IABS 10th Annual Statistics Workshop: Science & Statistics – Elevating CMC through Partnership

November 12-14, 2024
University of Maryland
Institute for Bioscience & Biotechnology Research (IBBR)

This year the IABS Statistics workshop is celebrating its 10th anniversary. This conference is aiming at bringing statisticians, subject matter experts and regulators together to exchange on the intersection of statistics and science, and to pave the way to improve the usage of CMC Statistics, data analytics, and modeling for Biologics. The beautiful venue at the Institute for Bioscience & Biotechnology Research at the University of Maryland will again be the place to host this conference.

To start the workshop, the conference provides interesting short courses about tolerance intervals as well as automating statistical analysis and GxP reporting. Four sessions will guide discussions through the remainder of the conference. These sessions focus on CMC Statistics and the intersection to Science, to Stability, to advanced analytical approaches and to comparability topics. The agenda is full of presentations covering current industry topics, application of statistical and data analytics tools to practical scientific challenges in CMC, impact of regulatory changes to data analysis applications and many more. We are pleased to have a variety of presenters on board, covering statistical experts, subject matter experts and regulators.

Scientific / Organizing Committee

Laura **Pack**, Co-Chair, Moderna
Ruojia **Li**, Co-Chair, Bristol-Myers Squibb
Irina **Gershgorin**, Novartis C&GT
Ashley **Giambrone**, Regeneron
Kristi **Griffiths**, Eli Lilly & Co.
Franz **Innerbichler**, Novartis
Jennifer **Kirk**, FDA/CBER
Jia **Liu**, Pfizer
Timo **Bailer**, Co-Chair, Boehringer Ingelheim
Madinina **Cox**, Events Manager, IABS/MC'Com
John **Oleynick**, Johnson & Johnson
Chuck **Miller**, Merck
Cristian **M. Oliva-Aviles**, Genentech
José **Ramírez**, Kite Pharma, a Gilead Company
Travis **Wolter**, Amgen
Tim **Schofield**, CMC Sciences, LLC

Workshop Program

Day 1: Tuesday, November 12, 2024

1.00 pm *Registration*

1.30 pm **Short Course: Tolerance Intervals**
Thomas MATHEW – University of Maryland

3.30pm **Short Course: Automating statistical analysis and GxP reporting**
Pierre LEBRUN – PharmaLex

4.30pm *End of Day 1*

Day 2: Wednesday, November 13, 2024

8.30am *Registration & Welcome Coffee*

9.00am *Introduction to IABS* – **Shawn NOVICK** – Vice-President, ABS

Welcome to Workshop
Laura PACK – Co-Chair, Moderna
Ruojia LI – Co-Chair, BMS
Timo BAILER – Co-Chair, Boehringer Ingelheim

Keynote Session

9.15am **Statistical Considerations During the Review of Gene Therapy Products**
Kimberly SCHULTZ – USFDA

Session I: Science & Statistics

Session Chairs: Jennifer Kirk, José Ramirez, Irina Gershgorin

10.20am *Session introduction*
José RAMIREZ - Kite Pharma, a Gilead Company

10.25am **Statistical Science & Statistical Engineering**
José RAMIREZ - Kite Pharma, a Gilead Company

10.55am **How do Theorists and Experimentalists Interact in a Biopharmaceutical Company?**
Kenneth LEE – AstraZeneca

11.25am **Break**

11.40am **The Selective Advantage of Synergy – One Biologist's Perspective on the Importance of Collaborating with Statisticians**
Nancy SAJJADI – Sajjadi Consulting

12.10pm **The Power of Statistics to Improve Science: Examples from CMC Statistics.**
Jennifer KIRK - FDA/CBER

12.40pm **Panel Discussion**
All speakers and Keynote speaker - Irina GERSHORIN, facilitator

1.15pm *Lunch*

Session II: Stability Innovations in Manufacturing Biologics

Session Chairs: John Oleynick, Cristian M. Oliva-Aviles

2.00 pm *Session Introduction*
Cristian M. OLIVA-AVILES - Genentech

2.05pm **Predictive Stability Modeling of mRNA Vaccines Based on Mechanisms of RNA Molecular Degradation**
Xingyi YANG & **Gang WANG** – Moderna, Inc

