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International Alliance for Biological Standardization

IABS 9th Statistics Workshop

Applying Statistics and Data Science to Evolving Technical and Regulatory Paradigms

November 7-9, 2023

Institute for Bioscience and Biotechnology Research

Rockville, U.S.A.

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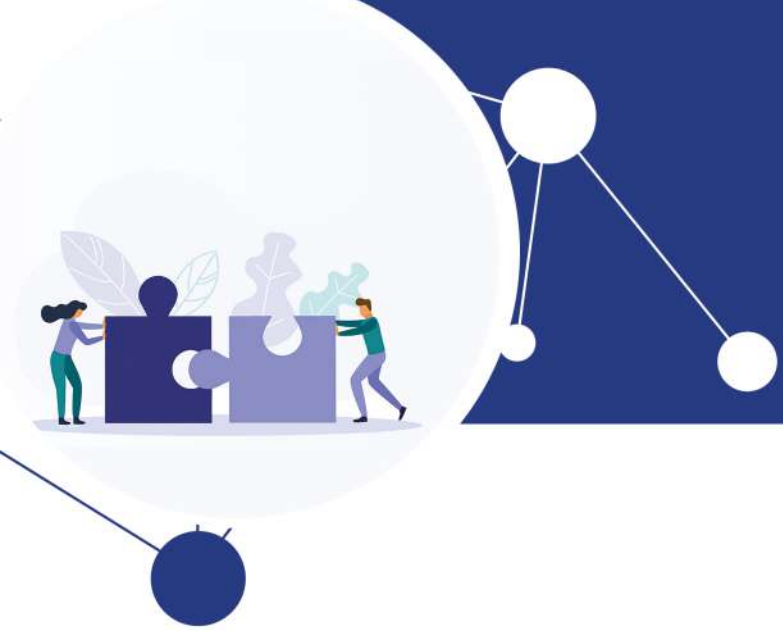

Sponsors

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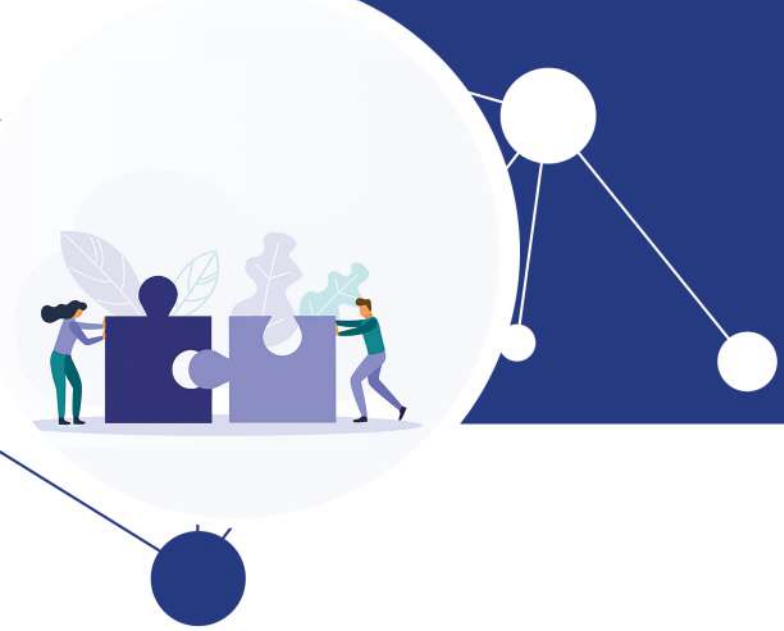

About the Conference

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.

Multiple aspects within the ever-evolving CMC landscape include: improving and developing innovative statistical methodologies to address key development decisions; 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 serve future generations of technical and regulatory innovation in biologicals development and lifecycle management.

Scientific and Organizing Committee

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Laura Pack, Co-Chair, Rezolute

Timo Bailer, Co-Chair, Boehringer Ingelheim

Tim Schofield, IABS Advisor, CMC Sciences, LLC

Catherine Cheng, Novartis Gene Therapy

Madinina Cox, Events Manager, IABS/MC'Com Agency

Jun Gao, Health Canada

Ashley Giambrone, Regeneron

Kristi Griffiths, Eli Lilly & Co.

Franz Innnerbichler, Novartis

Jennifer Kirk, FDA/CBER

Theo Koulis, Genentech

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

Scientific Program

Tuesday, November 7, 2023

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01:00 – 01:30	Registration
01:30 – 05:30	Short Course – Tolerance Intervals: The Bayesian Way **José Ramírez, Kite Pharma, a Gilead Company, and Fang Chen, SAS Institute**
05:30	End of Day 1

Scientific Program
Wednesday, November 8, 2023

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08:30 – 09:00	Registration & Welcome Coffee
09:00 – 09:10	Introduction to IABS – **Tim Schofield, IABS - CMC Sciences, LLC**
09:10 – 9:20	Welcome to Workshop – **Timo Bailer & Laura Pack**

