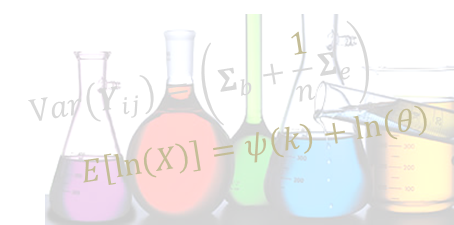


**ASA Biopharmaceutical Section**

**Nonclinical Biostatistics Conference**

June 19-21, 2023

*Science, Statistics and Regulatory driving Drug Discovery & Development*



Acknowledgements

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

|  |  |
| --- | --- |
| Text  Description automatically generated with medium confidence | **Logo, company name  Description automatically generated** |
|  |  |
| **Icon  Description automatically generated** | **A picture containing logo  Description automatically generated** |
|  | **Logo  Description automatically generated** |
|  |  |

Thank you to our generous corporate!

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

**Organizing Committee**

|  |  |  |
| --- | --- | --- |
| Name | Company | Role / Responsibility |
| Xin Huang | AbbVie | Co-chair |
| John Kolassa | Rutgers | Co-chair |
| Paul Faya\* | Eli Lilly | CMC section chair |
| Aili Cheng | Pfizer | CMC section Vice chair |
| Richard Montes | Alnylam | CMC section committee member |
| Yiming Peng | Genentech | CMC section committee member |
| José Ramirez | Kite Pharma | CMC section committee member |
| Ji Young Kim | Merck | CMC section committee member |
| Christopher Thompson | AstraZeneca | CMC section committee member |
| Chao Wang | FDA | CMC section committee member |
| Andy Liaw | Merck | Discovery/Biomarkers section chair |
| Jeonifer Garren | Pfizer | Discovery/Biomarkers section Vice chair |
| Katja Remlinger | GSK | Discovery/Biomarkers committee member |
| Jeonifer Garren | Pfizer | Discovery/Biomarkers committee member |
| Tianhui Zhang | AstraZeneca | Discovery/Biomarkers committee member |
| Koen Van den berge | J&J | Discovery/Biomarkers committee member |
| Jorge Andrade | Kite Pharma | Discovery/Biomarkers committee member |
| Tony Pourmohamad | Genentech | Safety/Pharmacology section chair |
| Yushi Liu | Eli Lilly | Safety/Pharmacology section Vice chair |
| Thomas Bradstreet | BMS | Safety/Pharmacology section committee member |
| Davit Sargsyan | Janssen | Computing/visualization section chair |
| Ondrej Libeger | Janssen | Computing/visualization section Vice chair |
| Stephanie Young | Janssen | Computing/visualization section committee member |
| Phillip Yates | BMS | Posters |
| Jyh-ming Shoung | J&J | Student outreach co-chair |
| Wei Zhao | Fate Therapeutics | Student outreach co-chair |
| Fanni Zhang | AstraZeneca | Student outreach member |
| Xiao Tan | AstraZeneca | Student outreach member |
| Oluyemi Oyeniran | Janssen | Student outreach member |
| Thomas Bradstreet | BMS | Student outreach member |
| Angel Lu | PharmaLex | Best Nonclinical paper award |
| Richard Baumgartner | Merck | Publicity |
| Tony Lonardo | Eli Lilly | Advisor emeritus |
| Stan Altan | J&J | Advisor emeritus |
| Don Bennett | Pfizer | Advisor emeritus -  Past chair |
| Yi Tsong | FDA | Advisor emeritus |
| Steven Novick | Eli Lilly | Advisor emeritus -  Past chair |
| Buffy Hudson-Curtis | GSK | Advisor - Past Section chair |
| Jason Zhang | Fate Therapeutics | Advisor - Past Section chair |
| Binbing Yu | AstraZeneca | Advisor - Past Section chair |
| Kjell Johnson | Stat Tenacity | Advisor - Past Section chair |
| Guilherme V Rocha | Lilly | Advisor - Past Section chair |
| Katja Remlinger | GSK | Advisor - Past Section chair |

\*2025 NCB conference chair

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Monday, June 19** | | | | | |
| **Time** | **Abstract #** | **Title** | **Presenter** | **Moderator** |
| 8:00 – 8:30 |  | Breakfast |  |  |
| 8:30 – 12:00 | Short course 1 | Bayesian Methods For Non-clinical Statisticians | Luwis Diya (Janssen)  Will Landau (Eli Lilly) |  |
| 8:30 – 12:00 | Short course 2 | Statistical Tolerance Intervals and Regions | Thomas Mathew (UMBC) |  |
| 12:00 – 1:00 |  | Lunch |  |  |
| 12:00 – 1:00 |  | Roundtable Discussion | See break-out tables |  |
| 1:00 – 1:10 |  | Welcome | John Kolassa (Rutgers) |  |
| 1:10 – 1:20 |  | NCB and ASA Biopharm | Eve Pickering (Pfizer) |  |
| 1:20 – 1:30 |  | Student Outreach | Jyh-ming Shoung (Janssen) &  Wei Zhao  (Fate Therapeutics) |  |
| 1:30 – 2:10 | I-C1 | From Observers to Participants: How Pharmaceutical Statisticians Contribute to Data Science, and Why They Must | Nelson Lee Afanador (Merck) | Paul Faya  Aili Cheng |
| 2:10 – 2:50 | I-V1 | Analysis and visualization of gut microbiome and metabolome altered by Nrf2 Knock Out and Phenethyl Isothiocyanate and Cranberry Rich Diets | Davit Sargsyan (Janssen) | Ondrej Libeger |
| 2:50 – 3:10 |  | Break |  |  |
| 3:10 – 3:50 | I-S1 | Bridging the gap between preclinical animal studies and phase I first-in-human trials | Haiyan Zheng (University of Cambridge) | Tony Pourmohamad  Yushi Liu |
| 3:50 – 4:30 | I-D3 | Bayesian cooperative learning for multi-omics data integration | Himel Mallick (Cornell) | Andy Liaw  Jeonifer Garren |
| 4:30 – 5:00 |  | Break |  |  |
| 5:00 – 6:00 |  | ASA Presidential Presentation  Statistics Is a Core Competency for Creating Effective Public Policy | Madhumita (Bonnie) Ghosh Dastidar  (RAND Statistics Group) | John Kolassa |
| 6:00 – 7:15 |  | Reception |  |  |

Key: CX = CMC, DX = Discovery/Biomarkers, SX = Safety/Pharmacology, VX = Statistical Computing and Visualization; I-XX = invited talks

|  |  |  |  |
| --- | --- | --- | --- |
| **Monday Lunch Roundtable Discussion, June 19** | | | |
| **Time** | **Abstract #** | **Topic** | **Moderator** |
| 12:00 – 1:00 |  | How to optimize statistician/client collaborations | Don Bennett (Pfizer) |
| 12:00 – 1:00 |  | Has Bayesian methodology changed nonclinical statistics and need for regulatory guidance? | Stan Altan (Janssen)  Dean Li (Pfizer) |
| 12:00 – 1:00 |  | How to get engaged with external preclinical communities: conferences, committees, and publications | Steven Novick (Eli Lliy) |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Tuesday Common Schedule, June 20** | | | | | |
| **Time** | **Abstract #** | **Title** | **Presenter** | **Moderator** |
| 8:00 – 8:30 |  | Breakfast |  |  |
| 8:30 – 9:10 | I-V2 | Visualizations for communicating information from dense longitudinal data | Stephanie Young (Janssen) | Davit Sargsyan  Ondrej Libeger |
| 9:10 – 9:50 | I-C2 | A Regulatory Perspective: The Application of Bayesian Statistical Methodology in CMC. | Jun Gao (Health Canada) | Paul Faya  Aili Cheng |
| 9:50 – 10:05 |  | Break |  |  |
| 10:05 – 10:45 | I-D2 | Multivariate outlier detection with application to hit screening | Steven Novick (Eli Lliy) | Andy Liaw  Jeonifer Garren |
| 10:45 – 11:25 | I-S2 | Statistical methods of cut point determination in Immunogenicity studies | Meiyu Shen (FDA) | Tony Pourmohamad  Yushi Liu |
| 11:25 – 12:15 | Poster | Poster Session |  |  |
| 12:00 – 1:00 |  | Lunch |  |  |
| 12:00 – 1:00 |  | Roundtable Discussion | See break-out tables |  |
| 1:00 – 2:50 |  | Parallel sessions | See break-out tables |  |
| 2:50 – 3:00 |  | Break |  |
| 3:00 – 4:50 |  | Parallel sessions |  |
| 4:50 – 5:00 |  | Break |  |
| 5:00 – 5:15 |  | Stan Altan Best Nonclinical Paper Award and Student Presentation Awards | Jason, Jyh-Ming, Wei |  |
| 5:15 – 6:15 |  | Keynote Speaker Presentation  Statistical Thinking and Pharmaceutical Professional development for 21st-century Pharmaceutical Quality | Ajaz S. Hussain | Steven Novick |
| 6:15 – 7:15 |  | Reception |  |  |

