IABS 9th Annual Statistics Workshop: Applying Statistics and Data Science to Evolving Technical and Regulatory Paradigm

Hybrid meeting

November 7-9, 2023
University of Maryland
Institute for Bioscience & Biotechnology Research (IBBR)

The impact of statistics and data science in Chemistry, Manufacturing & Controls (CMC) is constantly expanding, with the introduction of advanced statistical methods and the ability to mine "big data" in the development and lifecycle management of biological products.

There are multiple aspects that frame the application of statistics and datascience. Those include improving and developing innovative statistical methodologies to guide decision-making processes; addressing questions arising from yet unexplored modalities or technologies; advancing the regulatory framework through revised guidance; and implementation of harmonized statistical solutions.

This workshop will provide a forum for statisticians, data scientists, development engineers, and regulators to explore approaches that serves future generations of technical and regulatory innovation in biologicals development and lifecycle management.

Scientific / Organizing Committee

Laura **Pack**, Co-Chair, Rezolute
Tim **Schofield**, IABS Advisor, CMC Sciences, LLC
Catherine **Cheng**, Novartis Gene Therapy
Franz **Innnerbichler**, Novartis
Jun **Gao**, Health Canada
Ashley **Giambrone**, Regeneron
Kristi **Griffiths**, Eli Lilly & Co.
Theo **Koulis**, Genentech
Jennifer **Kirk**, FDA/CBER
Timo **Bailer**, Co-Chair, Boehringer Ingelheim
Madinina **Cox**, Events Manager, IABS/MC'Com
Ruojia **Li**, Bristol-Myers Squibb
Jia **Liu**, Pfizer
Chuck **Miller**, Merck
John **Oleynick**, Johnson & Johnson
José **Ramírez**, Kite Pharma, a Gilead Company
Travis **Wolter**, Amgen

Workshop Program

Day 1: Tuesday, November 7, 2023

1:00 pm *Registration*

1:30 pm **Short Course – Tolerance Intervals: The Bayesian Way**
José Ramírez, Kite Pharma, a Gilead Company, and **Fang Chen**, SAS Institute

5:30 pm *End of Day 1*

Day 2: Wednesday, November 8, 2023

8:30 am *Registration & Welcome Coffee*

9:00 am *Introduction to IABS* – **Rick Hill,** IABS

Welcome to Workshop – **Timo Bailer & Laura Pack**

Keynote Session

9:15 am **Keynote presentation: Process Control Strategy, Residual Uncertainty, and the Myth of Fingerprints**
Jeff Baker, Sr. Fellow with NIIMBL & USFDA (retired)

10:05 am **Break**

Session I: The Research Question: Its importance in achieving successful product development and regulatory review

Session Chairs: Jennifer Kirk, Tim Schofield, Chuck Miller

10:30am *Session introduction – Jennifer Kirk*

10:40 am **The question addressed using frequentist vs Bayesian methods**
Dave Leblond, Robert Singer Consulting

11:10 am **Assigning Ruggedness Factors as Fixed or Random Consistent with Goal of a Procedure Performance Qualification (Validation)**
Rick Burdick, Burdick Statistical Consulting

11:40 am **Review perspective**
Leslie Wagner, FDA

12:10pm **Panel Discussion**
All speakers – Chuck Miller, facilitator

12:40 pm *Lunch*

Session II: Innovative statistical methodologies in CMC

Session Chairs: Jun Gao, Franz Innerbichler, John Oleynick

2:00 pm *Session Introduction – John Oleynick*

2:10 pm **Process Characterization for continuous process based on simulation**
Yukun Ren, Sanofi

2:40 pm **Joint Assessment of Accuracy and Precision in Analytic Transfer**
Justin Pearson, Regeneron

3:10 pm **Considerations in Prior Knowledge Development for Product Stability**
Adam Rauk, Eli Lilly & Co.

3:40 pm **Break**

4:10 pm **Panel Discussion**
All speakers – John Oleynick, facilitator

4:40 pm **Break-Out Sessions**

5:40 pm *End of Day 2*

Day 3: Thursday, November 9, 2023

Session III: Application of CMC Statistics and Data Science to New Modalities and Technologies

Session Chairs: Travis Wolter, José Ramírez, Catherine Cheng

9:00 am *Session Introduction – Catherine Cheng*

9:10 am **CAR T-Cell Therapy Data : Long tails, mixtures, hurdles, censoring; definitively not normal**
José Ramírez, Kite Pharma, a Gilead Company

9:40 am **mRNA Platform: Analytical and Process Opportunities and Evolution**
Tingting Feng, Moderna

10:10 am **Overview of NGS technology and application of NGS for gene therapy**
Shuli Kang, Novartis

10:40 am **Break**

11:10 am **Panel Discussion**

All speakers – Catherine Cheng, facilitator

11:40 am **Break-Out Session**

12:40 pm *Lunch*

Session IV: Call to Action: Implementation of Statistical Solutions for CMC

Session Chairs: Jia Liu, Ruoija Li, Theo Koulis

1:55 pm *Session Introduction – Theo Koulis*

2:05 pm **Links between Total Analytical Error, Measurement Uncertainty, Analytical Target Profile and Quality Target Product Profile**
Bruno Boulanger, PharmaLex

2:35 pm **Insights on patient-centric specification setting and implementation for Vaccines**
Cristiana Campa, GSK and **Mathieu Vasselle**, GSK

3:05 pm **Ongoing Analytical Procedure Performance Verification**
Horacio Pappa, U.S Pharmacopeia

3:35 pm **Panel Discussion**
All speakers – Ruojia Li, facilitator

4:00 pm *Workshop Summary*

4:30 pm *End of Workshop and Invitation to 2024 Workshop*

Short Course Tolerance Intervals: The Bayesian Way

Chairperson: **José Ramírez**, Kite Pharma, a Gilead Company and **Fang Chen**, SAS Institute

In the pharmaceutical industry, most tolerance interval-related calculations to set acceptance criteria cannot use a normal distribution to model the data we encounter, and methods are neededthat account for distributions other than the normal.