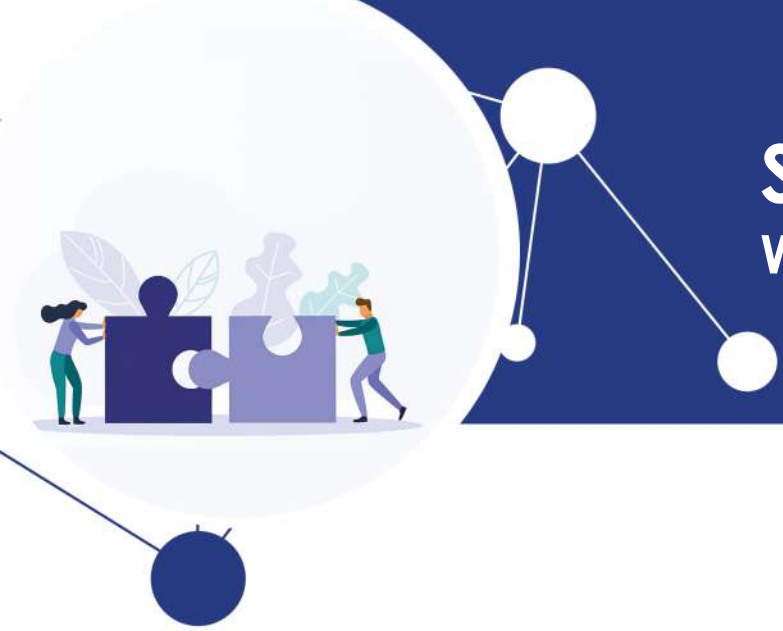
Keynote Session

09:20 – 10:10	Keynote presentation: Process Control Strategy, Residual Uncertainty, and the Myth of Fingerprints – **Jeff Baker, CBC**
10:10 – 10:40	**Break**

Session 1: The Research Question: Its importance in achieving successful product development and regulatory review

Session Chairs: Jennifer Kirk, Tim Schofield, Chuck Miller

10:40 – 11:10	The question addressed using frequentist vs Bayesian methods **Dave Leblond, Robert Singer Consulting**
11:10 – 11:40	Assigning Ruggedness Factors as Fixed or Random Consistent with Goal of a Procedure Performance Qualification (Validation) **Rick Burdick, Burdick Statistical Consulting**
11:40 – 12:10	Review perspective – **Leslie Wagner, FDA**
12:10 – 12:40	Panel Discussion – **All speakers – Chuck Miller, facilitator**
12:40 – 02:00	Lunch



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Session 2: Innovative statistical methodologies in CMC

Session Chairs: Jun Gao, Franz Innerbichler, John Oleynick

02:00 – 02:10	Session Introduction
02:10 – 02:40	Process Characterization for continuous process based on simulation **Yukun Ren, Sanofi**
02:40 – 03:10	Joint Assessment of Accuracy and Precision in Analytic Transfer **Justin Pearson, Regeneron**
03:10 – 03:40	Bayesian Statistics: Using Prior Knowledge to Enhance Understanding of Product Specific Stability – **Adam Rauk, Eli Lilly & Co.**
03:40 – 04:10	**Break**
04:10 – 04:40	Panel Discussion – **All speakers – John Oleynick, facilitator**
04:40 – 05:40	Break-Out Sessions
05:40	End of Day 2

Scientific Program
Thursday, November 9, 2023

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Session 3: Application of CMC Statistics and Data Science to New Modalities and Technologies

Session Chairs: Travis Wolter, José Ramírez, Catherine Cheng

09:00 – 09:10	Session Introduction
09:10 – 09:40	CAR T-Cell Therapy Data : Long tails, mixtures, hurdles, censoring; definitively not normal – **José Ramírez, Kite Pharma, a Gilead Company**
09:40 – 10:10	mRNA Platform: Analytical and Process Opportunities and Evolution **Tingting Feng, Moderna**
10:10 – 10:40	Overview of NGS technology and application of NGS for gene therapy **Shuli Kang, Novartis**
10:40 – 11:10	**Break**
11:10 – 11:40	Panel Discussions – **All speakers – Travis Wolter, facilitator**
11:40 – 12:40	Break-Out Session
12:40 – 02:00	**Lunch**

Session 4: Call to Action: Implementation of Statistical Solutions for CMC

Session Chairs: Jia Liu, Ruoija Li, Theo Koulis

01:55 – 02:00	Session Introduction

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Session 4: Call to Action: Implementation of Statistical Solutions for CMC

Session Chairs: Jia Liu, Ruoija Li, Theo Koulis

02:05 – 02:35	Uncertainty: how and why to combine criteria for accuracy and precision, as recommended in the newly revised Q2(R2) guidance **Bruno Boulanger, PharmaLex**
02:35 – 03:05	Insights on patient-centric specification setting and implementation for Vaccines – **Cristiana Campa, GSK and Mathieu Vasselle**
03:05 – 03:35	Ongoing Analytical Procedure Performance Verification **Horacio Pappa, U.S Pharmacopeia**
03:35 – 04:00	Panel Discussions – **All speakers – Ruojia Li, facilitator**
04:00 – 04:30	Workshop Summary
04:30	End of Workshop and Invitation to 2024 Workshop

Upcoming IABS Conferences and Workshops

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2023

Cross Learning Experience Human and Animal Vaccine Licensure based on Technology Platforms

Brussels, Belgium
To be scheduled

Biosketch

Timo Bailer

Head of CMC Statistics BioPharma
88397, Biberach, Germany
Boehringer Ingelheim Pharma

Tel: +49 7351 54-186841
E-mail: timo.bailer@boehringer-ingelheim.com

Timo studied econo-mathematics at Ulm University and the University of West Florida. He finished his M.Sc thesis within ht eparmaceutical area on Bayesian Modelling of Adverse Events. Afterwards he joined Boehringer Ingelheim and held different position within the field of CMC Statistics. Currently he is heading the global CMC Statistics BioPharma department of Boehringer Ingelheim and he is part of the quality site leadership team at the site Biberach, Germany.

Biosketch

Jeffrey C. Baker, Ph.D.