Key: CX = CMC, DX = Discovery/Biomarkers, SX = Safety/Pharmacology, VX = Statistical Computing and Visualization; I-XX = invited talks

|  |  |  |  |
| --- | --- | --- | --- |
| **Tuesday Lunch Roundtable Discussion, June 20** | | | |
| **Time** | **Abstract #** | **Topic** | **Moderator** |
| 12:00 – 1:00 |  | Machine Learning applications in CMC | Yang Tang (Roche) |
| 12:00 – 1:00 |  | Specification Setting | Brad Evans (Pfizer) |
| 12:00 – 1:00 |  | Comparability | Aili Cheng (Pfizer) |

|  |  |  |  |
| --- | --- | --- | --- |
| **Tuesday Afternoon Students, June 20** | | | |
| **Time** | **Abstract #** | **Title** | **Moderator** |
| 12:15 – 1:15 |  | Students and Early Career Roundtable discussion | Jyh-Ming Shoung (Janssen), Wei Zhao (Fate Therapuetics) |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Tuesday Afternoon contributed topic parallel sessions (room A), June 20** | | | | | |
| **Time** | **Abstract #** | **Title** | **Presenter** | **Moderator** |
| 1:00 – 1:25 | C1 | Estimating Shelf Life through Tolerance Intervals | James Schwenke, Applied Research Consultants, LLC | Paul Faya  Aili Cheng |
| 1:25 – 1:50 | C10 | Tolerance Intervals in Linear Mixed Models: an Application to Stability Data | Cristian Oliva Aviles, Genentech | Paul Faya  Aili Cheng |
| 1:50 – 2:15 | C6 | Stability analysis using mixed models: a critique of tolerance interval method and a probabilistic solution | Stan Altan, Janssen R&D | Paul Faya  Aili Cheng |
| 2:15 – 2:40 | C12 | Tolerance Intervals – an Adaptive Approach for Specification Setting | Brad Evans, Pfizer | Paul Faya  Aili Cheng |
| 2:40 – 2:50 |  | Q&A |  |  |
| 2:50 – 3:00 |  | Break |  |  |
| 3:00 – 3:25 | C5 | Predictive Control of Biologics Manufacturing | Yang Tang, Roche Canada | Paul Faya  Aili Cheng |
| 3:25 – 3:50 | C9 | Design and analysis of an autologous cell therapy site transfer comparability study as a 2x2 Crossover Equivalence Test | Kedar Dave, BMS | Paul Faya  Aili Cheng |
| 3:25 – 4:15 | C11 | Statistical approach for autologous cell therapy potency method comparability | Mia Teixeira, BMS | Paul Faya  Aili Cheng |
| 4:15 – 4:40 | C7 | A Multivariate Equivalence Test based on Mahalanobis Distance with a Data-Drive Margin via Bootstrap | Shaobo Liu, FDA | Paul Faya  Aili Cheng |
| 4:40 – 4:50 |  | Q&A |  |  |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Tuesday Afternoon contributed topic parallel sessions (room B), June 20** | | | | |
| **Time** | **Abstract #** | **Title** | **Presenter** | **Moderator** |
| 1:00 – 1:25 | D1 | Whole-cage randomization for animal studies with unequal cage or group sizes | Tianhui Zhang, AstraZeneca | Andy Liaw  Jeonifer Garren |
| 1:25 – 1:50 | D3 | In-vivo tumor burden profile modeling to predict proportion of animals required for efficacy study | Xuechen Wang, Janssen | Andy Liaw  Jeonifer Garren |
| 1:50 – 2:15 | D7 | Novel Data Extraction and Analysis Methods for High-Dimensional functional Heart Abnormalities in Fabry Disease Mouse Models | Reuben Retnam, Takeda | Andy Liaw  Jeonifer Garren |
| 2:15 – 2:40 | D9 | Sample size calculation for small-sized, large-scale biomarker selection studies | Olivier Thas, Hasselt University | Andy Liaw  Jeonifer Garren |
| 2:40 – 2:50 |  | Q&A |  |  |
| 2:50 – 3:00 |  | Break |  |  |
| 3:00 – 3:25 | D8 | A Comparison of Dose Response Model Packages in R | Jocelyn Sendecki, Janssen | Andy Liaw  Jeonifer Garren |
| 3:25 – 3:50 | S2 | Pseudo-empirical Bayes methods for parameter estimation involving many small samples (n=3,4,5) | Kanaka Tatikola | Tony Pourmohamad  Yushi Liu |
| 3:25 – 4:15 | S3 | Historical borrowing and meta-analysis in animal study | Veavi Chang | Tony Pourmohamad  Yushi Liu |
| 4:15 – 4:40 | S1 | An Improved Mixed-Effects Approach for EC50 Estimation Based on Multi-Donor Dose-Response Data | Weiliang Qiu | Tony Pourmohamad  Yushi Liu |
| 4:40 – 4:50 |  | Q&A |  |  |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Tuesday Afternoon contributed topic parallel sessions (room C), June 20** | | | | | |
| **Time** | **Abstract #** | **Title** | **Presenter** | **Moderator** |
| 1:00 – 1:25 | V1 | Bayesian Comparability Testing for Dissolution Data | Tony Pourmohamad, Genentech | Davit Sargsyan  Ondrej Libeger |
| 1:25 – 1:50 | V2 | CellVision: a Deep Learning-based Image Analysis Platform to Accelerate Data Processing for High-throughput Dengue Vaccine µPlaque Assay | Michelle Ngo, Merck & Co., Inc | Davit Sargsyan  Ondrej Libeger |
| 1:50 – 2:15 | V3 | A Novel Two-stage Deming Regression Model with applications to Multiple Risks Assessment | \*Yajie Duan, Rutgers University | Jyh-ming Shoung  Wei Zhao |
| 2:15 – 2:40 | V5 | Covariate-Driven Dimensionality Reduction of Single-Cell RNA-seq Studies | \*Sofia Prieto Leon, Hasselt University | Jyh-ming Shoung  Wei Zhao |
| 2:40 – 2:50 |  | Q&A |  |  |
| 2:50 – 3:00 |  | Break |  |  |
| 3:00 – 3:25 | SP1 | Accuracy Analysis of Diagnostic Tests using Youden Index and VUS in Presence of Verification Bias | \*Shuangfei Shi, Georgia State University | Jyh-ming Shoung  Wei Zhao |
| 3:25 – 3:50 | SP2 | Comparison of imputation methods for Below Limit Values | \*Ge Cheng, Rutgers University | Jyh-ming Shoung  Wei Zhao |
| 3:25 – 4:15 | D4 | Biomarkers detection in Microbiome experiments using Structural equation modelling | \*Thi Huyen Nguyen, Hasselt University | Jyh-ming Shoung  Wei Zhao |
| 4:15 – 4:40 |  |  |  |  |
| 4:40 – 4:50 |  | Q&A |  |  |

\* Students

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Wednesday, June 21** | | | | | |
| **Time** | **Abstract #** | **Title** | **Presenter** | **Moderator** |
| 8:00 – 8:30 |  | Breakfast |  |  |
| 8:30 – 9:10 | I-V3 | Modelling and visualization for high dimensional biomarkers discovery in microbiome experiments | Ziv Shkedy (Universiteit Hasselt) | Davit Sargsyan  Ondrej Libeger |
| 9:10 – 9:50 | I-D1 | Advancing precision oncology with machine learning on clinico-genomics and spatial omics | James Zou (Stanford University) | Andy Liaw  Jeonifer Garren |
| 9:50 – 10:10 |  | Break |  |  |
| 10:10 – 10:50 | I-S3 | Dose Selection Balancing Efficacy and Toxicity using Bayesian Model Averaging | Lawrence Gould (Merck) | Tony Pourmohamad  Yushi Liu |
| 10:50 – 11:30 | I-C3 | CAR T-Cell Therapy Data: Long tails, mixtures, hurdles, censoring; definitively not normal | José G. Ramírez (Kite, a Gilead Company) | Paul Faya  Aili Cheng |
| 11:30 – 11:45 |  | Concluding remarks | Xin Huang |  |
| 11:45 – 1:30 |  | Lunch / End of Conference |  |  |
| 1:30 – 2:15 |  | Organizing Committee |  |  |

Key: CX = CMC, DX = Discovery/Biomarkers, SX = Safety/Pharmacology, VX = Statistical Computing and Visualization; I-XX = invited talks

On Wednesday afternoon (directly after the conference), a tour of the [J&J museum](https://www.jnj.com/caring/patient-stories/museum) will be made available to conference participants (including non-J&J members). It is not normally open to the public, so this is a rare opportunity. Sign ups will take place during the conference.

Short Course Descriptions

* *Short Course 1*: Bayesian methods for non-clinical statisticians

*Instructors*: Luwis Diya (Janssen) and Will Landau (Eli Lilly)

*Description*:Bayesian methods have several advantages in the nonclincial space. Relative to the traditional frequentist paradigm, Bayesian models are more capable of nuanced inference, straightforward interpretation, quantification of prior evidence, and borrowing information across the features of a dataset. In this short course, we will introduce the Bayesian paradigm and motivate use cases in CMC, safety, and pharmacology. In addition, we will introduce Bayesian computation with JAGS and Stan so participants can begin implementing their first Bayesian analyses.

* *Short Course 2*: Statistical Tolerance Intervals and Regions

*Instructors*: Thomas Mathew (UMBC)

*Description*:Statistical intervals and regions, computed based on a random sample, have wide applicability. Confidence intervals and regions, and prediction intervals regions are well-known examples. The topic of the short course is on another type of intervals and regions, namely tolerance intervals and tolerance regions.

