SCIENTIFIC Conference

e-Book

International Alliance for Biological Standardization

IABS 10th Annual Statistics Workshop:

Science & Statistics – Elevating CMC through Partnership

November 12-14, 2024

Institute for Bioscience and Biotechnology Research

Rockville, U.S.A.

www.iabs.org

Table of Contents

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Back to Table of Contents

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About the Conference

Back to Table of Contents

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 and Organizing Committee

Back to Table of Contents

Scientific Committee

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

Organizing Committee

Laura Pack - Co-Chair, Moderna
Timo Bailer - Co-Chair, Boehringer Ingelheim
Ruojia Li - BMS (Co-Chair)
Madinina Cox - IABS, France
Marlène Louis - IABS, France

Scientific Program

Tuesday, November 12, 2024

Back to Table of Contents

1:00 - 1:30	Registration
1:30 - 3:30	Short Course: Tolerance Intervals **Thomas MATHEW**, University of Maryland
1:00 - 3:30	Short Course: Automating statistical analysis and GxP reporting **Pierre LEBRUN**, PharmaLex
4:30	End of Day 1

Scientific Program

Wednesday, November 13, 2024

Back to Table of Contents

8:30 - 9:00 Registration & Welcome Coffee

9:00 - 9:15 Introduction to IABS – **Shawn NOVICK –** Vice-President, IABS
Welcome to Workshop
Laura PACK – Co-Chair, Moderna
Ruojia LI – Co-Chair, BMS
Timo BAILER – Co-Chair, Boehringer Ingelheim

KEYNOTE SESSION

9:15 - 10:20 Statistical Considerations During the Review of Gene Therapy Products
Kimberly SCHULTZ – USFDA

Session I: Science & Statistics

Session Chairs: Jennifer Kirk, José Ramirez, Irina Gershgorin

10:20 - 10:25 Session introduction
José RAMIREZ - Kite Pharma, a Gilead Company

10:25 - 10:55 Statistical Science & Statistical Engineering
José RAMIREZ - Kite Pharma, a Gilead Company

Scientific Program

Wednesday, November 13, 2024

Back to Table of Contents

10:55 - 11:25	How do Theorists and Experimentalists Interact in a Biopharmaceutical Company? **Kenneth LEE** – AstraZeneca
11:25 - 11:45	Break
11:40 - 12:10	The Selective Advantage of Synergy – One Biologist's Perspective on the Importance of Collaborating with Statisticians **Nancy SAJJADI** – Sajjadi Consulting
12:10 - 12:40	The Power of Statistics to Improve Science: Examples from CMC Statistics **Jennifer KIRK** - FDA/CBER
12:40 - 1:15	Panel Discussion All speakers and Keynote speaker - **Irina GERSHORIN**, facilitator
11:25 - 11:45	Lunch

Scientific Program

Wednesday, November 13, 2024

Back to Table of Contents

Session II: Stability Innovations in Manufacturing Biologics

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

2:00 - 2:05	Session Introduction **Cristian M. OLIVA-AVILES** - Genentech
9:00 - 9:15	Predictive Stability Modeling of mRNA Vaccines Based on Mechanisms of RNA Molecular Degradation **Xingyi YANG** & **Gang WANG** – Moderna, Inc
2:35 - 3:05	A Bayesian Procedure to Allow Reliable Extrapolation from Short-Term Stability Data for Biologics **Chuck MILLER** – Merck
3:05 - 3:35	Break
3:35 - 4:05	Shelf-life estimation of pharmaceutical products through tolerance intervals under linear mixed models. **Cristian OLIVA-AVILES** – Genentech
4:05 - 5:05	Panel Discussion All speakers – **John OLEYNICK**, facilitator
5:05 - 6:05	Break-out session
6:05	End of Day 2

Scientific Program

Thursday, November 14, 2024

Back to Table of Contents

Session III: Enhancing Biologicals Development with Advanced Analytical Approaches

Session Chairs: Jia Liu, Kristi Griffiths

8:30 - 9:00	Registration & Welcome Coffee
9:00 - 9:05	Session Introduction **Jia LIU** - Pfizer
9:05 - 9:35	Clinically Relevant Specifications – A Regulatory Perspective **Jayda SIGGERS** – Health Canada
9:35 - 10:05	Analytical Characterization for Precision Biologics **Julia O'NEILL** – Direxa Consulting
10:05 - 10:35	A patient-centric approach to cell therapy manufacturing: Linking CAR-T product attributes and CQAs to clinical outcomes **Irina GERSHGORIN** – Novartis C&GT
10:35 - 11:05	Break
11:05 - 12:05	Panel Discussion All speakers – **Jia LIU**, facilitator

Scientific Program

Thursday, November 14, 2024

Back to Table of Contents

12:05 - 1:05 Lunch

1:05 - 1:35 Statistical opportunities related to ICH Q2(R2) and Q14
Tim SCHOFIELD – CMC Sciences, LLC

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

Session Chairs: Chuck Miller, Travis Wolter, Ashley Giambrone

1:35 - 1:40 Session Introduction
Chuck Miller - MERCK

1:40 - 2:10 An RShiny Application to guide the Planning and Evaluation of an Analytical Method Transfer
Tobias EILERT, Boehringer-Ingelheim