Senior Fellow in the NIIMBL
Senior Strategic Advisor for the Center for Biomedical Innovation at MIT Member of NASEM study groups
E-mail: jeff@bakersnextthing.com

Dr. Jeffrey Baker is a biochemist by training and spent over 20 years in the pharmaceutical industry leading process development and manufacture of both legacy and first in class biological products. He was at FDA for 10 years as Deputy Director, Office of Biotechnology Products, where he received six awards or citations for renewing and rebalancing OBP review, inspection, and research programs and in 2018 received an FDA Honors Award for contributions to "modernizing the U.S. regulatory system for biotechnology products through sustained creative leadership and collaboration". He was FDA liaison to Manufacturing USA and the Advanced Manufacturing National Program Office and participated in interagency responses to the COVID pandemic.

He retired from FDA in 2021 but remains active in the biotech community as a Senior Fellow for NIIMBL, Sr. Strategic Advisor for the Center for Biomedical Innovation at MIT, a participant in multiple NASEM study groups, and a university lecturer.

Abstract

Jeffrey C. Baker, Ph.D.

Sr. Fellow NIIMBL, former Deputy Director Office of Biotechnology Products CDER/FDA

Process Control Strategy, Residual Uncertainty, and the Myth of Fingerprints

This talk will discuss the role of uncertainty management in the development of biopharmaceutical process control strategies and suggest that articulating the scope, extent, and relevance of CMC uncertainties is central to the technical advocacy supporting regulatory filings, especially in the United States. It will also reflect upon a divergence between execution of statistical analysis and calculation and statistical understanding and communication of relevant uncertainties. The role of cognitive biases arising from speed to market initiatives and other business drivers will be discussed as well, concluding with the open question "Have we got this right?"

Abstract

Bruno Boulanger

Vice President, Head Global Statistics and Data Science, PharmaLex

Links between Total Analytical Error, Measurement Uncertainty, Analytical Target Profile and Quality Target Product Profile.

For decades, the pharmaceutical industry has focused on validating analytical processes to demonstrate the assay or bioassay's effectiveness in terms of accuracy, precision, and linearity. Over time, it has become evident that the primary goal is to ensure that laboratory results meet sufficient quality standards.

Numerous publications have illustrated that achieving acceptable accuracy and precision may not always guarantee appropriate result quality. The recent introduction of ICH Q2(R2), endorsing the concept of "combined accuracy and intermediate precision" or what has long been recognized as "Total Analytical Error," underscores the need to accurately convey the relationship between measurement uncertainty and result quality during method validation.

In this presentation, we will provide an overview of Target Measurement Uncertainty (TMU) as a crucial concept encompassing bias, precision, and their respective uncertainties across various concentration levels within the working range. We'll discuss how TMU can be derived from the product or intermediate acceptance limits (Quality Target Product Profile QTPP) to establish a well-defined Analytical Target Profile (ATP).

Lastly, we'll explore how TMU and QTPP can aid in identifying zones of uncertainty, especially when a measurement closely approaches a specification. We'll delve into how replication and a comprehensive understanding of the assay (e.g., Target Measurement Uncertainty MMU) can minimize these zones of uncertainty, ensuring that the measurement's quality consistently aligns with its intended purpose.

Biosketch

Richard K. Burdick, Ph.D.

Principal
Colorado Springs, CO, USA 80923
Burdick Statistical Consulting, LLC
Tel: +970-691-0535
Fax: NA
E-mail: RickBASU@aol.com

Rick is an Emeritus Professor of Statistics, on the faculty of Arizona State University for 29 years, and former Quality Engineering Director at Amgen, Inc. for 10 years. He presently serves as Principal for Burdick Statistical Consulting, LLC located in Colorado. He has been working on statistical issues concerning CMC applications for the past 18 years and has written over 80 journal articles and four books.

He is a Fellow of the American Statistical Association and served on the USP Statistics Expert Committee from 2010-2020. He received his Bachelor's degree in Statistics from the University of Wyoming and his Masters and Doctorate degrees in Statistics from Texas A&M University.

Abstract

Richard K. Burdick, Ph.D.
Burdick Statistical Consulting, LLC

Title: Assigning Ruggedness Factors as Fixed or Random Consistent with Goal of a Procedure Performance Qualification (Validation)

In accordance with the lifecycle approach for analytical procedures, demonstration that a procedure is fit for intended use requires a statistical test to prove that the standard uncertainty of the analytical procedure is less than the total measurement uncertainty (TMU). The selected experimental design should be chosen consistent with this objective. Ruggedness design factors such as analyst, day, or equipment must be properly classified as either fixed or random in order to achieve the experimental goal. This presentation will consider the case where analyst is an impactful ruggedness factor and demonstrate how designation as either fixed or random will impact the practicality of the experimental conclusions.

Biosketch

Cristiana Campa

Vaccines Technical R&D Advisor
GSK
Address: via Fiorentina 1, Siena, Italy
Tel: +393475737147
E-mail: cristiana.x.campa@gsk.com

Cristiana Campa, PhD, is currently a Technical R&D Advisor and Senior Fellow at GSK Vaccines, with more than 20 years' experience in Chemistry, Manufacturing and Control (CMC) in biologics research and development. In her current role, she is very active in CMC advocacy, with contributions to cross- company discussion on innovative technologies, specifications setting and accelerated development strategies, fostering dialogue with Regulatory Agencies. She is active in several trade associations, and in an elected member of the Parenteral Drug Association Board of Director since January 2023.

After her PhD and Post-Doc in Chemistry, she worked at Bracco Imaging SpA (2002-2006), first as a senior researcher and then as head of Trieste research laboratory. She joined Novartis Vaccines in 2006, Technical R&D; first as analytical senior manager and then as Head of Analytical Development, Italy. Since 2012, Cristiana has worked on Quality by Design principles implementation across different company sites in Europe and US. After acquisition of Novartis Vaccines by GSK in 2015, she has been the Head of QbD Integration and, until June 2018, the Head of Science and Development Practices in Global Technical R&D, covering Quality by Design, Knowledge Management and Development roadmaps.