A tolerance interval for a univariate population, computed using a random sample, is an interval that will include a certain proportion or more of the population distribution, with a given confidence level. In particular, an upper tolerance limit for a univariate population is such that with a given confidence level, a specified proportion or more of the population distribution will fall below the limit. This proportion is referred to as the content of a tolerance interval. Furthermore, the confidence level associated with the tolerance interval captures the sampling variability. A lower tolerance limit, or a tolerance interval having both lower and upper limits, satisfy similar conditions. For multivariate populations, we analogously have tolerance regions. The theory of statistical tolerance intervals and tolerance regions has undergone vigorous development, starting with the early works of Wilks (1941, 1942) and Wald (1943). A significant amount of recent and very recent literature is also available on the topic, motivated by specific applications and computational considerations. Applications of tolerance intervals and tolerance regions are varied and extensive. They include clinical and industrial applications: quality control, environmental monitoring, the assessment of agreement between two methods or devices, occupational exposure monitoring, the computation of reference intervals and regions in laboratory medicine, and a host of other applications. Starting with the simplest case of a univariate normal distribution, the short course will introduce the participants to the methodological developments and applications of tolerance intervals and regions under various scenarios: regression models, random effects models, multivariate normal models (including multivariate regression models), and non-parametric tolerance intervals and regions. In the multivariate case, the computation of both ellipsoidal and rectangular tolerance regions will be discussed, the latter being motivated by applications in laboratory medicine. Numerous applications will be presented, and computational issues will be briefly addressed.

Some of the material to be presented will be taken from the book Statistical Tolerance Intervals and Regions: Theory, Applications and Computations by Krishnamoorthy and Mathew (2009, Wiley). However, a significant part of the course will include more recent developments on the topic.

ASA Presidential Address

*Speaker*: Madhumita (Bonnie) Ghosh Dastidar, Head, RAND Statistics Group

*Title*: Statistics Is a Core Competency for Creating Effective Public Policy

*Abstract:* The ASA vision imagines a world that relies on data and statistical thinking to drive discovery and inform decisions. Policy makers and stakeholders are responsible for establishing regulations, formulating a plan, and setting a course of action in important arenas such as reducing drug overdose mortality, improving nutrition and health, increasing school attendance rates, ensuring equitable application of regulations, supporting essential technology development. The gold standard for public policy is evidence-based decision making—deliberate and strategic application of real facts and research-supported principles that yields objective evidence.

Statistical science is the foundation for evidence-based decision making. As an interdisciplinary science, it has applications to every field imaginable, making statisticians uniquely qualified to lend their expertise in multiple policy domains. Effectively informing policy requires becoming involved early in the design phase; understanding the nature of the issue; and knowing how to communicate, educate, and explain. In this talk, I will provide multiple examples from health policy to highlight both valuable contributions made by statistical scientists and lessons learned. Extrapolating from these successes, I will suggest areas for future contributions in which the stakes are very high and involving statistics will be essential for crafting effective policy approaches. Finally, I will highlight the ASA’s role, major initiatives and contributions to public policy making.

Keynote Speaker Presentation

*Speaker*: Ajaz S. Hussain

*Title*: Statistical Thinking and Pharmaceutical Professional development for 21st-century Pharmaceutical Quality

*Abstract:* Observations and experience suggest that statistical science, as applied in pharmaceutical development and manufacturing, can often be fraught with psychological and technical difficulties. This talk’s subject is the observations supporting this assertion and how to improve the quality of statistical applications and inferences. Furthermore, it is argued that far less attention has been given to cognitive problems in pharmaceutical statistics than technical issues. A path forward to address the core problems in pharmaceutical development and manufacturing, such as BAD-I breaches in the assurance of data integrity, will be explored. This discussion will be in the context of the FD&C Act stipulation of “scientific training and experience” to make “effectiveness” decisions “fairly and responsibly,” as relevant to professional development, organization management system maturity, and the increasing chaos in our social environment.

Invited Talk Abstracts

CMC

**I-C1**. *Presenter*: Nelson Lee Afanador (Merck)

*Title*: From Observers to Participants: How Pharmaceutical Statisticians Contribute to Data Science, and Why They Must

*Abstract*: In 2013 Dr. Marie Davidian wrote an article for AMSTATNEWS in which she asked, “Aren’t We Data Science” (Davidian, 2013). Dr. Davidian was prompted to write this article after the formation of the National Consortium for Data Science (NCDS) where she saw ample computer science representation but a dearth of statisticians. This question continues to be relevant for statisticians today given that the field of data science has grown immensely since the writing of Dr. Davidian’s article, wherein we’ve seen a large increase of data science departments in both industry and academia. One of the most important challenges statisticians have faced in the new ‘data science world’ is perception. Statistics, being a mature science with a sound theoretical framework, has been perceived as bringing low-tech solutions to high-tech problems. The latter being closely related to the exploration of increasingly large datasets and a shift to algorithmic modeling methods. This had led to statistician Leo Breimen (Breiman, 2001) predicting two cultures in statistical modeling: the stochastic data model and algorithmic approaches. The former is dominated by statisticians, the latter by what are now called data scientists. Given this reality, pharmaceutical statisticians must aspire to become multicultural data analysts. But this begs the question, how? This discussion will attempt to better define data science, examine how it is being applied in the pharmaceutical industry, and most importantly, identify opportunities for statisticians, along with statistical thinking, to contribute to data science and become the multicultural data analysts that our industry needs.

**I-C2.** Presenter: Jun Gao (Health Canada)

*Title*: A Regulatory Perspective: The Application of Bayesian Statistical Methodology in CMC.

*Abstract*: Over the past two decades, the use of Bayesian statistical methodology (BSM) has been increasingly prevalent in the research, development, and manufacturing of pharmaceuticals, biologics, and medical devices. The trend of application of BSM in Chemistry, Manufacturing, and Controls (CMC) has been noted by regulators, who have begun to recognize the promising potential of Bayesian methodology in drug CMC submissions. Despite generally positive attitudes towards the application of BSM in CMC submissions, there are challenges to be addressed. We will review recent developments in CMC-related Bayesian methodology and regulatory guidelines and will discuss potential solutions to these challenges from both industry and regulatory perspectives.

**I-C3.** *Presenter***:** José G. Ramírez (Kite, a Gilead Company)

*Title*: CAR T-Cell Therapy Data: Long tails, mixtures, hurdles, censoring; definitively not normal

*Abstract*: Autologous chimeric antigen receptor (CAR) T-cell therapies are customized for each individual patient by re-engineering T-cells, so they can recognize and attack cancer cells, especially in the treatment of some hematologic malignancies. In contrast to a traditional biologics process, where batches, or lots, of multiple units are manufactured, in a CAR T-cell GMP (Good Manufacturing Practices) process, each individual patient is the lot. A CAR-T dataset is then a composite of many individual patients, and this creates interesting opportunities for industrial statisticians. In this talk we explore some of the unique differences of CAR T-cell therapy data, and how the over reliance on the normal distribution and transformations don’t cut it anymore. We also discuss how the use of appropriate distributions and Bayesian techniques provide a useful methodology to gain insights from CAR T-Cell data.

Discovery & Biomarkers

**I-D1**. *Presenter*: James Zou (Stanford University)

*Title*: Advancing precision oncology with machine learning on clinico-genomics and spatial omics

*Abstract*: Precision medicine aims to identify treatments that work best for each individual based on their genomics and other personal features. In this talk, I will discuss new directions for precision oncology. We will first discuss leveraging large real-world clinico-genomics data and in silico trials to facilitate the discovery of predictive biomarkers that inform treatment choice. Then we will see how modeling rich spatial omics data with graph neural networks generate actionable biological insights into why some patients respond better than others.

**I-D2**. *Presenter*: Steven Novick (Eli Lilly)

*Title*: Multivariate outlier detection with application to hit screening

*Abstract*: In drug discovery, hit screening identifies compounds (or other perturbations) that interact with a target of interest. In this work, we tackle the problem of identifying a ‘hit’ from a multivariate assay. As with univariate, fit-for-purpose assays, a ‘hit’ from a multivariate assay can be defined as a compound that yields an assay value sufficiently far away in distance from the mean or central value of inactives (e.g., negative controls). Viewed another way, a ‘hit’ is an outlier from the distribution of inactives. For multivariate assays, Mahalanobis distance (the multivariate analogue to the Z statistic) is the standard metric for identifying hits via outlier detection. We developed a method for detecting multivariate outliers in high-dimensional data sets based on principal components and robust Mahalanobis distance that appears superior to competitor methods in the literature in terms of maintaining test size, false discovery rate, and/or true discovery rate. The method is illustrated by a CRISPR knockout phenotypic screen example.

**I-D3.** *Presenter*: Himel Mallick (Merck)

*Title*: Bayesian cooperative learning for multi-omics data integration

*Abstract*: We propose a new Bayesian method for multi-omics data integration. We formulate the multi-omics integration problem as a Bayesian cooperative learning problem that uses an "agreement" shrinkage to encourage agreement of predictions from different data layers. Our method combines Bayesian additive regression trees (BART) with the agreement shrinkage and we show that our Bayesian cooperative learning method achieves higher predictive accuracy on simulated data and real multi-omics datasets, outperforming frequentist cooperative learning methods in estimation, prediction, and variable selection while also facilitating uncertainty quantification. The open-source software implementation of our method is publicly available.