2.35pm **A Bayesian Procedure to Allow Reliable Extrapolation from Short-Term Stability Data for Biologics.**
Chuck MILLER – Merck

3.05pm **Break**

3.35pm **Shelf-life estimation of pharmaceutical products through tolerance intervals under linear mixed models.**
Cristian OLIVA-AVILES – Genentech

4.05pm **Panel Discussion**
All speakers – John OLEYNICK, facilitator

5.05pm Break-Out Session

6.05pm *End of Day 2*

Day 3: Thursday, November 14, 2024

Session III: Enhancing Biologicals Development with Advanced Analytical Approaches

Session Chairs: Jia Liu, Kristi Griffiths

8.30am *Registration & Welcome Coffee*

9.00am *Session Introduction*
Jia LIU - Pfizer

9.05am **Clinically Relevant Specifications – A Regulatory Perspective**
Jayda SIGGERS – Health Canada

9.35am **Analytical Characterization for Precision Biologics**
Julia O'NEILL – Direxa Consulting

10.05am **A patient-centric approach to cell therapy manufacturing: Linking CAR-T product attributes and CQAs to clinical outcomes**
Irina GERSHGORIN – Novartis C&GT

10.35am **Break**

11.05am **Panel Discussion**
All speakers – Jia LIU, facilitator

12.05pm *Lunch*

1:05pm **Statistical opportunities related to ICH Q2(R2) and Q14**
Tim SCHOFIELD – CMC Sciences, LLC

Session IV: Enhancing Analytical Method Transfer and Assessing Manufacturing Analytical Comparability: Statistical Approaches and Empowering Subject Matter Experts

Session Chairs: Chuck Miller, Travis Wolter, Ashley Giambrone

1.35pm *Session Introduction*
Chuck MILLER - Merck

1.40pm **An RShiny Application to guide the Planning and Evaluation of an Analytical Method Transfer**
Tobias EILERT - Boehringer-Ingelheim

2.10pm **Statistical assessment for analytical comparability between pre-change and post-change processes**
On behalf of Aili Cheng and the NCB comparability workstream:
José RAMIREZ – Kite Pharma
Irina GERSHGORIN – Novartis

2.40pm **Case Study in Comparability for an iPSC-Derived, Genome-Edited Cell Therapy Product**
Jennifer L. DASHNAU – Century Therapeutics

3.10pm	**Panel Discussion – Ashley GIAMBRONE**, facilitator **All speakers**
4.10pm	*Workshop Summary*
4.25 pm	*End of Workshop and Invitation to 2025 Workshop*

Short Course Tolerance Intervals

Thomas MATHEW – University of Maryland

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 Computation*s by Krishnamoorthy and Mathew (2009, Wiley). However, a significant part of the short course will include more recent developments on the topic.

Short Course Automating statistical analysis and GxP reporting

Pierre LEBRUN, PharmaLex

Analytical procedures play a crucial role within the CMC framework. Scientists who develop these analytical procedures must write statistical reports to justify that their method is fit for its purpose. Such reports are crucial for obtaining accreditation for labs or marketing authorization for pharmaceutical products (e.g., as evidence of the drug's correct active substance content). Hence, the reports must also be in line with the current EMA/FDA/ICH/ISO regulation.

However, writing statistical reports is time-consuming and error-prone. Compounding this issue is that scientists developing these procedures often lack the time to perform the analysis thoroughly, while perceiving the regulatory guidelines as more confusing than helpful.

To address these challenges, we developed a framework for automation, to reduce the time required to write these reports from days or even months to just a few minutes, requiring minimal understanding of statistics while, at the same time, ensuring both regulatory and quality (QA) compliance.

The solution requires a strong collaboration and alignment between scientists, statisticians, engineers, IT and QA. We will present the various challenges one may face and how they can be solved:

1. Conducting statistical analyses in accordance with guidelines.
2. Software for automated report writing.
3. Qualifying cloud infrastructure for GxP applications.
4. Complying with quality aspects (CSV\CSA) and (GxP) regulation.
5. Implementing end-to-end process automation.

We will demonstrate through a live real-world case study how we integrated this into a working solution for statistical report writing, suitable for use within GxP contexts. The case study will focus on the new ICH Q2(R2) guideline for analytical procedure validation, although we have other guidelines in the pipeline too, like the USP 1033 for potency bioassays and Q1E for drug product stability. The automation framework is generalizable and can be leveraged to standardize (GxP) reporting across the organization in line with any guideline.