In this 3-hour workshop we first review the basic ideas regarding tolerance bounds and tolerance intervals, and show some basic examples of their calculations using normal-based frequentists methods. We also review some basic Bayesian concepts and go over the Bayesian algorithms for calculating one-sided and two-sided tolerance bounds.

With several examples, we demonstrate the flexibility of the Bayesian methods for calculating tolerance limits when the probability density function is known. We also demonstrate how, via simulation, tolerance limits can be approximated if the pdf is either not known, or does not have a close form. We tie things up by showing that the exact normal-based tolerance limits are in very close agreement with the Bayesian tolerance limits.

Session I — The Research Question: It's importance in achieving successful product development and regulatory review

Chairperson: **Jennifer Kirk**, FDA/CBER**; Chuck Miller**, Merck**; Tim Schofield**, CMC Sciences, LLC

Careful implementation of CMC studies is an important aspect of biologicals development, quality control, and lifecycle management. Successful completion of such studies relies on formulation of the scientific questions that these studies are intended to answer first, as the scientific questions guide the choice of study design and analyses, facilitating regulatory acceptance. Without well- defined scientific questions, the chosen study designs and analyses may not provide the evidence needed to support CMC decisions or regulatory acceptance. In contrast, well-defined scientific questions facilitate the choice of not only appropriate but also efficient study designs and analyses. In addition, even for a single well-defined scientific question, several appropriate and efficient studydesigns and analyses may exist. This session will delve into several CMC scenarios, discussing the relevant questions to be answered and how different statistical approaches can address those questions, along with the regulatory perspective on these scenarios.

Potential areas of presentation and discussion include:

- *Bayesian statistics– How important is the difference in the questions which can be answered using Bayesian methods versus frequentist approaches? How does the question influence the choice of a prior distribution?*
- *Equivalence versus difference testing– When is one type of test appropriate over another? What are the issues related to choosing the wrong approach?*
- *Fixed versus random factors in a design– Many studies combine fixed and random effects into the study design. How should these be allocated according to the study objective?*

Session II Innovative statistical methodologies in CMC

Chairperson: **Franz Innerbichler**, Novartis; **Jun Gao**, Health Canada; **John Oleynick**, Johnson & Johnson

In recent years significant advances in statistical and data science methodologies were introduced into biologicals CMC development.

The applications of Bayesian statistical methodology are more and more accepted by regulatory authorities across the globe. Neural Networks have an ability to solve problems with very complex, unstructured, and noisy data, and are capable of dealing with data formats where classical statistical or mathematical methods are inadequate.

These provide a wide range of opportunities to address CMC paradigms such as the use of prior knowledge and the institution of technical and regulatory platforms. CMC development has been hampered in the past by the "small sample size" problem, leading either to delays in development or to decisions made with limited confidence.

Some potential topics that will be covered in this session are:

- *The uses of Bayesian statistical methods in the framework of current CMC regulatory expectations.*
- *The uses of principal components analysis, factor analysis, and regularization methods like lasso and ridge regression to reduce the number of variables in high dimensional data.*
- *Statistical and data science support of platform technologies.*

Session III — Application of CMC Statistics and Data Science to New Modalities and Technologies

Chairperson: **Catherine Cheng**, Novartis Gene Therapy; **José Ramírez**, Kite Pharma, a Gilead Company; **Travis Wolter**, Amgen

All areas of biologicals are embracing new technologies, whether they are new modalities such as mRNA, more sensitive analytics such as next generations sequencing, or new manufacturing paradigms such as Industry 4.0 (digitization of manufacturing). New technologies offer opportunities for innovative statistical and data science support, with challenges related to data acquisition, processing, and standardization.

These opportunities are expected to accelerate development, testing, and regulatory review. Statistics and Data Science will be critical in addressing questions such as, how to introduce these advancements into the highly regulated industry of biologicals development and manufacturing or what sorts of evidence will be required to demonstrate their utility and their robustness in practice?

This session will focus on new modalities and technologies such as:

- *Examples of applications of next generation sequencing to biological development and quality control*
- *Validation of data processing and data management of "big data" applications*
- *Statistical and regulatory challenges moving from batch release to continuous manufacturing*

Session IV — Call to Action: Implementation of Statistical Solutions for CMC

Chairperson: **Ruojia Li**, Bristol-Myers Squibb; **Jia Liu**, Pfizer; **Theo Koulis**, Genentech

The use of statistical methods has significantly increased across the product development and lifecycle with the adoption of ICH Q8 through Q12. Statistical support is essential at every stage of the project lifecycle to accelerate product development, understand the risk and uncertainty and achieve desirable quality. Analytical guidelines such as ICH Q2(R2) and Q14, and USP <1220> have embraced a Quality by Design approach to analytical methods while plans are underway to revise Q6A and Q6B and the stability guidelines.

This session includes case studies that showcase the approaches for integrating statistical support into product development & lifecycle management in keeping with previous and ongoing quality guidelines.

Topics which are being considered for this session include:

- *Examples of the adoption of quality guidelines related to product development and lifecycle management (Q8-Q12).*
- *Changes in approaches for analytical method development based on newly issued quality guidelines (ICH Q2 and Q14, USP <1220> and <1210>)*
- *Statistical support of pending revisions to specifications and stability guidelines.*