2:10 - 2:40 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

Scientific Program

Thursday, November 14, 2024

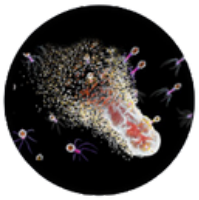
Back to Table of Contents

2:40 - 3:10	Case Study in Comparability for an iPSC-Derived, Genome-Edited Cell Therapy Product **Jennifer L. DASHNAU** – Century Therapeutics
3:10 - 4:10	Panel Discussion All speakers – **Ashley GIAMBRONE**, facilitator
4:10 - 4:25	Workshop Summary
4:25	End of Workshop and Invitation to 2025 Workshop

Upcoming IABS Conferences and Workshops

Back to Table of Contents

2024



Avoiding Antimicrobial Resistance: Veterinary use of Phages for Prevention, Therapy and Control of Bacterial Infections

Virtual meeting
November 19-20, 2024

4th Conference on Next Generation Sequencing for Adventitious Virus Detection in Biologics for Humans and Animal

NGS Training Workshop
December 3, 2024
4th NGS Conference
December 4 & 5, 2024
Frankfurt, Germany

2025

Advances in Analytical Technologies for Biopharmaceutical Products

Rockville, MD, USA
March 19-21, 2025

Leveraging Analytical and Bioprocess Platforms for Biological Product Development and Commercialization

Brussels, Belgium
May 14-15, 2025

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

Brussels, Belgium

Biosketch

Timo Bailer

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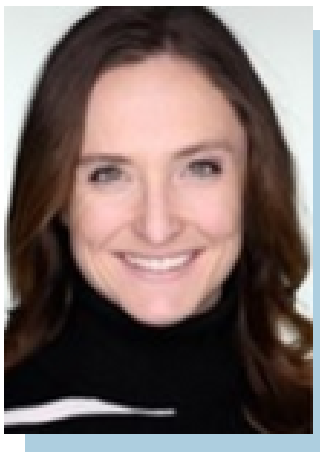
Timo studied econo-mathmatics at Ulm University and the University of West Florida. He finished his M.Sc thesis within the pharmaceutical area on Bayesian Modelling of Adverse Events in 2014. Afterwards he joined Boehringe Ingelheim and helf different positions within the field of CMC Statistics.

Currently he is heading the global CMC Statistics BioPharma department of Boehringer Ingelheim responsible for the life-cycle products at all global production sites in Germany, Austria, USA and China.
Timo is part of the IABS Statistics Workshop since 2018 and supports the Scientific Organization Committee since 2021. As of 2023, Timo is also co-chairing the Scientific Organization Committee of the IABS Statistics Workshop.

Biosketch



Jennifer Dashnau PhD, MBA

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Jennifer Dashnau is Vice President of Analytical Research & Development at Century Therapeutics, where she is responsible for bioanalytical & molecular assay development, in vitro pharmacology, genome safety, quality control testing and environmental monitoring. Prior to joining Century, she held various leadership roles at Merck in their Manufacturing and Supply Division, where she was responsible for process and assay development, technology transfer, process characterization and comparability, and validation for vaccine and monoclonal antibody products. While at Merck, she led CMC activities for six vaccine and two monoclonal antibody programs supporting late-stage development, licensure and commercial manufacturing. Jennifer began her career at Ortho-Clinical Diagnostics, a subsidiary of Johnson & Johnson, supporting quality control for in-vitro diagnostic products. She received her BS in Biotechnology and MBA in Technology Management and Quality & Applied Statistics from Rochester Institute of Technology and her PhD in Biochemistry and Molecular Biophysics from the University of Pennsylvania.

Abstract

Jennifer Dashnau

Case Study in Comparability for an iPSC-Derived, Genome-Edited Cell Therapy Product

During the product development lifecycle, manufacturing changes - such as a new facility introduction, process optimization, or raw material change - may be implemented to improve product quality, supply, or process efficiency. Given that manufacturing changes can pose a potential risk to quality, safety, and efficacy, the execution of comparability studies to assess the effect of these changes on the product is required for both investigational and licensed products. While a framework for evaluating comparability exists for biological products, additional factors may need to be considered for cell and gene therapy products due to the complexity of the product and manufacturing process. Last year, the FDA issued draft guidance for industry to address considerations for manufacturing changes and comparability for cell and gene therapy products. In this session, we present a case study for demonstrating comparability of a new facility introduced during Phase 1 for clinical production of an iPSC-derived, genome-edited cell therapy product, which demonstrates application of these principles.

Biosketch

Tobias Eilert

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Dr. Tobias Eilert is a Senior Principal CMC Statistician, owner of the Management System "Statistics & Data Science" and responsible for the training platform Statistics Academy at Boehringer Ingelheim that aims at the statistical enablement of SMEs in their daily work life.

Abstract

Tobias Eilert

An RShiny Application to guide the Planning and Evaluation of an Analytical Method Transfer

The planning and evaluation of an analytical method transfer is inherently a statistical procedure. However, the whole process of the transfer is the responsibility of the subject matter experts (SMEs). Since only faced irregularly with a method transfer, SMEs usually lack experience or at least regular training in statistical study planning. On the other hand, in view of the usually huge number of analytical methods to transfer and the necessary subject matter knowledge, the statistical part cannot be performed solely by the statistician.