Session I Science & Statistics

Chairperson: Jennifer Kirk, José Ramirez, Irina Gershgorin

Although often overlooked, statisticians play a key role in the practice of science. Generation of high-quality evidence requires study designs and analyses that align with the scientific questions of interest. Furthermore, coordinated development of study designs and analyses can result in more efficient studies that optimally address important sources of variation. Statisticians bring a unique skillset to this process, as they are trained to think skeptically, to interrogate assumptions, and to consider multiple sources of both variation and bias. Yet statisticians are often only involved at the end of this process, as Sir Ronald Fisher captured in his 1938 Presidential Address to the First Indian Statistical Congress, : "To consult the statistician after an experiment is finished is often merely to ask him to conduct a postmortem examination. He can perhaps say what the experiment died of." Forty years later, Prof. George Box in his Presidential Address to the 138th meeting of the American Statistical Association commented: “By invention of the concept of Experimental Design, Fisher promoted the statistician from a curator of dusty relics to a valued member of a scientific team, responsible for planning and taking part in the conduct of an investigation.” Eighty years later, then ASA President Lisa LaVange echoed Fisher’s sentiment in her 2018 presidential address when she decried the misuse of statistics in pharmaceutical science, saying “Statisticians to the rescue, please!”

This session will discuss some key statisticians who were also scientists, as well as the key role statisticians play as a part of a scientific team. The session will also include the perspective of scientists and engineers on how they partner with statisticians, as a catalyst for better science and engineering. We will discuss how to promote statisticians as scientific collaborators.

Session II Stability Innovations in Manufacturing Biologics

Chairperson: John Oleynick, Cristian M. Oliva-Aviles

Monitoring products on stability is critical to determine how long they will remain safe and efficacious, and a major area where statistics are used in manufacturing biologics. Traditional stability studies for biologics take years to complete, but work is being done to use accelerated studies to determine or estimate shelf life more quickly. This session will have two presentations on estimating shelf life more quickly, one for mRNA vaccines and therapies, and one for biologics in general. Although regulatory guidance specifies one statistical method that can be used to determine shelf life, other methods are frequently used because of limitations with that method. One presentation in this session will discuss a novel method of using tolerance intervals to estimate shelf life, and discuss a method for estimating tolerance intervals for linear mixed models with unbalanced data, which can also be applicable for other stability analyses.

Session III Enhancing Biologicals Development with Advanced Analytical Approaches

Chairperson: Jia Liu, Kristi Griffiths, Tim Schofield

This session will explore the transformative journey of analytical methods in the biologics sector, highlighting the shift from traditional control strategies to cutting-edge approaches. We will delve into the modernization of analytical characterization, which is crucial for the rapid development and approval of gene therapies, cell therapies, and novel vaccines. The session will discuss the challenges and opportunities presented by the ICH Q2(R2) and Q14 guidelines, emphasizing the role of CMC statisticians in ensuring the fitness for use of analytical procedures. Additionally, we will examine a patient-centric approach to cell therapy manufacturing, focusing on the link between CAR-T product attributes and clinical outcomes. Through examples from recent successful submissions and clinical trials, the session aims to stimulate Quality by Design thinking and showcase the lifecycle management of analytical methods. Join us for a comprehensive discussion on enhancing biologic development with advanced analytical approaches and the role of statisticians in shaping the future of biologics.

Session IV — Enhancing Analytical Method Transfer and Assessing Manufacturing Analytical Comparability: Statistical Approaches and Empowering Subject Matter Experts

Chairperson: Chuck Miller, Travis Wolter, Ashley Giambrone

This conference session will feature presentations addressing the statistical aspects of analytical method transfer and manufacturing analytical comparability. One presentation focuses on empowering subject matter experts (SMEs) in method transfer by providing them with the necessary statistical training. Another presentation discusses statistical approaches for assessing manufacturing analytical comparability, considering the challenges posed by highly variable data and limited batch sizes in cell and gene therapies. These presentations aim to highlight the importance of statistical consultation and the impact on overall quality and efficiency in the pharmaceutical industry.