Computing & Visualization

**I-V1.** *Presenter*: Davit Sargsyan

*Title*: Analysis and visualization of gut microbiome and metabolome altered by Nrf2 Knock Out and Phenethyl Isothiocyanate and Cranberry Rich Diets

*Abstract*: Nrf2 is a master regulator of antioxidant and anti-inflammatory pathways. Nrf2 knock out (KO) can lead to increased inflammation. Many studies have shown that gut bacteria can actively alter the inflammation in guts through interaction with the host immune cells via bacterial metabolites. The type and the amount of the metabolites depends on bacterial species and the availability and the hosts’ food intake. Anti-inflammatory compounds such as phenethyl isothiocyanate (PIETC) and foods rich in anti-inflammatory compounds (e.g., cranberry) support beneficial bacterial species and increase production of bacterial metabolites that activate regulatory T-cells, resulting in homeostasis in the host’s guts.

We examined data from three in vivo experiments. Microbiome was analyzed using 16S sequencing and operational taxonomic units (OTU) mapped to SILVA reference database. Metabolomics analyses was also performed on fecal samples using liquid chromatography mass spectrometry (LC-MS). The bacterial counts were used to compare the samples across the diet and phenotypes groups using alpha and beta diversity measures, and the multidimensional data visualized using a variety of techniques. A combined analysis of microbiome and metabolome was conducted, and the results visualized via the Compositional Omics Model-Based Integration (COMBI) framework.

**I-V2.** *Presenter*: Stephanie Young (Janssen R&D)

*Title*: Visualizations for communicating information from dense longitudinal data

*Abstract*: Recent technological developments have allowed us to collect large amounts of fine-grained time-series data. In the drug-development space, activity monitors are generating minute-level data that are increasingly being explored to identify biomarkers for physical and neurological issues. These kinds of data are already in use in both animal and human studies.

These large datasets are a boon to data scientists and statisticians who can pull meaningful signals from the noise. However, the techniques we use to analyze the data are often opaque to many audiences. For analytical work to have impact, it is necessary to generate compelling, but honest, visualizations to communicate findings from these data.

In this talk, we discuss some of the challenges that arise from analyzing dense longitudinal data as well as some options for visual representation. We will share examples of visualizations of data gathered from animal studies as well as exploratory human studies. We will also discuss some tools that can be helpful for handling dense longitudinal data and challenges that can occur when dealing with continuous monitoring data.

**I-V3.** *Presenter*: Ziv Shkedy (Universiteit Hasselt)

*Title*: Modelling and visualization for high dimensional biomarkers discovery in microbiome experiments

*Abstract*: In the last few years there is an increasing interest to study the association between compositions of microbial communities and different diseases. Although methods to identify different compositions of microbial communities across diseases levels are well developed, the development of new methods to identify microbiome biomarkers i.e., methods to assess the association between the composition of a microbial community and a clinical outcome, is of primary interest.

In this talk, we give an overview about new methods that can be used to identify high dimensional microbiome biomarkers for the different type of clinical outcome of interest taking into account possible intervention (such as treatment, medication intake, diet etc.). We present different modelling approaches and we focus on the setting in which multiple microbiome variables are used. We present the modelling approach for a single biomarker framework in which each biomarker is evaluated separately and we extend this to setting in which a joint biomarker is developed based on information available from multiple microbiome variables. Our modelling approach can be applied to any type of clinical response of interest (binary, continuous, time to event, etc.) and at each level of the microbiome eco system (OTU, family and kingdom levels).

We present R software tools that can be used for modelling and for visualization so the impact and influence of a potential biomarker on the clinical outcome of interest (taking into account possible intervention) can be clearly assessed.

Safety & Pharmacology

**I-S1.** Presenter: Haiyan Zheng (University of Cambridge)

*Title*: Bridging the gap between preclinical animal studies and phase I first-in-human trials

*Abstract*: Before a new medicine is evaluated in a first-in-man trial, preclinical studies are typically performed in animals to characterise the safety profile. It is thus reasonable to suppose some animal toxicity data are available at the time of designing phase I clinical trials. Investigators may nonetheless be uncertain about whether and how to leverage such information, as it could either enhance or jeopardise decision making in the human trials.

This talk will introduce a Bayesian decision-theoretic approach for the dynamic use of animal data phase I dose-finding trials. Specifically, animal data are incorporated via a two-component mixture prior for the human dose-toxicity parameters. The prior weights assigned to the informative component, which is formulated using animal data, are chosen according to its predictive utility for the observed human toxicity outcomes. Such weights are updated after completion of each cohort and recalculated given the latest prediction accuracy for the toxicity in humans. The proposed methodology leads to a robust Bayesian dose-escalation procedure that down-weights animal data quickly in situations of a prior-data conflict. Data examples and a simulation study will be presented to illustrate the trial operating characteristics. Perspectives will also be given on the future methodology development for leveraging preclinical data to improve decision making in early phase clinical trials.

**I-S2.** Presenter: Meiyu Shen (FDA)

*Title:* Statistical methods of cut point determination in Immunogenicity studies

*Abstract*: Currently, screening cut point (CP) calculated from an assay validation with replicates are applied to an immunogenicity study with non-replicates, for which the ADA rate is determined. IID treats the replicate of a sample as coming from another independent sample. AVE uses average results from each sample across runs but inter-assay variability is reduced. Therefore, we propose a random effect model (REM) for calculating CP. Method: We investigate impact of non-compatibility design between validation and immunogenicity studies on CP and compare these methods. Conclusion: IID may not fit for use when replicates’ variability dominates all sources of uncertainty. REM considers covariance structure of repeated measurements. CP by REM is smaller than that by IID but larger than that by AVE.

**I-S3.** Presenter: Lawrence Gould (Merck)

*Title:* Dose Selection Balancing Efficacy and Toxicity using Bayesian Model Averaging

*Abstract*: Successful pharmaceutical drug development requires finding correct doses that provide an ‘optimum’ balance between efficacy and toxicity. Competing responses to ‘dose’ such as efficacy and toxicity often will increase with ‘dose’, and it is important to identify a range of doses to provide an acceptable efficacy response (minimum effective dose) while not causing unacceptable intolerance or toxicity (maximum tolerated dose). How this should be done is not self-evident. Relating efficacy to dose conditionally on possible toxicity may be problematic because whether toxicity occurs will not be known when a dose for a patient needs to be chosen. Copula models provide an appealing approach for incorporating efficacy-safety association when the functional forms of the efficacy and toxicity dose-response models are known, but may be less appealing in practice when the functional forms of the dose-response models and the particular copula association model are unknown. This paper explores the use of the BMA-Mod Bayesian model averaging framework that accommodates efficacy and toxicity responses to provide a statistically valid, distributionally flexible, and operationally practical model-agnostic strategy for predicting efficacy and toxicity outcomes both in terms of expected responses and in terms of predictions for individual patients. The performance of the approach is evaluated via simulation when efficacy and toxicity outcomes are considered marginally, when they are associated via gaussian and Archimedean copulas, and when they are expressed in terms of clinically meaningful categories. In all cases, the BMA-Mod strategy identified consistent ranges of acceptable doses.

Contributed Talk Abstracts

CMC

**C1**. *Presenter*: James Schwenke (Applied Research Consultants, LLC)

*Title*: Estimating Shelf Life through Tolerance Intervals

*Abstract*: A stability study is conducted with three or more batches of a pharmaceutical product stored under environmental conditions for a specified duration of time. Observations of product quality are recorded for statistical analysis at designed storage times. Random coefficient mixed regression models are used to characterize the stability response profile accounting for the between batch and within batch variation. Tolerance intervals provide an effective and flexible advance in shelf life estimation where shelf life is defined in terms of risk as the proportion of the batch mean or product stability distribution allowed out of specification. An example of shelf life estimation for a linear response is discussed. If time allows, a risk profile will be presented as a summary of product degradation and an example of shelf life estimation for a nonlinear response will be discussed.

**C5**. *Presenter*: Yang Tang (Roche Canada)

*Title*: Predictive Control of Biologics Manufacturing

*Abstract*: Biologic drugs are made with highly complex manufacturing processes that involve living cells. The product quality and yield can be impacted by various sources of variation, such as raw materials, process parameters, etc. In this talk, we present a predictive control case study in which the product quality and yield are heavily influenced by the raw materials and initial process settings.

With a gradient boosting regressor that learns the effect of the raw materials characteristics and their complex relationship, we are able to predict the expected manufacturing performance. This method then leads to a data-driven decision to keep or discard a particular raw material batch.

In addition, we present the model life cycle and re-training strategies for the predictive control. This approach can be easily generalized to deal with different raw materials and processes.

**C6**. *Presenter*: Stan Altan (Janssen R&D)

*Title*: Stability analysis using mixed models: a critique of tolerance interval method and a probabilistic solution

*Abstract*: In recent years, approaches using a tolerance interval for the calculation of a shelf life of a drug product have been presented in the literature. The tolerance interval approach addresses the belief that shelf life should be related to control of a certain proportion of batches being out of specification. We question the appropriateness of this approach. Our concerns relate to the computational challenges and practical interpretations of the method. We provide an alternative Bayesian approach which directly controls the desired proportion of batches falling out of specification assuming a controlled manufacturing process. The Bayesian approach has an intuitive interpretation and risk is expressed as a clear probability statement applicable to the manufacturing process. If prior information on the fixed and random parameters is available, a Bayesian approach can provide additional benefits both to the company and the consumer. It also avoids the computational complexities of the tolerance interval methodology.