Abstract

Cristiana Campa & Mathieu Vasselle, GSK

Insights on Patient-Centric specification setting and implementation for Vaccines

BACKGROUND

Specification setting is a critical deliverable in the development of any new pharmaceutical product. As discussions are on-going to revise the main guidance documents on this topic (ICH Q6A & 6B), the concept of Patient-Centric Specification (PCS) has been at the center of key discussions in pharmaceutical industry during the recent years (notably, at the IABS Conference on Global Harmonized Specifications: current state and future opportunities, 2023).

CHALLENGES

In a recent position paper published by EFPIA (June 2023), PCS was defined as "a set of CQAs and acceptance ranges to which product quality attributes should conform for the product to be safe and effective when used as labeled". Yet, it is not always straightforward to link the quality attributes to the clinical outcomes; moreover, it seems impossible to define a unique standard approach for PCS determination, considering the diversity of pharmaceutical products and their mechanisms of action, along with the different types of associated quality attributes. Finally, the more traditional procedure consisting in deriving acceptance ranges from variability observed in manufacturing history may still be considered as the preferred approach for file submission.

PROPOSED APPROACH

This talk will notably give an overview of advantages of PCS approach compared to the more traditional one, with emphasis on implementation of QbD principles for pharmaceutical development. The talk will be focused on application for Vaccines products, and will provide some illustrative examples for different product families and attributes.

Biosketch

Fang Chen, Ph.D.

Director, Advanced Analytics
27513, Cary, NC, USA
SAS Institute Inc.
R4250 SAS Campus Drive
Tel: +1 919-531-0019
E-mail: fangk.chen@sas.com

Dr. Fang Chen is Director of Analytical Software Development at SAS Institute Inc. and a Fellow of the American Statistical Association. He manages the development of statistical software for SAS/STAT®, SAS/QC®, and analytical components that drive SAS® Visual Statistics software. Also among his responsibilities is the development of Bayesian analysis software and the MCMC procedure, the flagship Bayesian procedure in SAS software. Before joining SAS, he received his PhD in statistics from Carnegie Mellon University.

Biosketch

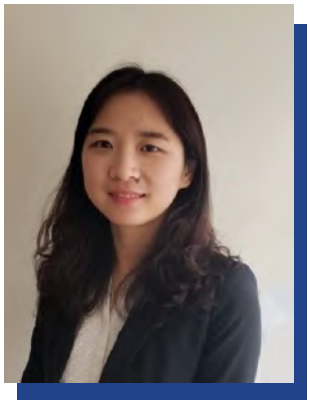
Catherine Cheng

Director, Biostatistics
Novartis Gene Therapies
10210 Campus Point Dr, San Diego, CA 92121, USA

E-mail: catherine-1.cheng@novartis.com

Catherine Cheng is a CMC statistical lead at Novartis Gene Therapies. Her team provides technical expertise and statistical support from analytical development to commercialization. Prior to joining Novartis Gene Therapies, Catherine worked at Merck, BMS and Eli Lilly from 2001 to 2020. Catherine holds a BS in Chemical Engineering and MS in Statistics and Engineering.

Biosketch



Tingting Feng

Statistician
Cambridge (MA), 02421, USA
Moderna
Address: 200 Technology Square
Tel: +1 (617) 528-8951
E-mail: Tingting.Feng@modernatx.com

Tingting earned her master's degrees in chemistry from Tulane University and in statistics from North Carolina State University. She has worked in both analytical chemistry and statistics fields. Currently she is a member of the CMC statistics team of Moderna, supporting Moderna's late phase program development and regulatory filing.

Abstract

Tingting Feng
Statistician, Moderna

mRNA Platform: Analytical and Process Opportunities and Evolution

mRNA has proved to be a revolutionizing technology, evidenced by the rapid development of the COVID vaccine. Moderna has been able to utilize its mRNA platform to accelerate the development of its mRNA vaccine and therapeutic programs. This talk will focus on explaining the mRNA platform approach, its advantages and challenges. Examples of successfully applying the platform approach in analytical and process development will be shared. An additional example illustrating the limitations of the platform approach will also be discussed.

Biosketch

Jun Gao

Senior Biostatistician/Epidemiologist
Office of Biostatistics, Biologic and
Radiopharmaceutical Drugs Directorate
Health Canada
LCDC Building, Tunney's Pasture, Ottawa K2J 0T6
Tel: 613-491-1168
E-mail: Jun.Gao@Canada.ca

Jun Gao is a Senior Biostatistician/Epidemiologist at the Office of Biostatistics, Biologic and Radiopharmaceutical Drugs Directorate (BRDD), Health Canada with 20 years of experience on Statistical methods/applications in CMC, clinical studies, oncological population Epidemiology, Virology and stem cell research. At his current position, he is responsible for providing support to Biologics quality review and regulatory-based scientific research (such as virology and cell therapies) at BRDD. As a CMC Statistician, he is keen on promoting the understanding and application of advanced statistics, such as, Bayesian statistics, in regulatory settings for Biologics quality review. In addition to his role as a CMC Statistician, Jun is also an active member at Drug Safety and Efficacy Network (DSEN); working with scientists and researchers, he helped the initialization of several research projects on the stem cell treatment for autoimmune disorders.

Biosketch

Ashley Giambrone, PhD.

Manager of Statistics
Troy, NY, 12180 USA
Regeneron Pharmaceuticals, Inc.
Tel: +1 518 258 7455
E-mail: ashley.giambrone@regeneron.com

Ashley studied Biostatistics at State University of New York at Albany. She finished her PhD in the statistical area of non-likelihood-based model evaluation in 2013. Afterwards she completed a post-doctoral program at Weill Cornell Medical College in the School of Epidemiology and Biostatistics. Currently, she is leading a team of statisticians at Regeneron Pharmaceuticals, Inc. supporting all aspects of drug manufacturing. Ashley joined the IABS Scientific Organizing Committee in 2022.

