I error rate and power (for global tests), and false discovery rate and sensitivity (for pointwise tests). The ultimate objective of the simulation study is to identify a single method that is overall conservative as compared to other methods, while still having reasonable sensitivity. The application of this method is assumed to avoid discussions about the exact definition of additivity to be used, for the risk for false discoveries is minimized over all these definitions.

P1-V. Presenter: Traymon Beavers (Janssen)

Title: Data Nuggets: A Method for Reducing Large Datasets While Preserving Data Structure

Big data has created new challenges for data analysis, particularly in the realm of creating meaningful groups or clusters of data or classification. Clustering techniques, such as K-means or hierarchical clustering, based on pairwise distances of N objects, are popular methods for performing exploratory analysis on large datasets such as these. Unfortunately, these methods are not always possible to apply to big data due to memory or time constraints generated by calculations of order N^2. A work-around is to take a random sample of the large dataset and perform the clustering technique with the reduced dataset; however, this is not a foolproof solution since the structure of the dataset, particularly at the edges of the dataset, is not guaranteed to be maintained. We propose a new solution through the concept of "data nuggets". These data nuggets reduce a larger dataset into a small collection of nuggets of data, each containing a center, weight, and a scale parameter. Once the data is re-expressed as data nuggets, we may apply algorithms that compute standard statistical methods, such as principal components analysis (PCA), clustering, classification, etc. We apply the methodology of data nuggets to the analysis of a dataset from flow cytometry in Biopharmaceutical research. This was conducted by performing weighted PCA and weighted K-means clustering on a dataset containing millions of observations (B-cells), and the objective was to find clusters that characterize cells according to which proteins are active on their surfaces. An R package was also developed to conduct these methods.

P2-V. Presenter: Jianfang Hu (Merck)

Title: A Shiny App - "Bag Selection Tool"

The R Shiny app “Bag Selection Tool” was developed to generate combinations of drug substance (DS) bags mixed with stabilizer to produce final formulated bulk (FFB) that meet certain criteria. The function recursively searches for combinations of DS bags mixed with a calculated volume of stabilizer that meet the requirements on target potency, final volume range, and pH range. To allow users to select older DS bags over recently manufactured DS, the app was designed to allow users to force bags with older DS into the generated combinations. The interface also allows users to narrow the ranges of pH and/or FFB volume. The combinations of DS bags and required volumes of stabilizer is displayed in a table sorted by descending FFB volume and users can export the combinations into Excel file. Because the search function is nearly exhaustive, this app can generate optimal combinations to maximize product yield and increase efficiency.

Student posters (alphabetical by presenter last name)

P1-Student. Presenter: Yi Hua (University of Illinois at Chicago)

Title: An extended Youden design for biological assays

Cell-based biological assays (also called bioassays) are an indispensable part of the quality assessment in the pharmaceutical industry and could determine the relative potency of drug substances in a sample against a standard preparation. In the design of bioassays, orthogonality between preparations and the nuisance factors is desired. Block design is an efficient tool to assay multiple preparations simultaneously and mitigate bias from multiple sources, including the cell-culture plates used, locations within plates, and the operators. The construction of a block design of a bioassay is challenging because of the treatment/control setup and the multiple block effects. Another challenge is that, in practice, when absolute orthogonality is not feasible, we need a design that achieves "near-orthogonality". As a solution to these challenges, we proposed an Extended Youden Design with mathematical constructions. We also developed an efficient algorithm implementation with R. Numerical results showed that Extended Youden Design is the optimal design for the given scenario.

P2-Student. Presenter: Jinyuan Liu (University of California, San Diego)

Title: The Effect of Estimating Residual Variance on Post-Selection Inference of LASSO in High-Dimensional Settings