**C7**. *Presenter*: Shaobo Liu (FDA)

*Title*: A Multivariate Equivalence Test based on Mahalanobis Distance with a Data-Drive Margin via Bootstrap

*Abstract*: Multivariate equivalence testing is needed in a variety of scenarios for drug development. For example, drug products obtained from natural sources may contain many components for which the individual effects and/or their interactions on clinical efficacy and safety cannot be completely characterized. Such lack of sufficient characterization poses a challenge for both generic drug developers to demonstrate and regulatory authorities to determine the sameness of a proposed generic product to its reference product. Another case is to ensure batch-to-batch consistency of naturally derived products containing a vast number of components, such as botanical products. The equivalence or sameness between products containing many components that cannot be individually evaluated needs to be studied in a holistic manner. Multivariate equivalence test based on Mahalanobis distance may be suitable to evaluate many variables holistically. Existing studies based on such method assumed either a predetermined constant margin, for which a consensus is difficult to achieve, or a margin derived from the data, where, however, the randomness is ignored during the testing. In this study, we propose a multivariate equivalence test based on Mahalanobis distance with a data-drive margin with the randomness in the margin considered. Several possible implementations are compared with existing approaches via extensive simulation studies.

**C9**. *Presenter*: Kedar Dave (BMS)

*Title*: Design and analysis of an autologous cell therapy site transfer comparability study as a 2x2 Crossover Equivalence Test

*Abstract*: Analytical comparability exercises demonstrate that quality attributes remain highly similar after making a manufacturing process change. Such studies are typically evaluated using an equivalence test for means (such as TOST). In autologous cell therapy comparability studies, ‘within-patient’ comparisons are possible by processing the starting material (typically a healthy donor’s cells) under both pre and post change conditions and subsequent analyses are blocked on the donor.

Autologous cell therapy manufacturing processes are broadly divided into two stages: production of cryopreserved leukapheresis material, and downstream processing of that material into drug product. This feature presents a unique opportunity to frame comparability studies supporting manufacturing site transfers as a 2x2 or AB/BA crossover design commonly used in clinical trials. This presentation describes the design and analysis of such a study. Example results, alternate models, and practical interpretations are discussed.

**C10**. *Presenter*: Cristian Oliva Aviles (Genentech)

*Title*: Tolerance Intervals in Linear Mixed Models: an Application to Stability Data

*Abstract*: The analysis of stability data of biological products, influenced by industry guidelines such as ICH Q1E, has been mainly focused on making inference about population means or worst-case scenarios represented by parameters of fixed effects models. However, in recent years, Linear Mixed Models (LMMs) have been shown to be a more appropriate alternative to model stability data because of their capability to model batch-to-batch variability. Moreover, tolerance intervals have been claimed to be a more adequate tool for shelf-life determination, since they allow drawing conclusions regarding the entire population of batches. In spite of that, the use of tolerance intervals in the analysis of stability data modeled with LMMs has been limited by the lack of statistical methods to compute them. In this talk, a novel method to compute tolerance intervals for general unbalanced linear mixed models, based on Generalized Pivotal Quantities, will be presented. Also, illustrative applications of the method for shelf-life determination and end-to-end stability calculations will be shared.

**C11**. *Presenter*: Mia Teixeira (BMS)

*Title*: Statistical approach for autologous cell therapy potency method comparability

*Abstract*: Analytical method comparability studies are a key part of method life-cycle management. Such studies are needed for conducting analytical method transfers, bridging (i.e., transitioning) to new methods, or implementing an improvement for an existing method.

A unique aspect of autologous chimeric antigen receptor (CAR)-T cell products is the individualized nature of this class of drugs. The life-cycle management of analytical methods that can ensure that the method continuously produces reliable and reproducible data is challenging due to several reasons: the inherent complexity of cellular drug products, lack of existing reference standards and appropriate calibration materials as well as limited regulatory guidelines. Accordingly, analytical method transfer and bridging studies for CAR-T products should take into consideration these unique product and analytical method characteristics.

In this talk, we present our approach and real-world experiences, including regulatory feedback, with method comparability for autologous cell therapy. We will discuss study design based on power analysis, data analysis and interpretation for method transfer & bridging studies of an AlphaLISA potency method. Statistical methods used for our approach to method comparability includes equivalence test using a linear mixed model, Deming regression and concordance correlation. Practical challenges (e.g., determining appropriate acceptance criteria) and some resolutions will also be discussed. Authors: Mia Teixeira, Ifrah Javed, Sangwook Choi.

**C12**. *Presenter*: Brad Evans (Pfizer)

*Title*: Tolerance Intervals – an Adaptive Approach for Specification Setting

*Abstract*: Specification setting is a critical component in the development of every new pharmaceutical product. Many specifications are set based on compendial, clinical, safety, and efficacy limits. However, there are times when specifications are set based on non-clinical data collected during development and manufacturing transfer. Statistics plays an important role here, leveraging the knowledge gained through development and in particular based on the analytical data collected from relevant scale batches. Setting data-driven specifications is challenging due to the sample size available at the time the specification is required. This presentation covers an adaptive approach based on Tolerance Intervals, with consideration given to both large and small sample scenarios, as well as producer risk vs. consumer risk. The approach and summary measures will be presented to help understand the risks under different scenarios.

Discovery & Biomarkers

**D1**. *Presenter*: Tianhui Zhang (AstraZeneca)

*Title*: Whole-cage randomization for animal studies with unequal cage or group sizes

*Abstract*: For in-vivo studies, randomization is used to allocate animals to two or more treatment groups to eliminate selection bias and to balance known and unknown confounding factors. For most studies, randomization is implemented at the individual animal level so that a technique, such as block randomization, can balance across pre-treatment measurements. There are cases, however, for which individual animal randomization is not possible. For example, it is well known that co-housed male mice may fight, which can interfere with study result interpretation. Nonetheless, due to new ethical considerations, our company decided to co-house male mice. We determined that placing familial male mice in the same cage will dramatically reduce fighting. As a consequence, randomization proceeds at the whole-cage level to keep family members together. While this serves to reduce the amount of fighting, when the number of animals per cage or the treatment group sizes are unequal, there is no algorithm in the literature to perform the task of sample allocation. We propose a novel, fast, and reliable algorithm to provide a whole-cage randomization that balances one or more baseline variables across groups. The algorithm was applied to a realistic example data set.

**D3**. *Presenter*: Xuechen Wang (Janssen)

*Title*: In-vivo tumor burden profile modeling to predict proportion of animals required for efficacy study

*Abstract*: In oncology, performing in-vivo experiments is an essential step to understanding the efficacy of a new compound. Ethical guidelines for the use of animals in research advocates for replacement, reduction, and refinement. Statisticians can help facilitate the reduction of animals used by helping design and power a study. In-vivo studies often require tumor burdens to be within a pre-determined range on the day of randomization. Due to the nature of the biology of the animals and the cancer, there may be large heterogeneity in the rate of tumor growth. This heterogeneity impacts the proportion of animals in the predetermined range. This proportion needs to be understood to properly design an experiment. Current practice is to base the number of animals needed on the proportion investigators obtained from previous studies (e.g., kinetics or historical efficacy studies) which might not account for the animal-to-animal variability.

We developed a modeling framework that captures both the complex longitudinal tumor burden profile and the animal-to-animal heterogeneity based on either the kinetics or historical efficacy data. The final model can be used to predict the proportion of animals that are required for an efficacy study. Five mixed effect models were considered in this study, and their performance was evaluated and compared under several simulation scenarios.

**D7**. *Presenter*: Reuben Retnam (Takeda Pharmaceuticals)

*Title*: Novel Data Extraction and Analysis Methods for High-Dimensional functional Heart Abnormalities in Fabry Disease Mouse Models

*Abstract*: Echocardiography of mouse models has been widely adopted in pharmaceutical discovery research to assess cardiac functions of disease models. However, multiple standard features derived from echocardiography data often lack the sensitivity needed to identify subtle changes in heart function during the very early phase of cardiac disease pathology. This is especially true when functional abnormalities in muscle contractility slowly and progressively emerge, as happens in lysosomal storage diseases such as Fabry disease. Detection of these minute changes in the complex contractility of the myocardium can be achieved through myocardial strain analysis.

We propose a novel algorithm to fully leverage both myocardial strain analysis and classical echocardiography features, coupling machine learning-based image analysis of strain echocardiography with advanced dimension reduction techniques. First, we utilized a technique based on transfer learning onto a convolutional neural network to segment echocardiography videos of contracting heart tissues during a heartbeat. This technique allowed the extraction of the area under curve and peak amplitude of the endocardium, epicardium, and radial strain curves. Then, we built an unsupervised learning technique on top of the popular UMAP method to create a parsimonious summary of changes in echocardiography features between age-matched wild-type and Fabry disease model mice and allow for the assessment of differences utilizing the set of all variables. Finally, we demonstrate that this method identifies cardiac phenotypic differences between Fabry and wild-type mice.