Thus, we developed a training concept that teaches the SME every step from data acquisition over planning and finally evaluation of an analytical method transfer. The hands-on work of an SME is supported by an RShiny application that guides the SME from the evaluation of the data, over setting risk-based acceptance criteria, computing the necessary number of transfer measurements as well as evaluating/visualizing the final result. This working scheme enabled the SMEs to fulfill their task more confidently and independently while still being in contact with statisticians. This led to an increase in efficiency as well as in quality of the transfers.

We would like to present the statistical background as well as the flow of the app. We hope to show what is possible by the enablement of SMEs with proper statistical consultation and would like to open the discussion with the CMC community how in general the usage of self-developed statistical apps is seen/judged.

Abstract

Tobias Eilert

An RShiny Application to guide the Planning and Evaluation of an Analytical Method Transfer

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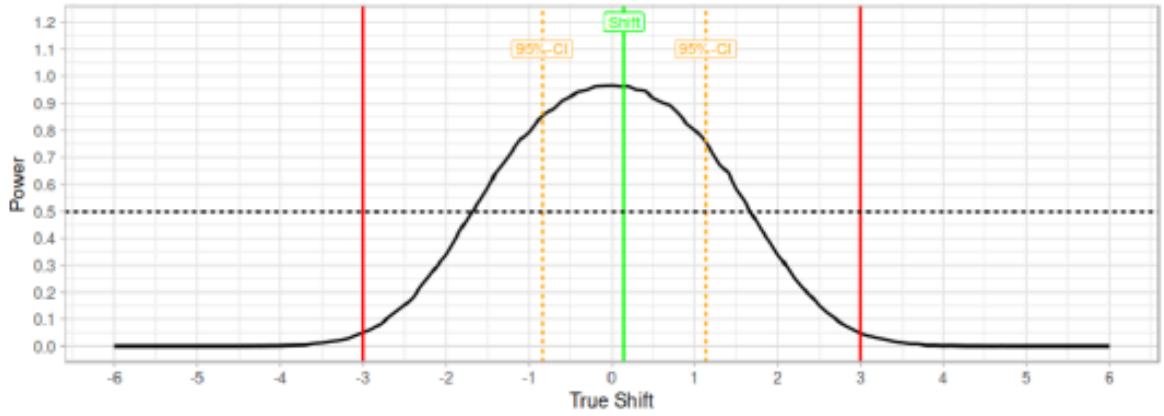
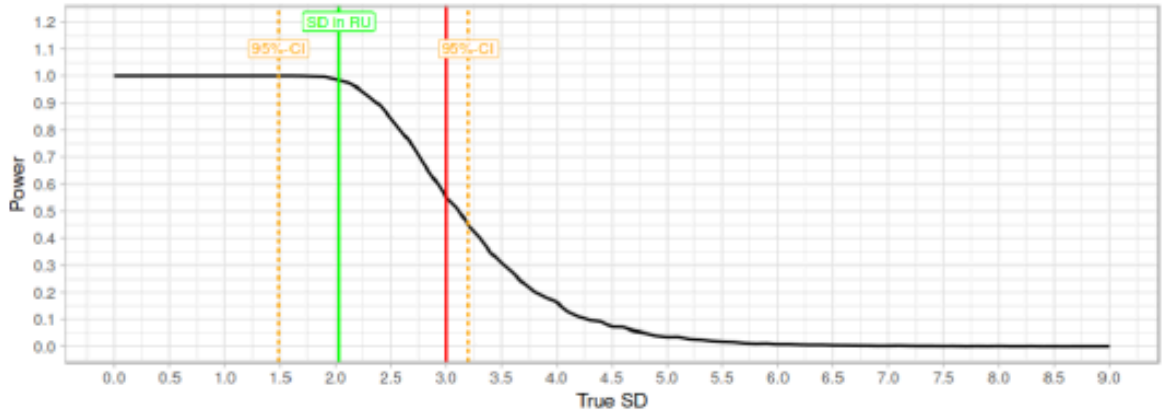
11	11	95.88

Site	SD	Shift
SU	1.56	0.15
RU	2.03	0.15





Biosketch

Irina Gershgorin, Dr.

Associate Director
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Irina Gershgorin received her Hon. B.Sc. from University of Toronto and her PhD in computational biology from Courant Institute at NYU. For the past 7 years, Irina has been working in Cell and Gene therapies in Novartis, first supporting the first ever approved cell therapy KYMRIAH and then early and late stage development pipeline. In addition to regular CMC support, Irina applied machine learning methods to perform correlational analyses for KYMRIAH which have been presented in ASH, ASCGT and AACR.

Abstract

Irina Gershgorin

A patient-centric approach to cell therapy manufacturing: Linking CAR-T product attributes and CQAs to clinical outcomes

CAR-T cell therapy has demonstrated a high rate of durable responses and a manageable safety profile in patients with adult relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL), follicular lymphoma and pediatric acute lymphoblastic leukemia (r/r pALL).
In cell therapy, each batch represents a unique patient which translates to a very high batch to batch variability. Thus, cell therapy needs to manufacture a consistent final product that reliably meets release specifications from a very heterogeneous incoming patient material (apheresis). Given that the cell therapy product is basically the patient's own cells, the link between product attributes and clinical outcomes becomes essential. Relating the apheresis and final product characteristics to manufacturability, clinical efficacy and safety is key to refining our understanding of critical quality attributes (CQAs), specifications and any potential improvements to this breakthrough therapy.
During Novartis' ELIANA (r/r pALL) and JULIET (r/r DLBCL) clinical trials, each batch was extensively characterized for cell composition (immunophenotypes) and final release criteria. This produced a high dimensional dataset where the number of variables exceeds the number of observations. Statistical and machine learning methods (e.g. LASSO/elastic net, random forest, decision trees, logistic and COX regressions) were applied to elucidate which immunophenotypes and CQAs for the CAR-T products may be of significance.