Biosketch

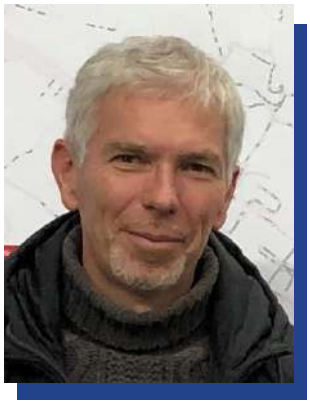
Kristi L. Griffiths, Ph.D.

Associate Vice President, Statistics – Discovery / Development
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN, 46285 USA
Tel: +1 317-433-1449
E-mail: klgriff@lilly.com

Kristi L. Griffiths received a doctorate in statistics from Virginia Tech in 1995 and joined Eli Lilly and Company to support pharmaceutical product development. She has provided technical contributions for numerous product development programs and has been instrumental in the design and implementation of the Lilly Quality by Design strategy.

She is currently an Associate Vice President and serves as the statistical advisor for the bioproduct portfolio. Kristi actively served on the International Pharmaceutical Aerosol Consortium on Regulation and Science (2000-2006) and the USP Statistics Expert Committee (2005-2010). She was an associate editor of the American Statistical Association's Biopharmaceutical Report (2021-2022) and continues to serve on the IABS Statistics Workshop Scientific Organizing Committee.

Biosketch



Franz Innerbichler, MSc, MSc

Associate Director Data Science
Novartis
Biochemiestrasse 10
Langkampfen
6336, Austria
Tel: +43 664 8271472
E-mail: franz.innerbichler@novartis.com

Franz Innerbichler is Associate Director Data Science in Biologics development department at Novartis with 20 years of experience within pharmaceutical industry. He worked on pharmacokinetics and clinical efficacy of small molecules as well as on statistical questions in biologics drug development and manufacturing. Specifically, he contributed to PK-analyses, Quantitative Structure Activity Relationship (QSAR), Parallel Line Assay and controlling variability of bioassays, Machine Learning models on particle images, RAMAN and chromatography data, and several statistical root-cause investigations. He is passionate in making the work of scientists easier by coding apps in computer language "R" which are used frequently to solve complicated statistical tasks within a few clicks.

Franz was the functional lead in the statistical network of Novartis biopharmaceuticals development and manufacturing.

He received his Master of Sciences in Microbiology from the University of Innsbruck and Master in Data Science from College of Natural Sciences in Kufstein/Austria. He finished several advanced university courses on statistics.

Biosketch

Shuli Kang, PhD

Novartis Gene Therapies
92121 San Diego, CA, United States
Tel: +1 747-777-3330
Fax: NA
E-mail: shuli.kang@novartis.com

Shuli Kang holds a Ph.D. in Microbiology from Wuhan University in China. He has 18 years of experience in bioinformatics, has published papers as the first or co-first author with over 1,000 citations, and he is the co-inventor of a US-patented method for blood-based cancer diagnosis. Currently, he is working on developing software for next-generation sequencing (NGS) assays and analyzing the NGS data to address inquiries and concerns from health authorities.

Abstract

Shuli Kang, PhD
Senior Data Scientist

Titre Overview of NGS technology and application of NGS for gene therapy

Next-Generation Sequencing (NGS) technology offers unparalleled access to genomic information, revolutionizing the development of gene therapy products. NGS assay can be employed to identify genetic variations, verify viral genomes, and quantify impurities in drug products, thus playing a vital role in guaranteeing product quality and safety. This technology also serves as a potent tool for characterizing individual DNA or RNA sequences in drug products, frequently used to address inquiries or concerns raised by health authorities. Data scientists are crucial in the realm of NGS assay development and data interpretation. Their responsibilities involve designing and implementing robust data processing pipelines, as well as employing statistical models and machine learning algorithms to analyze and interpret complex biological data.

Biosketch

Theo Koulis, PhD

Senior Principal Statistical Scientist
94080 South San Francisco (CA), USA
Genentech
1 DNA Way

Tel: +1-650-303-4853
E-mail: koulist@gene.com

Theo Koulis obtained his PhD in Statistics from the University of Waterloo in Canada. His professional interests include: functional data analysis, computational statistics, design of experiments, and statistical consulting. Theo is a Senior Statistician in Nonclinical Biostatistics at Genentech, Inc. supporting CMC statistics activities and specializes in measurement theory, assay development, and validation.

Biosketch

David Leblond, PhD

Principal Associate
95370 Sonora, (California), USA
Robert Singer Consulting
Address: 20555 Upper Hillview Drive
Sonora, California, 95370
Tel: +1 224-730-3402
Fax: NA
E-mail: david.leblond@sbcglobal.net

Dave LeBlond has a PhD in biochemistry and an MS in statistics. His experience includes 34 years as a scientist and statistician supporting in vitro diagnostics and pharmaceutical development at Abbott/Abbvie followed by a decade as a consultant in CMC and bioassay statistical studies with Robert Singer Consulting.

Abstract

David Leblond
Robert Singer Consulting

When is a Bayesian answer the right answer to a CMC question?

The thesis of this talk is that coherent modeling is essential in properly addressing CMC questions. CMC statisticians should assume leadership roles in soliciting group scientific knowledge needed to justify and share useful models.