**D8**. *Presenter*: Jocelyn Sendecki (Janssen R&D)

*Title*: A Comparison of Dose Response Model Packages in R

*Abstract*: As of March 2023, a quick search of R packages on CRAN reveals that there are 18 different packages that were created to directly address dose response analysis. This doesn't even include traditional non-linear regression packages like 'nlme' where the user has freedom to specify their models directly. From 'dr4pl' and 'drc' to 'minpack.LM' and 'clustDRM', how does the non-clinical statistician on a deadline know which paskage will be the best choice for their data? This presentation will provide an overview and comparison of current R packages intended for dose-response analyses, including their positives, negatives, and quirks.

**D9**. *Presenter*: Thas Olivier (Hasselt University)

*Title*: Sample size calculation for small-sized, large-scale biomarker selection studies

*Abstract*: The diagnosis of diseases, or the prediction of the response to a treatment is nowadays often based on molecular or genetic markers. For example, immunotherapy can work very well for the treatment of certain types of cancer, but it does not work for all patients. A predictive biomarker that can be measured in a biopsy can be used to predict the efficacy of the treatment. Such biomarkers have to be selected from a huge set of potential biomarkers (large-scale). Nowadays, within a single blood sample or biopsy, tens to hundreds of thousands of potential markers can be measured, but this makes it hard to find a marker that can be used as a reliable predictive biomarker; it is like searching for a needle in a haystack. This problem becomes even worse when the number of samples in the study is quite small (small-sized study). Unfortunately, we still see that such studies are set up.

In this presentation I will illustrate the issue and propose a new flexible methodology that allows calculating the minimum sample size required to have a reasonable chance for finding a good biomarker.

Computing & Visualization

**V1**. *Presenter*: Tony Pourmohamad (Genentech)

*Title*: Bayesian Comparability Testing for Dissolution Data

*Abstract*: Dissolution studies are an integral part of small-molecule pharmaceutical development, yet not much attention has been given in the way of Bayesian methods for comparability testing of dissolution data. One of the main bottlenecks to the adoption of Bayesian methods for analyzing dissolution data is the lack of available, easy-to-understand resources for implementing Bayesian techniques practically. This talk will present the BayesDissolution R package, which can be used as a practical tool for implementing comparability testing of dissolution data under a Bayesian paradigm. In particular, two Bayesian approaches to comparability testing motivated by the well-established f2 statistic will be shown. We demonstrate the use of these custom R functions on a real dissolution data set from Ocaña et al. (2009) and show how a Bayesian analysis for comparability testing of dissolution data can be carried out in practice. R computer code for both of the Bayesian methods are provided in this presentation for ease of understanding and use. Overall, this talk will highlight the benefits of using Bayesian techniques in comparability testing of dissolution data, and provides a useful resource for researchers and analysts looking to incorporate these methods into their workflows for analyzing dissolution data.

**V2**. *Presenter*: Michelle Ngo (Merck)

*Title*: CellVision: a Deep Learning-based Image Analysis Platform to Accelerate Data Processing for High-throughput Dengue Vaccine µPlaque Assay

*Abstract*: The µPlaque assay was developed in 2017 to support potency tests for the Dengue vaccine process and formulation samples. Since then, it has screened over 40,000 samples and has been proven adaptable to support various programs as needed. This automated assay runs on 96-well plates in an integrated robotic system, and the resulting fluorescent images necessitate manual inspection. Thus, the current workflow requires 1-2 business days per run for manual image examination and plaque count verification; this process is labor-intensive and increases sample turnaround time. To address these issues, we present CellVision, a novel deep learning-based pipeline that accurately detects and quantifies plaques in cell culture wells. The pipeline is robust, precise, and user-friendly, providing analysts with more confidence in the results and flexibility to examine overall plate information and individual cell culture images. We estimate that CellVision will shorten image analysis time from 1-2 business days to 1-2 hours for each run containing up to 24 96-well plates. Thus, CellVision will shorten sample turnaround time and accelerate studies in both Dengue vaccine process and formulation development, as well as future programs that require µPlaque assay support. CellVision also serves as a great example for applying deep learning in transforming cell-based assay image data analysis within the analytical field.

Safety & Pharmacology

**S1**. *Presenter*: Weiliang Qiu (Sanofi)

*Title*: An Improved Mixed-Effects Approach for EC50 Estimation Based on Multi-Donor Dose-Response Data

*Abstract*: Dose–response relationships are important in assessing the efficacy and potency of drugs, which can usually be characterized by a 4-parameter logistic (4-PL) model with 4 parameters: EC50, slope factor, lower asymptote, and upper asymptote. EC50, the concentration of a drug that induces a response halfway between the baseline and maximum, is a key quantity to evaluate drug potency. For multi-donor dose-response data, it is often the interest to estimate the overall EC50 and its 95% confidence interval (CI). A few multi-donor EC50 estimation methods have been proposed in literature. Jiang and Kopp-Schneider (2014) systematically compared meta-analysis approach and mixed-effects approach and concluded that meta-analysis approach is simple and robust to summarize EC50 estimates from multiple experiments, especially suited in the case of small number of experiments, while mixed-effects approach has issue of convergence failure probably due to overparameterization. In this presentation, we propose an improved mixed-effects approach that substantially alleviates the issue of convergence failure, even for small number of donors (e.g., n = 3), and achieves better coverage probability of 95% confidence interval and smaller median bias than meta-analysis approach when number of donors is not too small (e.g., n ≥ 7).

**S2**. *Presenter*: Kanaka Tatikola (Janssen R&D)

*Title*: Pseudo-empirical Bayes methods for parameter estimation involving many small samples (n=3,4,5)

*Abstract*: Toxicology and discovery studies are not always statistically powered for estimation or hypothesis testing. Typically 3 to 5 animals per group are used, especially in early toxicology studies. Normally the studies are done on several different type of control(s) and/or compound(s) at various dilutions or doses. If we estimate mean and variance or in general some population parameters, in most cases the confidence interval will be of little use since it is based on a very small sample size. However, if historical/concurrent data of similar characteristics is available from similar experimental studies, then the information provided from all the data could be incorporated into the estimation method by using an empirical Bayesian approach. To implement this method, the existing data is used to form prior distributions for our parameters, which combined with the sample data will produce posterior distributions for our parameters.

To form the prior distributions for the mean and standard deviation, the means and variance of all the different samples are combined and used as a basis for defining the prior distributions. For the mean parameter, the posterior distribution is approximated by normal distribution, covering the range of all samples. For the variance parameter the prior distribution is approximated with a half normal or a chi-square with carefully chosen boundaries. Then empirical Bayes will combine the prior distributions with the observed small sample to obtain the posterior distribution for the mean and for the variance of that particular experiment. Such an automated strategy, of using the combined data from multiple samples to develop a common prior distribution that borrows strength across all the data will reduce the variability of the estimates and improve the estimation of individual parameters. This method is a combining borrowing strength ideas with Empirical Bayes(Tukey meets Robbins!) (coauthors: Kanaka Tatikola, Fetene Tekle, Davit Sargsyan, Javier Cabrera, Helena Geys)

**S3**. *Presenter*: Veavi Chang (Eli Lilly and Company)

*Title*: Historical borrowing and meta-analysis in animal study

*Abstract*: Animal studies play an important role for preclinical and clinical research to better understand the underlying mechanisms and dose response relationship for a treatment.

Most of the dose response animal research are conducted in multiple animal studies with limited number of animals usage per treatment arm. Therefore, across-studies results and robust inferences with small subjects are not always straightforward in animal research. In fact, these challenges are not unique in animal research. In clinical research, a rich collection of literature is available on how to deal with indirect comparison across studies and utilizing historical control data to increase statistical power for limited subjects.

In this talk, we will discuss the pros and cons of three approaches: [1] currently used independent frequentist approach and two proposed approaches [2] independent Bayes approach and [3] historical borrowing Bayes approach. The performance of statistical power and type I error are evaluated via a simulation study.

Student Presentation Abstracts

**SP1**. *Presenter*: Shuangfei Shi (Georgia State University)

*Title*: Accuracy Analysis of Diagnostic Tests using Youden Index and VUS in Presence of Verification Bias

*Abstract*: A three-class Youden Index and volume under the ROC (receiver operating characteristic) surface have been widely used for the assessment of accuracy of diagnostic tests. Due to the drawbacks of gold standard (GS) test, statistical evaluation based only on data from subjects for verified disease status are typically biased. We developed new Youden Index and VUS (volume under the ROC surface) estimators with correction of verification bias. The newly proposed methods provide a comprehensive guide to dealing with the verification bias in diagnostic test accuracy studies and lead to better choice of diagnostic tests.

**SP2**. *Presenter*: Ge Cheng (Rutgers University)

*Title*: Comparison of imputation methods for Below Limit Values

*Abstract*: Below-limit values, also known as left censored data, always happen in studies where measurement falls below threshold value, for example in cytokine. To incorporate these data in statistical analysis or modeling fitting, imputation methods, like censoring value divided by two($\frac{CV}{2}$), are widely used in industry. In this paper, we perform simulations to compare these methods in data that represents the real-world cytokine release dataset, and then, we simulate single-study data and multi-study data from Weibull distributions and Lognormal distribution. It is noted that we used a novel censoring mechanism to assign censored values and compared five imputation methods based on MSE, Mean Ratio, and Power analysis. In general, we find that, if the data comes from Weibull distribution with the $k$ larger than 1.8 or from Lognormal distribution with $\sigma$ less than 0.9, $\frac{CV}{\sqrt{2}}$ is a better imputation method, otherwise, $\frac{CV}{2}$ works better.