Results from these multivariable analyses revealed subsets of parameters associated with the response. Different sets of variables were identified for the pediatric and adult indications. The immunophenotypes and CQAs that were teased out help inform future development and provide insights into the manufacturing and control strategy. Importantly, the analyses also confirmed that the manufacturing process can handle the highly varied starting material and consistently deliver quality final product to the patients.

Abstract

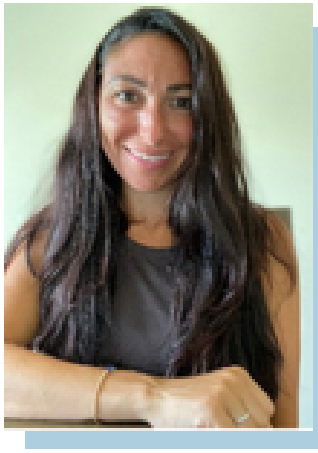
Irina Gershgorin - José G. Ramírez

Statistical assessment for analytical comparability between pre-change and post-change processes.

On behalf of Aili Cheng and the NCB comparability workstream

The FDA draft guidance on "Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products" (2023) recommends statistical approaches such as quality ranges and equivalence tests to assess manufacturing analytical comparability between pre-change and post-change processes. The Critical Quality Attribute (CQA) data underlying such analyses in the fields of cell and gene therapies are highly variable and usually have a limited number of batches. Thus, it is a challenge to demonstrate comparability with enough statistical power. Furthermore, the CQAs may not always follow a normal distribution and the standard approaches which assume normality may not be optimal for these data. Naively applying quality ranges and equivalence acceptance criteria (EAC) solely based on some multiplier of standard deviation (SD) could lead to misleading results, with safe and effective products being discarded. This presentation will focus on key topics relating to comparability in cell and gene therapy, such as study design, acceptance criteria, sample size and important assumptions about the distributions of the data. Additionally, insights from correlational analyses between CQAs and clinical outcomes can be leveraged to assess whether or not the observed ranges and/or results of comparability studies may be meaningful from a practical, scientific and clinical perspective.

Biosketch



Ashley Giambrone, PhD.

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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, PhD.

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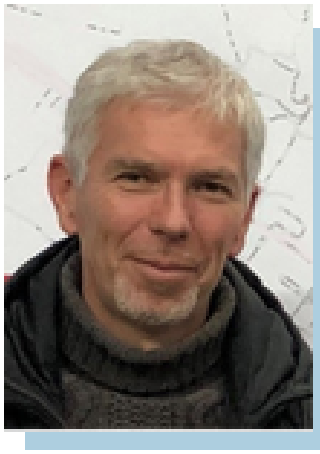
Kristi L. Griffiths received a doctorate in statistics from Virginia Tech in 1995 and joined Eli Lilly and Company to support pharmaceutical product development. She has provided technical contributions for numerous product development programs and has been instrumental in the design and implementation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

She is currently an Associate Vice President and leads the CMC statistics team. 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



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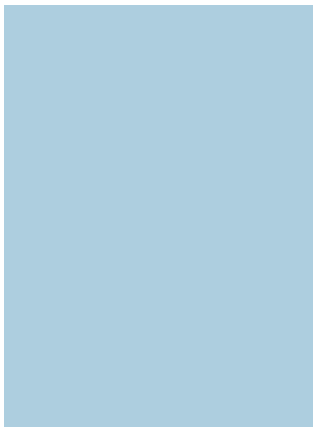
Franz Innerbichler is Associate Director Data Science in Biologics development department at Novartis with 20 years of experience within pharmaceutical industry. He worked on pharmacokinetics and clinical efficacy of small molecules as well as on statistical questions in biologics drug development and 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



Pierre Lebrun

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Pierre Lebrun is Director Statistics at Cencora Pharmalex, Belgium. He holds a PhD in sciences and statistics and cumulates 15 years of experience in several areas of pharmaceutical research and industry, including assay development and validation, discovery, and drug manufacturing (CMC, from R&D to commercial). Pierre is also since 2015 Lecturer at the Université of Liège, in the School of Pharmacy, teaching Design of Experiments and Statistics. He is a USP panel member since 2018. Pierre has authored or co-authored more than 100 peer-reviewed publications, conference proceedings, and book chapters.

Abstract

Pierre Lebrun

Automating statistical analysis and GxP reporting (e.g., ICH Q2R2) across the organization

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.

Biosketch

Jennifer L. Kirk, Ph.D.

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Jennifer L. Kirk received her doctorate in biostatistics from the University of Washington. Previously, she completed a two-year post-baccalaureate fellowship at the National Institute of Allergy and Infectious Diseases. In 2017, she joined the U.S. Food and Drug Administration's Center for Biologics Evaluation and Research as a statistical reviewer of clinical and product quality/CMC statistics for vaccines, allergenics, and live biotherapeutics. She is currently a Lead Mathematical Statistican in the Device and Non-Clinical Evaluation branch, where she leads the product quality/CMC team for all of CBER's products.