Addressing CMC questions involves decision making and risk assessment in the face of uncertainty and variability. Ideally, it is a group effort that leverages knowledge and skill from diverse stakeholders to form a shared vision (model). Such models are built on prior knowledge. They describe the quantitative causal relationships between variables, parameter uncertainty, and measurement variability. The model frames the CMC question and directs study design. It provides a basis for continuous knowledge building and prediction as acquired data better inform model parameter values. Models from different development domains can potentially be linked in chains and/or hierarchies to facilitate knowledge building on larger scales, connecting CMC questions to patient experiences.

Statistical stakeholders are skilled in the art of uncertainty modeling and probabilistic risk prediction. As such, statisticians are uniquely qualified to serve a leadership role in soliciting group scientific knowledge, build group consensus around predictive models, and identify links among models in different development domains.

Some tools for communicating and interrogating hierarchical models such as causal diagrams, directed acyclic graphs, and full probabilistic modeling will be illustrated in typical CMC contexts.

Biosketch

Ruojia Li, PhD

Scientific Director
Bristol-Myers Squibb
Address: 1 Squibb Drive
08903 New Brunswick, (NJ), U.S.A.
E-mail: ruoja.li@bms.com

Ruojia Li leads the Quantitative Sciences & Digital Transformation group within the Biologics Development organization at Bristol-Myers Squibb. Her team is responsible for CMC statistics, data science, clinical method performance monitoring, and manages digital transformation efforts across the organization. Ruojia holds a bachelor's in Mathematics from Peking University, and a Ph.D. in Statistics from University of Wisconsin-Madison.

Biosketch

Jia Liu, PhD

Associate Director
Pfizer
1 BURTT RD
Andover, MA 01810
Tel: +19782473157
E-mail: jia.liu2@pfizer.com

Jia got her PhD degree in statistics from Iowa State University. She has worked as a CMC statistician in Pfizer since 2013. Jia has substantial knowledge and experience in analytical method development, bioassay evaluation, reference material bridging, assay validation and transfer. She has successfully supported multiple CMC regulatory submissions. Jia is also interested in Bayesian methodology, machine learning, design of experiments, and linear-mixed models.

Biosketch

Chuck Miller

Director
West Point PA
Tel: +1 215 – 652 - 1989
E-mail: charles_miller3@merck.com

Chuck Miller has been working at Merck for 14 years as team leader for biological and vaccine process, laboratory, and stability support team. The team provided statistical support from late-stage development through supply. Typical activities include design of experiments, investigations, assay method validations and transfers, qualification of biologic critical reagents, and stability study designs and evaluations.

Biosketch

John Oleynick

Associate Director
Janssen Research & Development, LLC
Spring House, PA 19477
E-mail: joleynic@its.jnj.com

John is an Associate Director in the Manufacturing and Applied Statistics Department at Janssen Research & Development, LLC, supporting the development of biologics in areas such as specification setting, shelf life, cell banking, and method validations and transfers. His areas of interest include linear mixed effects models, tolerance intervals, and Bayesian methods. He holds a BS in Computer Science from Northeastern University, an MS in Computer Engineering from Santa Clara University, an MS in Statistics from Rutgers University, and a PhD in Public Health/Biostatistics from the University of Medicine and Dentistry of New Jersey.

Biosketch

Laura Pack

Sr. Director, QC & Statistics
Rezolute, Inc.
E-mail: Laura@rezolutebio.com

Laura has leveraged her scientific and statistical expertise to drive innovation in biotechnology across operations functions for the past 19 years. Throughout her career, Laura has focused on supporting clinical, late-stage, and commercial biologics and small molecule programs, including determining specifications, evaluating comparability, developing analytical & product lifecycle management practices, and setting overall product quality strategy. She is passionate about teaching statistics to the many dedicated scientists that she encounters in the CMC community.

Laura currently leads the QC & CMC statistics functions at Rezolute, where she partners with scientists across CMC functions to integrate statistical thinking into everyday decision making so that the company can advance important medicines through clinical trials.

Laura holds Bachelor's degrees in chemistry and biochemistry from the University of Colorado and a Master's in applied statistics from Colorado State University. She has served on the IABS Statistics Workshop Scientific Organizing Committee since 2018 and on the AAPS CMC Statistics Community Leadership Team since 2016.

Biosketch

Dr. Horacio Pappa

Senior Director of the General Chapters Department,
Global Science and Standards Division
United States Pharmacopeia
Rockville, MD 20852
USA
E-mail: HP@usp.org

Dr. Pappa has been with USP since 2003. He is currently the Senior Director of the General Chapters Department, Global Science division of the USP. He provides scientific leadership to a team of scientific liaisons responsible for the activities of seven different expert committees that cover the majority of the USP General Chapters. Horacio earned his Ph.D. in Pharmaceutical Chemistry from the University of Buenos Aires. He has authored many publications and peer-reviewed articles and is a frequent speaker and instructor on topics related to Chromatography and Validation. Prior to joining USP, he worked in the pharmaceutical industry in QA/QC.

Horacio held the position of Assistant Professor of Quality Control in the Faculty of Pharmacy at Buenos Aires University, and Executive Secretary of the Argentine Pharmacopeia in the period 1997-2001. He is a Quality Engineer certified by the American Society for Quality.

Abstract

Dr. Horacio Pappa
CQE, Ph. D.

Title: Ongoing Analytical Procedure Performance Verification

The Analytical Procedure Life Cycle (APLC) offers a comprehensive framework to ensure the suitability of analytical procedures. In accordance with the USP general chapter <1220>, which addresses analytical procedure validation activities throughout the entire analytical procedure life cycle, a three-stage framework is provided for its execution. Stage 3 involves the ongoing verification of analytical procedure performance (OPPV) to maintain procedure control beyond the procedure performance qualification phase. This stage entails an ongoing data collection and analysis program pertaining to procedure performance.