**V3**. *Presenter*: Yajie Duan (Rutgers University)

*Title*: A Novel Two-stage Deming Regression Model with applications to Multiple Risks Assessment

*Abstract*: Risk assessment models are widely used in clinical settings, such as CHADS2 for predicting one-year risk of stroke after the initial atrial fibrillation diagnosis, and HAS-BLED for bleeding risk assessment in patients taking blood thinners. However, there are few risk assesment models focused on the relationship between multiple risks. For instance, patients with high risk of stroke are usually treated with anticoagulants, but anticoagulants inherently increase bleeding risks. This suggets that risks of stroke and bleeding should be modeled jointly to decide whether or not to treat with anticoagulants. To help with this decision making, a novel framework with a two-stage Deming regression model is proposed to predict stroke and bleeding risks simultaneously and provide the relationship between them. The first stage of the proposed model estimates the risks of stroke and bleeding with their corresponding standard errors, and after suitable transformations for linearizing the relationship, in the second stage, a Deming regression line is fitted to the transformed risks. The model accounts for the prediction errors with known variance and measurent errors, which is much more reasonable than using traditional regression models directly. The proposed method could be applied to analysis between multiple risks, especially those weighed against each other such as risks of illness and side effects of drugs. In addition, patients’ subjective opinions about the outcomes can also be included in this innovated multiple risk assessment model.

**V5**. *Presenter*: Sofia Prieto Leon (Hasselt University)

*Title*: Covariate-Driven Dimensionality Reduction of Single-Cell RNA-seq Studies

*Abstract*: Consider the setting where we have single-cell RNASeq data for multiple subjects. These data often come with other subject-level data (e.g. baseline characteristics, treatment information, outcome, …). We propose a new visualization method for exploring the relationships between the subject-specific single-cell gene expression and subject-level covariates. The central idea is that we look for a dimension reduction method (to two dimensions) such that at the subject level the scRNASeq data can be summarized into parameter estimates of a bivariate distribution. This dimension reduction is performed by some transformation matrix U. The aim is to find U such that the parameters of the resulting bivariate distribution are maximally associated with the covariates. We have developed an iterative procedure for this problem. Since we enforce a sparse solution, important genes can be identified.

In this talk, we will present the method, demonstrate its capabilities in a simulation study, and illustrate the method on a dataset.

**D4**. *Presenter*: Thi Huyen Nguyen (Hasselt University)

*Title*: Biomarkers detection in Microbiome experiments using Structural equation modelling

*Abstract*: Biomarker is a characteristic that is objectively measured and evaluated as an indicator of biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (Alonso et al., 2016). Recently, the need for biomarkers in diagnosing disease and assessing the responses of patients to therapy has become crucial. Detection of biomarkers which aims to identify candidate biomarkers for the disease of interest is one of the important steps in the development of biomarkers (Mussap et al., 2013).

In this study, we focus on the detection of microbiome biomarkers in intervention experiments with the goal (1) to explore how the intervention factors (Z) influence the microbiome (X) as well as a clinical outcome of interest (Y), and (2) to model the association between the microbiome biomarkers and clinical outcomes of interest taking into account the possible intervention.

The structural equation modeling (SEM) approach is applied to address the questions since it allows us to investigate several causal models that could explain the relationship between the variables in our setting. SEM is also a flexible method which can be used for different types of outcomes such as continuous, binary, and time-to-event. Since the direction of the association is known within the biomarker setting, we only considered 8 possible causal models for the triplet (Xij, Yi, Zi) for biomarker detection (Danner et al., 2015). Moreover, in order to compare and select the best causal model among the eight possible models, the model averaging techniques (Burnham, 2002) are employed.

The proposed method is applied to the transPAT data (Ruiz et al., 2017) a microbiome experiment consists of an antibiotic intervention study at each time point separately in different resolutions of the taxonomic hierarchy. Relative abundance was used at Operational Taxonomic Unit (OTU) level while Shannon index was chosen at family and kingdom levels. The analysis was done for all active OTUs, families, and kingdom level at all time points. AIC and BIC were used as information criteria in order to calculate posterior probabilities.

Poster Abstracts

**C2**. *Presenter*: Christian Schmid (F. Hoffmann - La Roche)

*Title*: Improving Production Capacity and Asset Utilization of Biologics Drug Product Lines Through Simulation

*Abstract:* Scheduling a production plan for a drug product line comes with many challenges. The planner has to account for the available equipment, working times of operators, and scheduled maintenance operations. Other constraints are related to the products being manufactured, as each product has a specific format and process duration. In addition, there can also be unplanned events which require a total redesign of the schedule.

In order to facilitate the planning process, we have developed a data-driven simulation tool that accounts for all of these constraints and provides explicit planning schedules that can be easily geared to the needs of each product line. The simulation can identify ideal production plans for different priorities, e.g., schedules that maximize the overall equipment effectiveness (OEE), minimize the end-to-end lead time, or even decrease the amount of manual labor between the change over of different products. In addition, this simulation can use historical data to evaluate the chances of successfully running a given production plan and, in consequence, identify potential bottlenecks. It can also help process managers to quickly adapt and optimally assign tasks especially during unplanned events.

We have successfully scaled and applied our method to multiple lines at Roche. The results will be shared and lessons learned will be discussed. The simulation tool helps increase the asset utilization and production capacity, which ultimately enables more drug products to be delivered to our patients.

**C3**. *Presenter*: Zhong Lai (MRL)

*Title*: Assessment of Pharmaceutical Quality: Tolerance intervals for SEC Data

*Abstract:* Aggregation of monoclonal antibody may compromise the efficacy of drug product. Thus, it is critical to monitor low molecular weight species (monomer) to ensure the quality of drug product. Size-exclusion chromatography (SEC) is a method in which molecules in solution are separated by their size, and in some cases molecular weight. Assessment of % monomer often used tolerance intervals. SEC data are bounded data and must be considered in the calculation. In this investigation, we consider a beta distribution when one of the parameter is unknown to model SEC data. We show that tolerance intervals under beta with one unknown parameter based on Bayesian, Fiducial, and Frequentist Inference are the same. We also conducted a simulation study and demonstrate the tolerance intervals have good statistical properties.

**C8**. *Presenter*: Jeff McLeod (BMS)

*Title*: Case Studies for Autologous CAR T Cell Therapy Comparability

*Abstract:* Analytical comparability studies are conducted in the regulated pharmaceutical industry to improve product through the reduction in process variation, addition of manufacturing facilities, implementing new technology, increasing efficiency, optimizing resources, and improving patient experience through innovation. These studies need to demonstrate that product made under the post-change condition maintains the safety and efficacy of the pre-change product. Comparability studies for autologous CAR T products and processes are particularly challenging because of the inherent complexity and high levels of variability driven by the starting material. We present several case studies associated with BMS’s two approved CAR T products. This involves several alternative scenarios along with the statistical approaches employed – prospective study designs, data analysis, and interpretation of results, as well as the lessons learned from regulatory agencies’ feedback. Examples include site transfers and process version changes for apheresis material, lentiviral vector, cellular drug product, and changes in critical raw material. Additionally, we also discuss the analysis of retrospective manufacturing data.

**D2**. *Presenter*: Zihuan Liu (AbbVie Inc.)

*Title*: Shapley Value Based Interpretable Predictive Biomarker Identification

*Abstract:* To advance precision medicine, several frameworks have been proposed for predictive biomarker signature development by modifying objective/loss functions. Under these frameworks, popular machine learning methods are readily applicable to identify predictive effects of candidate biomarkers without the potential confounding prognostic effects. Upon completion of the model training, the challenging remains in the interpretation of the model results to facilitate efficient communication with the clinical team. In this manuscript, we discuss the use of Shapley values for predictive biomarker identification based on existing frameworks. Simulation studies are conducted to compare the performance of Shapley values based on existing frameworks. Real-world examples are also used to demonstrate the utility of the proposed Shapley value methods.

**D5**. *Presenter*: Wei Meng (Bristol Myers Squibb)

*Title*: Statistical Considerations for Autologous CAR-T Critical Quality Attributes Assessment

*Abstract:* Critical Quality Attributes (CQAs) are the attributes that enable ensuring the desired product quality, and hence play a central role in modern drug development based on Quality by Design (QbD) principles. CQA assessment is a key step in the development of the control strategy, and this task is particularly challenging and important for autologous Chimeric Antigen Receptor T-Cell (CAR-T) products for several reasons: autologous CAR-T products have demonstrated remarkable benefit to patients but are inherently complex. For example, the autologous nature of these products results is high levels of variability. Additionally, owing to their novelty and complexity, product and manufacturing process understanding is still quite limited, particularly so with regards to the underlying mechanisms of action. This complexity is also reflected in the associated data - non-normal and varied data distributions, and disparate data characteristics such as categorical, continuous, or time-to-event data.