Abstract

Jennifer Kirk

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x

Biosketch

Jia Liu, PhD.

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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

Kenneth Lee

Director
Gaithersburg MD, USA
AstraZeneca

Ken received his PhD from the University of Birmingham, UK, in Chemical Engineering in 2009, after which he took up a position at TAP Biosystems, now Sartorius, as a development engineer on the ambr15 fed-batch workstation. He then joined AstraZeneca in 2011 and has been working as part of the cell culture bioreactor development team in Cambridge, UK then in Gaithersburg, US primarily on early phase projects. In 2020 Ken took an internal move to lead the Upstream Continuous Processing Platform team. As part of this role Ken was able to bring recirculating loop perfusion to AstraZeneca and demonstrate a robust and scalable process from ambr250 to 50L.

Abstract

Kenneth Lee

How do theorists and experimentalists interact in a biopharmaceutical company?

Engineers and statisticians are both disciplines involved in drug development who rely heavily on applied mathematics. However the approaches and areas of interest differ greatly between our two areas. Engineering papers are full of carefully controlled experimental data designed to eliminate all sources of variability and to show the nature of the impact of variables of interest on the response. In contrast the statistician begins by looking with the noise in the data to work back to the signal. While in theory these approaches should be highly complementary, in practice they are often siloed and practiced in isolation.

In my lab we work on developing new methods for the next generation of manufacturing processes for biologics and have worked closely with our statistician colleagues. Through a number of case studies we will describe how we approach a new area of interest from an engineering perspective and how and when we think about statistical approaches to model building and data analysis. From searching for signal from soft sensors, to process optimization, to thinking about control strategy in the era of continuous processing, there are many areas where engineering and statistics overlap. There are multiple areas where we have worked well together in the past, and more where we can improve in the future.

Biosketch

Ruojia Li, PhD.

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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

Thomas MATHEW

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Thomas Mathew is Professor, Department of Mathematics & Statistics, University of Maryland Baltimore County. He earned his PhD in statistics from the Indian Statistical Institute in 1983, and has been a faculty member at UMBC since 1985. His research interests are on both methodological and applied topics, including cost-effectiveness analysis, bioequivalence testing, exposure data analysis, meta-analysis, mixed and random effects models, and tolerance intervals. He is the co-author of two books: Statistical Tests in Mixed Linear Models and Statistical Tolerance Regions: Theory, Applications and Computation, both published by Wiley. He has served on the Editorial Boards of several journals, and is currently an Associate Editor of Journal of Multivariate Analysis, and Sankhya. Dr. Mathew is a Fellow of the American Statistical Association, and a Fellow of the Institute of Mathematical Statistics. He has also been appointed as Presidential Research Professor at his campus.

Abstract

Thomas MATHEW

Statistical Tolerance Intervals and Regions

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 short course will include more recent developments on the topic.

Biosketch

Chuck Miller

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Chuck Miller has been working at Merck for 15 years as team leader for biological and vaccine process, laboratory, and stability support. His team provides 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.

Abstract

Chuck Miller

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Biosketch

Shawn Novick

IABS Biotherapeutics Committee Chair
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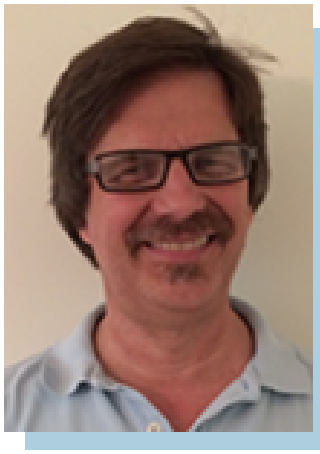
Shawn Novick graduated from New York University and has been working in various positions in the Biotechnology industry for over 30 years, primarily focused on analytical development, characterization, and quality control. She has worked on several clinical and commercial products, including mAbs, ADCs, and other therapeutic proteins. Currently Shawn is a consultant with BioPhia Consulting and is Chair of the IABS Biotherapeutics Committee.

Biosketch



John Oleynick

Sr. Principal Scientist, Manufacturing Statistics
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John is a Senior Principal Scientist 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

Cristian Oliva-Aviles, PhD.

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Cristian joined Genentech in 2018 as a nonclinical biostatistician, specializing in providing statistical support to enable CMC activities. In recent years, he has focused on exploring innovative statistical approaches for analyzing stability data. Prior to Genentech, he earned his PhD in Statistics from Colorado State University, where he refined his expertise in developing statistical methodologies for linear models. In his early years, Cristian was awarded a Bronze Medal at the International Mathematical Olympiad.

Abstract

Cristian Oliva-Aviles

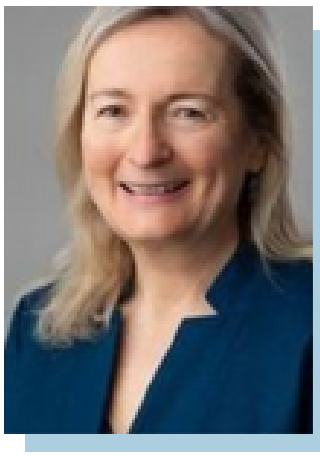
Shelf-life estimation of pharmaceutical products through tolerance intervals under linear mixed models.