Patients with Type II diabetes are at high risk for mortality and comorbidities, particularly chronic kidney disease (CKD). We test the accuracy of a published 13- metabolite signature to predict kidney disease progression over and above clinical variables, with the primary outcome of eGFR slope, a continuous slope obtained from Generalized Linear Mixed Model (GLMM). Using a sample of 1000 Type 2 diabetic patients, we applied the penalized model selection method, LASSO, to identify new multivariate metabolite sets that are significantly associated with CKD after adjusting for clinical variables. With an extensive simulation study comparing various methods for estimating residual variance in high-dimensional settings, we found that the sparseness of predictors, signal-to-noise ratio (SNR) and the correlation structures in the design matrix all inform the choice of the optimal method to achieve higher statistical power. Preliminary simulation results show that all residual variance estimation methods will lead to covariance test statistics achieving correct coverage probability. However, the sparseness of predictors, SNR and the correlation structures in the design matrix are all important factors that can affect the statistical power of the covariance test. Therefore, in order to achieve higher statistical power, it is crucial to assess the condition of the data before choosing the post-selection inference procedure. By comparing different post-selection inference methods, we evaluated criteria for which methods give optimal performance after model selection from LASSO, which can be particularly useful when we are dealing with large scale "–Omics" data.

P3-Student. Presenter: Yuelin Liu (Baylor University)

Title: Bayesian Estimation on a Two-level Model consisting Dose-response and Survival Model Linked by Antibody with heterologous prime-boost Ebola Vaccine Application

Since the massive 2013-2016 Ebola virus outbreaks in West Africa, there has been an urgent need to develop and implement strategies to prevent and mitigate future epidemics. Lots of resources have been dedicated in developing Ebola vaccine that can provide durable immunity. Several candidates are being pursued by the pharmaceutical industry. In this poster, we discuss research in preclinical stage of a two-dose heterologous prime-boost vaccine development, particularly on experiments among non-human primates (NHP). The heterologous regimen consists a prime dose of Ad26.ZEBOV and a boost dose of MVA-BN-Filo. We establish two key relationships. First, we model the relationship of the designed dosages and the antibody count induced. Second, we model the relationship of the antibody count and probability of survival when experimental subjects are exposed to Ebola virus in a controlled setting. Furthermore, we employ the combination of such models with dose as the predictor to predict the probability of survival for future subjects.

P4-Student. Presenter: Perceval Sondag (University of Liege)

Title: Multivariate equivalence zone for Parallelism Testing in Potency Assays

The aim of potency assays is to compare the biological activity produced by a test product to the one of a reference. This comparison is usually made using a single measure: the relative potency (RP). The RP is the ratio of concentrations necessary to obtain a same response. It is estimated from a log(concentration)-response function, often a four-parameter logistic (4PL) curve and is computed by the horizontal distance between the functions of the reference and that of the test product. This estimation is only meaningful if the two functions are parallel. Several equivalence-testing approaches exist to test the parallelism between two curves. One issue, however, is that equivalence tests require equivalence margins. These usually need to be derived using historical data. However, historical data might not be available, and alternatives are expensive. In this poster, I will present how to build equivalence margins when historical data are not available, using Bayesian statistics. I will also present an alternative to commonly used equivalence tests for parallelism, based on a multivariate credibility interval over the joint posterior distribution of parameter ratios.

P5-Student. Presenter: Kunbo Wang (Johns Hopkins University)

Title: Bayesian Tensor on Tensor Regression

We propose a Bayesian framework of regression model to predict a multidimensional array (tensor) of arbitrary dimensions from another multidimensional array of arbitrary dimensions. The framework is based on the contracted product of tensors and Tucker decomposition of regression coefficient tensor. Proper prior distributions are given to factor matrices of Tucker decomposition as well as core tensor, resulting in full posterior conditional distributions given in closed form formulas. Metropolis-Hastings method is used to choose the dimensions of core tensor. Posterior predictive distribution is given via Gibbs sampling method. A fast computing method is also given to speed up computation. We also numerically compare our Bayesian Tucker-based tensor regression model with the newly developed CP regression model on both simulated data and real facial imaging data and demonstrate the effectiveness of our model against CP model.