Knowledge gathered during the first and second stages, which encompass procedure design and performance qualification, serves as the foundation for creating a routine monitoring plan to support performance verification in the third stage. The extent of routine monitoring required is determined through risk assessment, taking into account procedure complexity, its intended purpose, and knowledge regarding process and procedure variability.

The Analytical Target Profile (ATP) serves as a valuable tool for setting acceptance criteria when verifying procedure performance in routine use (e.g., System/Sample Suitability Test (SST) or criteria for procedure changes or transfers). It's important to note that OPPV can be conducted without an ATP as a mandatory requirement. In cases where the complete APLC framework is not utilized, verification criteria can be established by drawing upon existing validation or system suitability criteria. Moreover, elements of the life cycle approach can be retrospectively applied if they prove to be beneficial.

Biosketch

Justin Pearson, MS

MS
Principal Statistician
12180 Troy, NY, United States
Regeneron Pharmaceuticals, Inc.
Address: 1 Global View
Tel: +518-227-9264
Fax: N/A
E-mail: justin.pearson@regeneron.com

Justin obtained an MS in Applied Statistics from Rochester Institute of Technology in 2016, and has worked in industrial statistics at Regeneron since then. His professional interests include experimental design, sampling plans, methods for assessing drug stability, and the art of technical communication. Outside of work, he can be found hiking local trails, reading sci-fi novels, and trying new recipes.

Abstract

Justin Pearson, MS
Principal Statistician, Regeneron Pharmaceuticals, Inc.

Title: Joint Assessment of Accuracy and Precision in Analytic Transfer"

INTRODUCTION
US Pharmacopeia (USP) <1224> requires a documented process to qualify new laboratories to use analytical procedures originating from another lab. As statistical methods for transfers are not prescribed, a comparative testing approach was developed.

CHALLENGES
Though USP suggests setting criteria on relative standard deviation for variability, which requires no prior data to set, it becomes unstable as means approach zero. Even with historical data informing criteria, challenges such as unsuitable distribution, outliers, and failure to meet criteria should be considered. Alignment in criteria should also be considered, as methods of comparable risk should be transferred with comparable rigor.

PROPOSED APPROACH
A comparative testing approach is proposed using standardized data to jointly assess bias and variability between labs. Confidence intervals are applied to quantify worst case plausible differences and determine their acceptability. Justification for setting criteria may include scientific rationale, impact to specification, historical performance, and risk-based quality decisions.

CONCLUSIONS
The proposed approach allows a desirable tradeoff between bias and variability while preventing the mutual extremes allowed by independent criteria. Statistical power is improved by leveraging historical data from the originating lab in both criteria setting and the transfer itself, and the approach remains functional when historical data is absent. Finally, uniformity of scale allows for risk-based alignment between methods and standardization of criteria.

Biosketch

José G. Ramírez, Ph.D.

Chief Statistician
Global MSAT
Kite, A Gilead Company
E-mail: jramirez13@kitepharma.com

José is currently the Chief Statistician within the Global MSAT group at Kite, a GILEAD company. In this role, he provides statistical leadership in the use, promotion, and adoption of best statistical approaches, including Bayesian methods. In his many years of experience in the semiconductor, electronics, and biotech industries, he has worked closely with engineers and scientists to help them make sense of data, and through collaborative education, help promote statistical thinking.

José received a licentiate degree in mathematics from Universidad Simón Bolívar in Caracas, Venezuela, and both an MS in applied statistics and a PhD in statistics from the University Wisconsin-Madison, where he was one of the founding members of the Center for Quality and Productivity Improvement. He has won both the SAS Users Group International (SUGI) best-contributed statistics paper, and the SAS User Feedback Award, and has written two books for SAS Press.

Abstract

José G. Ramírez, Ph.D.
Kite, a Gilead Company

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

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.

Biosketch

Adam Rauk

Sr. Advisor
46285 Indianapolis, IN, USA
Eli Lilly and Company
Tel: +1 317-277-4007
Fax: NA
E-mail: rauk_adam@lilly.com

Adam Rauk holds a Masters of Science in statistics from the University of Chicago. He has almost 20 years of experience in the pharmaceutical industry within chemistry manufacturing and controls, and currently supports bioproduct research and development.

Abstract

Adam Rauk
Senior Advisor at Eli Lilly & Co.

Considerations in Prior Knowledge Development for Product Stability

Bayesian statistics offers an inference approach that requires prior distributions for model parameters. These distributions must be selected for any given analysis and can vary from highly informative – confining the parameter within a narrow range – to weakly informative or relatively non-informative. This talk will explore how prior selection, and the use of targeted informative priors, can facilitate efficient conclusions. An example that determines product shelf-life using a Bayesian approach will be shared that offers a stronger product-wide inference statement than the ICH Q1E alternative. There will be additional discussion on the prior distributions selected for this analysis and the sensitivity to resulting conclusions.

Biosketch

Yukun Ren

CMC Statistician Expert Leader
Sanofi
49 New-York Ave
Framingham, MA 01701, USA
E-mail: yukun.ren@sanofi.com

Yukun Ren is a dedicated professional currently employed at Sanofi, where he plays a crucial role in offering statistical expertise to bolster global CMC operations. His responsibilities encompass a wide range of areas including BioAnalytics, Mammalian Platform, Formulation, and the Genomic Medicine Unit. With extensive knowledge and a wealth of experience, Yukun excels in providing statistical support in Design of Experiments (DoE), Quality by Design (QbD), analytical method development, stability analysis, specification setting, and bioprocess development, among others. Before his tenure at Sanofi, Yukun worked at Pfizer (consultant) and Genzyme from 2001 to 2011.