Establishing the shelf life of pharmaceutical products is of critical importance in drug development, as it forms the foundation for ensuring proper quality, efficacy and safety throughout their lifecycle. To fulfill this objective, stability studies are undertaken to provide information of the drug quality over time when exposed to various environmental conditions.

While the analysis of stability data through tolerance intervals under linear mixed models has been claimed to be an adequate approach for shelf-life estimation, its implementation has been limited by the lack of well-established statistical methods to compute such intervals in the presence of unbalanced datasets. In this talk, a novel method to compute tolerance intervals for unbalanced linear mixed models, based on Generalized Pivotal Quantities, will be presented.

Moreover, a practical demonstration of the method for determining shelf life will be shared.

Biosketch



Julia O'Neill, PhD.

Founder of Direxa Consulting
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Since 2005, Julia O'Neill has supported approval of multiple accelerated products including vaccine, gene therapy, microbiome, and regenerative medicines. From 2020 to 2023 she was a Distinguished Fellow on the Moderna Technical Development Leadership Team, where she built and led a new department, CMC Modeling and Statistics, while a member of the Spikevax vaccine technical development team. She was named a Fellow of the American Society for Quality in 2020 in recognition of her passion for connecting people and data across disciplines to accelerate delivery of life-changing medicines to patients at commercial quality scale. She is the 2023 recipient of the ASA Gerald J. Hahn Quality & Productivity Achievement Award.

Abstract

Julia O'Neill

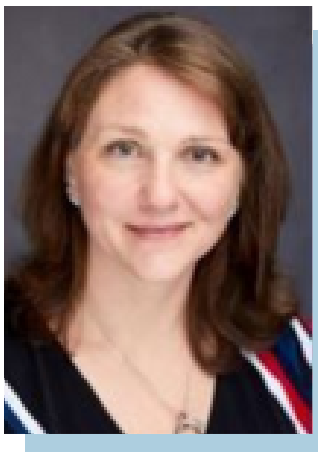
Analytical Characterization for Precision Biologics

Developers of biologic products are modernizing analytical control strategies at an amazing pace. Recent advances in analytical characterization provide a foundation for accelerated development and approval for gene therapies, cell therapies, novel vaccines and other pioneering biotherapies.

Control strategies for biologics also depend on a rich legacy of methods and practices established over decades of experience. Functional assays may provide an intuitively direct link to safety or efficacy. However, in some cases older methods such as cell-based potency assays are handicapped by inherently lower precision and accuracy relative to newer methods. The transition to modern methods for analytical characterization can be unfamiliar and complex.

Examples from recent successful submissions will be introduced to illustrate possibilities in this new era, and to stimulate discussion about Quality by Design thinking to bridge the gap between familiar and novel analytical control strategies. In this new paradigm, analytical methods can naturally be managed using a lifecycle approach.

Biosketch



Laura Pack

FSr. Director, CMC Quantitative Sciences
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Laura has leveraged her scientific and statistical expertise to drive innovation in biotechnology operations functions for the past 20+ years. Throughout her career, Laura has focused on supporting clinical, late-stage, and commercial biologics and small molecule programs, CMC statistics and 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 CMC Quantitative Sciences function at Moderna, Inc. Her team includes CMC statisticians, data scientists, & mechanistic/predictive modelers who partner with scientists across CMC functions to support objective decision making so that the company can bring important medicines to patients.

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

José G. Ramírez, Ph.D.

Chief Statistician
Global MSAT
Kite, A GILEAD Company
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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.

Prior to Kite, José was the Chief Statistician in the Quality Data Sciences group at Amgen, Inc, where he provided statistical leadership for both biosimilars and mAbs. He has worked in the semiconductor and electronics industries as a member of the Quality and Reliability group of the Semiconductor division of Digital Semiconductor, and the electronics division of W.L. Gore & Associates. 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

Statistical Science & Statistical Engineering

The engineer-scientist Theodore von Kármán said, "Scientists discover the world that exists; Engineers create the world that never was." Over the centuries, this balancing act of discovery and creation has become one of the main sources of knowledge generation, and economic progress. Statistics is a science, that, as Sir David Cox argues, "provides a unifying set of general ideas and specific methods relevant whenever appreciable natural variation is present." Because natural variation is almost always present in any scientific and engineering study, and because variation introduces uncertainty, statistics becomes the catalyst that allows us to do better science and engineering. This is because statisticians bring a unique skillset as they are trained to think skeptically, to interrogate assumptions, to consider multiple sources of both variation and bias, and to quantify uncertainty.

In this session we will discuss statistical science, statistical engineering, the role of statistics within the scientific method, some key statisticians who were also scientists and engineers, as well as the key role statisticians play as a part of a scientific and engineering team, not in a service-oriented role, but as scientific collaborators that can help solve complex problems.

Abstract

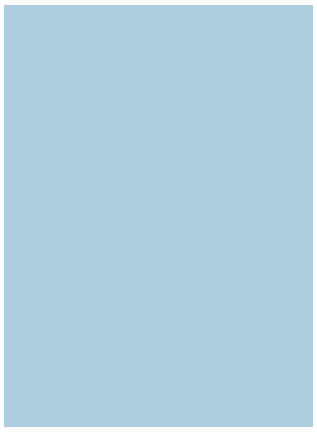
Irina Gershgorin - José G. Ramírez

Statistical assessment for analytical comparability between pre-change and post-change processes.