NCB 2019 Attendee List (as of June 3rd)

Agarwal, Divyansh - University of Pennsylvania
Alharbi, Abdulwahab
Altan, Stan - Janssen
Alvarado, Janet - Merck
Avey, Stefan - Janssen
Banton, Dwaine - Janssen
Baumgartner, Richard - Merck
Beavers, Traymon - Janssen
Bennett, Donald - Pfizer
Bergquist, Mandy - GSK
Bergum, James
Bernier, Craig - J&J
Bijnens, Luc - J&J
Bounma, Viengpasone - GSK
Bowsher, Phil - RStudio
Boyer, Joseph - GSK
Bradstreet, Thomas - BMS
Burdick, Richard - Burdick Statistical Consulting
Cai, Xiaoyu - FDA
Cheng, Catherine - Merck
Choeurng, Voleak - Genentech
Clark, Seth - Merck
Clark, William - Eli Lilly
De Los Santos, Plinio - Merck
Dong, Ranran - Genentech
Dong, Yijie - BMS
Egozcue, Juan Jose - Universitat Politecnica de Catalunya
Faya, Paul - Eli Lilly
Gaffney, Patrick - Pfizer
Gardner, Samuel - Elanco
Garren, Jeonifer - Pfizer
Gatling, Jael - Pfizer
Gehan, Don - Rutgers University
Gehman, Andrew - GSK
Gerveshi, Carina
Geys, Helena - J&J
Gorko, Mary Ann - Astra Zeneca
Hawinkel, Stijn - Ghent University
He, Kuang-Lin - GSK
Hu, Jianfang - Merck
Hua, Yi - University of Illinois at Chicago
Huang, Shuguang - Stat4ward LLC
Huang, Xin - AbbVie
Janszen, Derek - Precision for Medicine
Kafadar, Karen - University of Virginia
Kariuki, George - Merck
Kats, Irina - BIM, Inc.
Kim, Boyoung - Celltrion
Kim, Ji Young - Merck
Kolassa, John - Rutgers University
Kuhn, Max - RStudio
Lansky, David - Precision Bioassay
Lee, Daniel - Generable
Lerch, Nancy - Eli Lilly
Li, Qianqiu - Janssen
Li, Richard
Li, Ruojia - BMS
Liang, John - Pfizer
Libiger, Ondrej - Janssen
Liehr, Robert - Merck

Liu, Dan - BMS
Liu, Fangfang - Pfizer
Liu, Jinyuan - University of California, San Diego
Lu, Yuelin - Baylor University
Lubomirski, Mariusz - J&J
Mallick, Himel - Merck
McKeen, Andrew - Pfizer
Ni, Xiao - Novartis
Novick, Steven - MedImmune
Oleynick, John - J&J
Oliva, Cristian
Ortego, Maribel - Universitat Politecnica de Catalunya
Owusu, Asabere
Oyeniran, Oluyemi - J&J
Patel, Milauni - Merck
Pawlikowska Dobler, Iwona - Takeda
Pazdan, James - Novartis
Peng, Yiming - Genentech
Peterson, John - GSK
Pinheiro, Jose - J&J
Porter, William - Peak Process Performance Partners
Pourmohamad, Tony - Genentech
Quiroz, Jorge - Merck
Rahman, Mohammad - Sanofi
Remlinger, Katja - GSK
Sargsyan, Davit - J&J
Schofield, Timothy - Independent Consultant
Shoung, Jyh-Ming - J&J
Song, Jia - Pacira
Su, Cheng - BioMarin
Szumiloski, John
Tan, Charles - Pfizer
Tatikola, Kanaka - Janssen
Teng, Chi-Hse - Novartis
Thas, Olivier - Ghent University
Tran, Hong - J&J
Tsong, Yi - CDER/FDA
Vazquez, Jorge - Merck
Wang, Chao - FDA
Wang, Kai-fen - GSK
Wang, Ke - Pfizer
Wang, Kunbo - Johns Hopkins University
Weng, Yu-Ting - FDA
Witkowski, Krista - Merck
Xiao, Jing - Merck
Xiao, Ping - Pfizer
Yang, Harry - AstraZeneca
Yates, Phillip - BMS
Young, Stephanie - Janssen
Zeng, Lingmin - AstraZeneca
Zhang, Donghui - Sanofi
Zhang, Huizi
Zhang, Jianchun - AstraZeneca
Zhang, Jingnan - University of Florida
Zhao, Caixia - Otsuka
Zhao, Jie - Merck
Zhao, Wei - AstraZeneca
Zhao, Yanxing - Otsuka
Zhou, Huanyu - Teva