Yukun's educational background includes a Bachelor of Science degree and a Master's degree in Forest Products, as well as a Master's degree in Applied Statistics.

Abstract

Yukun Ren
CMC Statistician Expert Leader, Sanofi

Bioreactor Process Characterization for Continuous Processes Based on Statistical Modelling Simulation

INTRODUCTION
Continuous bioprocessing is of paramount importance in biotechnology and pharmaceuticals, as it enhances productivity, maintains product consistency, reduces waste, and offers operational flexibility. It enables real-time control, accelerates time-to-market, and deepens process understanding. Moreover, continuous bioprocessing has the potential to increase product yields, reduce costs, and promote sustainability.

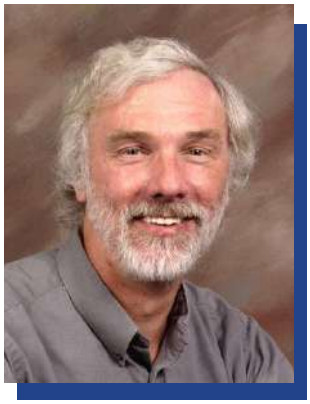
Process characterization is crucial in bioprocessing because it ensures product quality, regulatory compliance, and process efficiency. It also helps in reducing risks, making informed decisions, and ultimately contributes to the success and sustainability of bioprocessing operations.

CHALLENGES
Perfusion cultures exhibit dynamic behavior throughout their duration. To gain a comprehensive understanding of how process parameters influence both culture performance and product quality, including the entire harvest phase, it's essential to integrate time-based data into the analysis alongside the tested process variables. However, it's important to recognize that time-based data points are not independent, making it inappropriate to conduct statistical analyses for time effects while assuming no interrelationships among responses at each time point.

PROPOSED APPROACH
To address this challenge, a mixed model with repeated measures was employed for the analysis of harvest phase data. Additionally, simulations to model the entire harvest process were conducted to evaluate Proven Acceptable Ranges (PARs).

CONCLUSIONS
Utilizing predictive models with mixed models and repeated measures facilitates time-dependent analysis, enhancing process knowledge. These predictive models also enable Monte Carlo simulations for determining PARs.

Biosketch



Tim Schofield

Owner & Consultant
CMC Sciences, LLC
Maryland, USA
Tel: +1 (240) 654-2867
E-mail: tim@cmcsciences.com

Tim Schofield is the Owner & Consultant at CMC Sciences, LLC. Prior to starting his own consulting business Tim worked at:

- GSK as a Senior Advisor in Global Vaccines Technical R&D, and previously a Director in US Regulatory Affairs,
- MedImmune as a Senior Fellow in Analytical Biotechnology,
- Arlenda as US Managing Director and Head of Nonclinical Statistics, and
- Merck Research Laboratories heading the Nonclinical Statistics department.

Tim received a Bachelor of Science degree in Mathematics from Lafayette College, and a Master of Arts degree in Statistics and Operations Research in 1976 from the Wharton School of the University of Pennsylvania. Tim is a member of the USP Statistics Expert Committee and has participated in industry initiatives related to Quality by Design, analytical method development and validation, stability and specifications. He is the Chairman of the IABS Communications Committee, and on the editorial board and is the business lead for the journal Biologicals.

Biosketch

Mathieu Vasselle

Lead Statistician
Rixensart, Belgium
GSK
89 rue De L'Institut
Tel: +32 10 85 3021
E-mail: mathieu.x.vasselle@gsk.com

Mathieu holds a Master's degree of Computer Sciences with a specialization in Data Mining, from the University of Technology of Compiègne (UTC). He has been working at GSK for 17 years, applying CMC statistical sciences through different positions in the organization, covering small and large molecules. He currently works in the Technical Research & Development department for Vaccines, providing statistical support to process and analytical development for different projects.

Abstract

Cristiana Campa & Mathieu Vasselle, GSK

Insights on Patient-Centric specification setting and implementation for Vaccines

BACKGROUND

Specification setting is a critical deliverable in the development of any new pharmaceutical product. As discussions are on-going to revise the main guidance documents on this topic (ICH Q6A & 6B), the concept of Patient-Centric Specification (PCS) has been at the center of key discussions in pharmaceutical industry during the recent years (notably, at the IABS Conference on Global Harmonized Specifications: current state and future opportunities, 2023).

CHALLENGES

In a recent position paper published by EFPIA (June 2023), PCS was defined as "a set of CQAs and acceptance ranges to which product quality attributes should conform for the product to be safe and effective when used as labeled". Yet, it is not always straightforward to link the quality attributes to the clinical outcomes; moreover, it seems impossible to define a unique standard approach for PCS determination, considering the diversity of pharmaceutical products and their mechanisms of action, along with the different types of associated quality attributes. Finally, the more traditional procedure consisting in deriving acceptance ranges from variability observed in manufacturing history may still be considered as the preferred approach for file submission.

PROPOSED APPROACH

This talk will notably give an overview of advantages of PCS approach compared to the more traditional one, with emphasis on implementation of QbD principles for pharmaceutical development. The talk will be focused on application for Vaccines products, and will provide some illustrative examples for different product families and attributes.

Biosketch

Travis Wolter

MSPA
Principal CMC Statistician
Amgen Inc.
1 Amgen Center Dr
Thousand Oaks, CA, 91320 USA
Tel: +1 805-447-3098
E-mail: twolter@amgen.com

Travis R. Wolter received a masters in predictive analytics from Northwestern University and bachelors of science in statistics from the University of Wisconsin-Madison. He has held multiple positions in biotech product and process development with a focus on statistical applications to address novel unmet need. Currently he is a member of the global CMC statistics team at Amgen, part of the wider Quality and Operations team.