On behalf of Aili Cheng and the NCB comparability workstream

The FDA draft guidance on "Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products" (2023) recommends statistical approaches such as quality ranges and equivalence tests to assess manufacturing analytical comparability between pre-change and post-change processes. The Critical Quality Attribute (CQA) data underlying such analyses in the fields of cell and gene therapies are highly variable and usually have a limited number of batches. Thus, it is a challenge to demonstrate comparability with enough statistical power. Furthermore, the CQAs may not always follow a normal distribution and the standard approaches which assume normality may not be optimal for these data. Naively applying quality ranges and equivalence acceptance criteria (EAC) solely based on some multiplier of standard deviation (SD) could lead to misleading results, with safe and effective products being discarded. This presentation will focus on key topics relating to comparability in cell and gene therapy, such as study design, acceptance criteria, sample size and important assumptions about the distributions of the data. Additionally, insights from correlational analyses between CQAs and clinical outcomes can be leveraged to assess whether or not the observed ranges and/or results of comparability studies may be meaningful from a practical, scientific and clinical perspective.

Biosketch



Nancy Sajjadi, M.Sc.

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Nancy Sajjadi holds an M.Sc. degree in genetic engineering and has no formal statistics training. She has worked in the cell and gene therapy space since joining a start-up company as a bench scientist in 1989. In 2000, she left her position as Director, Quality Control and since then has worked as a consultant with more than 50 organizations involved in the development and quality control of complex, cutting-edge experimental medicines. Her interest in statistics derives from early challenges she faced in preparing assay development and validation documentation to support investigational new drug applications (INDs) at a time when there was limited guidance available. She has gained experience and insights into CMC statistics through participation on the first USP panels that drafted informational chapters address bioassay design, development, and validation as well as ongoing work helping clients address complex CMC issues to support the success of cutting-edge biologics. She has collaborated with Janice Callahan on multiple projects since 1990 and they have co-authored several publications.

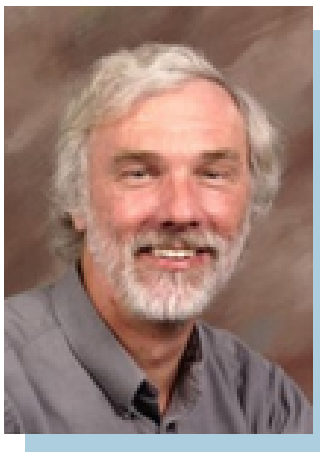
Abstract

Nancy Sajjadi

The selective advantage of synergy – one biologist's perspective on the importance of collaborating with statisticians

Human beings are one of the most successful species on the planet.Our capacity to cooperate is an important underpinning. Operating as groups, humans have enjoyed the selective survival advantages offered by synergistic outcomes. Diversity in forms and function are hallmarks of synergistic systems and for living systems, they explain how billions of years of evolution has given rise to incredible complexity. Similarly, modern organizations involved in drug development rely on the benefits derived from the interaction of diverse and highly specialized teams. The power of relationships between scientists and statisticians is rooted in complementarity and is critical to effectively managing and mitigating the risks associated with data driven decisions needed to deliver safe and efficacious products to patients. Based on learnings from experience (n=me and <30 statisticians over 35 years), this presentation will highlight some of the challenges encountered in interacting with statisticians and how embracing the idea of a "shared fate" enabled advancements in the field of cell and gene therapy.

Biosketch



Timothy Schofield

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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.

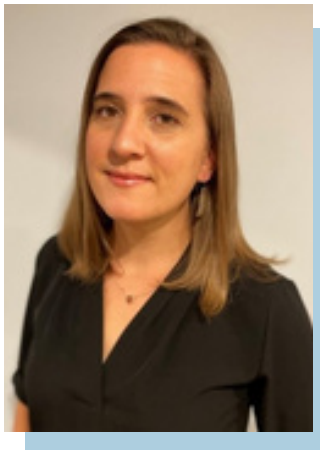
Abstract

Timothy Schofield

Statistical opportunities related to ICH Q2(R2) and Q14

With the publication of ICH Q2(R2) and Q14 comes numerous opportunities for CMC statisticians to collaborate with their laboratories, to help ensure fitness for use of their analytical procedures. Key among these are the introduction of confidence and prediction intervals as the basis for establishing conformance of a procedure to its performance requirements. This challenges the laboratory to address validation study risks through strategic design and analysis of their studies. While traditional approaches may be suitable for small molecule analytical methods, the inherent variability of procedures used to control biological products forces a company and reviewers to manage this more carefully through validation design. Additional concepts that should appeal to CMC statisticians are the use of validation results to develop CMC procedures during development, for release, and for comparability. Given the size and duration of most validations studies, the use of ongoing procedure performance verification has been proposed as a means to improve the understanding of procedure behavior. This talk will describe the elements of these guidelines that every CMC statistician should be aware of, and efforts to support the guidelines through the introduction of training materials.

Biosketch



Kimberly Schultz, PhD.

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Kimberly Schultz is Director of Division 2 in the Office of Gene Therapy at FDA's Office of Therapeutic Products in the Center for Biologics Evaluation. Kim joined the FDA in 2015 as a Commissioner's Fellow to conduct a cross-study analysis of CAR T cell CMC data and contributes to FDA review, guidance, and policy. Prior to joining the FDA, she received her PhD from the University of Wisconsin and conducted postdoctoral studies at Johns Hopkins Bloomberg School of Public Health specializing in virology and immunology.