While CQA assessment is a multidisciplinary task, we present a systematic statistical approach for the data analysis and interpretation elements of the exercise. Our approach is simple, yet effective and has gained widespread regulatory approval. It involves identifying correlations and potential correlations between drug product release attributes (continuous) and clinical outcomes (efficacy, safety and pharmacokinetics). Wilcoxon rank-sum test as well as standardized effect sizes (Cohen’s d) are used for categorical clinical endpoints. Spearman’s correlation coefficients are used for continuous PK parameters. Cox-regression is used to estimate the relationship based on hazard ratios of time-to-event clinical endpoints. Finally, the Benjamini-Hochberg procedure (q-value) is used to control false discovery rate for each clinical endpoint across all the quality attributes.

**D6**. *Presenter*: Sangwook Choi (Bristol Myers Squibb)

*Title*: Improving process and product understanding in autologous cell therapy products using multivariate variance component analysis

*Abstract:* Process and product characterization data for autologous cell therapy products are multivariate in nature. Moreover, the inherent biological complexity, multiple sources of variability and higher levels of variation involved in autologous cell therapy processes makes it challenging to gain a comprehensive understanding of the manufacturing process and final drug product. It is therefore critical to quantify the sources of variation in cell therapy processes by partitioning the total variability into variability arising from its three main sources: starting (donor/patient) material, manufacturing process and analytical methods. The outcome of such a variance component analysis (VCA) enhances overall process and product understanding and can form the basis for a variety of key CMC activities including Process Characterization, Process Comparability, Product Release specifications and Assay development. Such an enhanced understanding eventually translates into a better product that improves our patient’s lives.

However, the standard univariate VCA approach has the limitation of not considering the underlying correlation across attributes. In this study, we propose to use a multivariate VCA approach. As a combination of VCA and dimension reduction techniques, this approach partitions total variation into different components based on multiple attributes, while accounting for correlations across attributes. Analysis using multivariate VCA enables a comprehensive interpretation regarding sources of variation for a group of similar attributes that can be chosen to reflect common biological characteristics and provide a high-level insight. Three versions of multivariate VCA: (1) principal component-based, (2) factor-based and (3) kernel principal component VCA were introduced, and simulation studies were conducted to evaluate and compare the performance of these methods. In addition, these approaches were performed on the in-process and quality data of cell therapy products.

**S4**. *Presenter*: Yu-Ting Weng (FDA)

*Title*: Statistical Approaches to Evaluate Positive Control Drug and Classify Investigational Product using hERG Safety Assay

*Abstract:* The assessment of hERG safety assay is a key component of estimating the risk for delayed repolarization and QT interval prolongation prior to first administration in humans. hERG safety assay similarity assessment can be challenging since no consensus quantitative assessment has been developed. In this project, we developed a two-stage statistical framework to conduct quantitative assessment of hERG safety assay by using either a variance-adjusted equivalence testing or fixed margin equivalence testing approach. In Stage 1, given a pre-specified safety margin under the agreement between the stakeholder and the regulator, we assess the similarity for positive controls between stakeholder’s lab and historical information. Note the historical information can be from the stakeholder’s prior hERG assay of the positive controls or from external labs that follow ICH E14 S7b Q&A Best Practice recommended protocol. In Stage 2, we predict the risk category of an investigational product (IP). Note two risk categories are QT effect is equivalent to or more than 10 msec and QT effect is less than 10 msec. Since the safety margin of the risk category is drug-dependent and unknown, we first fine tune the safety margin by the positive controls passed Stage 1 and then apply the fine-tuned safety margin to classify IP. We treated a positive control from one stakeholder’s lab as IP and applied our proposed method. The proposed equivalence testing methods can classify the IP accurately.

**P2**. *Presenter*: Xiao Tan (AstraZeneca)

*Title*: Unit Allocation Using a Minimization Algorithm for in vivo Experiments

*Abstract:* Animal allocation is generally straightforward when animals enter an experiment at the same time point, and homogeneous experimental units among groups are desired after allocation. However, for certain in vivo arthritis experiments where animals enter them sequentially, the usual animal allocation scheme may give rise to significant bias because animals are assigned to treatment groups only after their symptoms of arthritis are severe enough and the severity of induced arthritis varies from animal to animal at the same time point. To address this issue, we propose a method called minimization allocation, which dynamically balances continuous baseline attributes among groups as animals enter the experiment sequentially. Moreover, our method allows for the adjustment of the importance of each baseline attribute by assigning different weights. To simplify the allocation process for in vivo scientists, we have developed a Shiny app that facilitates animal allocation based on uploaded baseline attributes. The app also provides related summary statistics and data visualization to monitor the balance of baseline attributes after allocation.

**P3**. *Presenter*: Ying Lin (IQVIA)

*Title*: Stability Analysis and Risk Assessment for the Hardness of Chewable Tablets Using A Non-linear Mixed Model and Bayesian Simulation

*Abstract:* Hardness is one of the Quality Attributes for Chewable Tablets and specifications are required by regulatory and manufacturers to ensure that the product would impart the desired mouthfeel throughout the shelf life while being able to withstand the rigors of shipping and downstream processing/packaging. In this study we applied statistical evaluations to assess the hardness stability data of the Chewable Tablets packaged in blisters to support the extension of shelf life to 36 months. The study focuses on calculating failure rates based on average hardness of 5 tablets from two manufacturing sites at 24 and 36 months, considering the current regulatory specification. In order to characterize the non-linear stability behaviors of tablets hardness and the multiple sources of variabilities due to manufacturing and analytical works, a nonlinear mixed effects model was used accounting for fixed effects due to site-specific asymptote, common scale and change rate, and random effects due to batch-specific asymptote, analytical run-to-run and within-run variability. The common scale and change rate across batches/sites were evaluated and confirmed from preliminary analysis and applied to the final model. Based on the nonlinear mixed effects model, Bayesian simulation with weak priors was employed to estimate the failure rates at selected time points for each site to support the filed specification and the goal of extending product shelf-life.

**P4**. *Presenter*: Hong Tran (Johnson & Johnson)

*Title*: Bayesian Power Prior Tolerance Intervals under common variance assumption

*Abstract:* Product performance qualification (PPQ) analysis is a routine part of process validation in manufacturing. Often statistical tolerance intervals (TI) with 99% coverage and 95% confident are calculated from PPQ batches to determine if a product meets specification requirements. Under common within-batch variability assumption, PPQ batches can be pooled together to estimate within-batch variability. Subsequently, batch-specific tolerance intervals are obtained by combining batch means and pooled within-batch variability. When historical data are available, Bayesian TI can incorporate prior knowledge into its calculation whereas traditional frequentist approach disregards this useful information. However, fully incorporating prior in Bayesian when prior data are not in agreement with current PPQ data can lead to inaccurate inference. This research is to propose an approach to apply power priors (i.e. utilize all or part of priors depending on level of compatibility between current PPQ and historical data) to obtain Bayesian TI. Our real data examples show that using either frequentist approach, ignoring prior data or fully incorporate prior in Bayesian resulted in either out of specification or lower coverage confident while correctly incorporate part of prior information resulted in all batches meet specification requirements with higher coverage confident. Simulations based on real PPQ data also show that the power prior Bayesian TI achieved desirable level of confident and content coverage.

**P5**. *Presenter*: Shannon McKearnan (GSK)

*Title*: Integration of automated data processing with advanced synergy scoring for profiling of in vitro drug combination matrices

*Abstract:* Drug combination therapy has become a cornerstone of treatment for complex diseases such as cancer, asthma, and immunological disorders. The development of a rational combination therapy provides opportunity for better efficacy, decreased toxicity, and reduced drug resistance. Studying the effects of drug combinations in comparison to single agents has become a mainstay for numerous GSK research programs as evidence of the superiority of combinations over monotherapy informs clinical opportunity and asset positioning. While combination matrix formats enable testing of a broad range of concentrations and inform in vivo dose selection, analysis of these experiments has historically been tedious and limited due to the manual data processing steps. We developed an automated pipeline that takes data input directly from lab equipment, processes and analyzes the data in R, and outputs quality control measures, curve fits, and combination synergy metrics. Because the methods for calculating synergy are founded upon various underlying assumptions, we use effect-based and dose-effect-based approaches to calculate multiple metrics for a comprehensive interpretation. We quantify synergy across the entire matrix of doses by excess over Bliss and report Combination Index for specific dose ratios of interest. The analysis pipeline provides summary figures and tables in an easy-to-use format suitable for inclusion in patent applications and easily scales to the desired number of drug combinations and cell lines. The integration of automated data processing with advanced synergy scoring allows high throughput profiling of in vitro drug combination synergy thereby increasing throughput and reducing data processing time by up to 90%.

**P6**. *Presenter*: Yanbing Zheng (AbbVie Inc.)

*Title*: Establishing Limits for Dosage Units in Early Phase Process Control Using Bayesian Methods

*Abstract:*  Statistical process control is considered a key tool in manufacturing. In the pharmaceutical industry, process control is essential to ensure consistent processes that yield products with satisfactory quality. Control limits play a major role in process monitoring. The purpose of this presentation is to present a Bayesian application in which in-process control limits are established during early (Phase I) control chart formation for uniformity of dosage units (UDU) based on weight variation. The Bayesian approach utilizes posterior predictive distributions based on noninformative and informative priors (through a power prior) and the resulting control limits are compared to those obtained from more typical approaches (± 3 sigma, ±5% of mean, Monte Carlo simulation). The Bayesian methods, which incorporate uncertainty in the parameter estimates, provide wider control limits than some of the typical approaches investigated and proffer a potential justification of the ad hoc ±5% of the mean approach for the data analyzed.