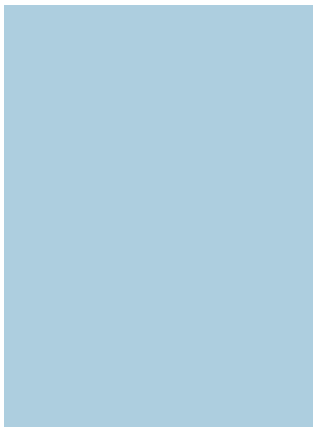
Abstract

Kimberly Schultz

Statistical Considerations During the Review of Gene Therapy Products

Gene Therapy (GT) development has rapidly expanded over the last two decades, with products progressing to licensure. Statistical methods are used during product development and review from early clinical studies through licensure, and post-licensure to evaluate different aspects of GT manufacturing and testing including determination of lot release specifications, process control, and product comparability. GT products have several unique product characteristics, and it is important to identify appropriate statistical approaches for evaluation. Ultimately, understanding the relationship between the product biology and the statistical approach is paramount to support GT development.

Biosketch



Jayda Siggers, Dr.

Senior Biologist/Evaluator in the Biologics and Radiopharmaceutical Drugs Directorate (BRDD)
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Dr. Jayda Siggers is a Senior Biologist/Evaluator in the Biotherapeutics Quality Divisions (BQD) of the Centre for Blood, Blood Products and Biotherapeutics (CBBB), in the Biologics and Radiopharmaceutical Drugs Directorate (BRDD) at Health Canada. Jayda leads the quality review of pre and post market drug submissions for biologic therapies. She holds a Master of Science in toxicology from the University of Saskatchewan, a PhD in immunology from the University of Copenhagen and completed a post-doctoral fellowship in the department of Biochemistry, Microbiology, and Immunology at the University of Ottawa. Jayda represented Health Canada on the WHO drafting group for the WHO Guideline for the production and quality control of monoclonal antibodies and related products intended for medicinal use. She is currently Co-Chair of a draft Parenteral Drug Association (PDA) standard titled Analytical Method Qualification / Validation for Biologics and leads an internal working group for ICH Q2(R2) / Q14. In her spare time, you will find Jayda chasing her family down mountains and up hills on one of her bikes.

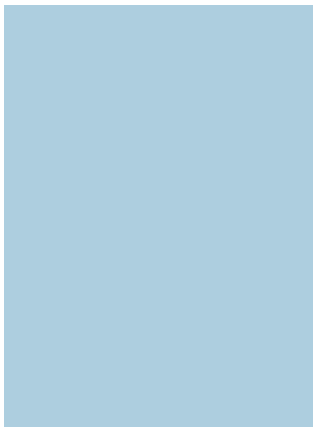
Abstract

Jayda Siggers

Clinically Relevant Specifications – A Regulatory Perspective

Traditionally, specifications are set as a final check that the biologic drug product is representative of the marketing authorization and are intended to ensure that a product is safe and efficacious when used as labeled. Often, setting specifications is primarily based on manufacturing experience from a limited number of batches at the time of the marketing application. This approach may not wholly represent the true safety and efficacy of the drug and creates a challenge for both industry and regulators in defining and authorizing appropriate specifications that support the product lifecycle and supply to patients. Establishing acceptance criteria based on manufacturing experience may result in limits that are narrow and lead to unnecessary batch rejection. In contrast, establishing acceptance criteria based on statistical analysis of a limited number of batches may result in limits that are broad and lead to inappropriate lot release. Comprehensive approaches are needed to define the most appropriate specifications. One such approach has been coined clinically-relevant (or patient-centric). Clinically-relevant specifications have been defined as a set of criteria and acceptance ranges to which drug products should conform to deliver the therapeutic benefit indicated in the label. The resultant specifications often extend beyond the manufacturing experience. From a regulatory perspective, the setting of specifications should consider all available data to ensure that decisions regarding the suitability of the product appropriately includes the line between rejecting lots that are likely to perform as expected and releasing lots that fail to meet the expectations. The justification should be supported by additional sources of data such as structure-function data, in vitro data, platform experience, or prior knowledge. The presentation will focus on the regulatory experience and expectations when setting biologic product specifications that exceed the manufacturing experience at the time of the market application.

Biosketch



Gang Wang, Dr.

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Dr. Gang Wang is the lead for mechanistic modeling and machine learning in the Technical Development department of Moderna, Inc. He graduated from MIT with a Ph.D. degree in chemical engineering, and has applied mechanistic modeling and machine learning technologies in the chemical and biopharmaceutical industries.

Abstract

Gang Wang - Xingyi Yang

Predictive Stability Modeling of mRNA Vaccines Based on Mechanisms of RNA Molecular Degradation

mRNA encapsulated in lipid nanoparticles (LNPs) is an important new platform for vaccines and therapeutics, with the demonstrated potential to be developed in record time to support public health emergencies. Characterizing drug properties during traditional long-term storage stability studies may be the slowest step in pharmaceutical development. Predictive stability models are essential to support rapid development while long-term stability studies proceed. Empirical models of stability are common and useful, but models based directly on scientific understanding of mRNA-LNP degradation mechanisms are required to enable the prediction of stability for new mRNA products with potential extrapolation of stability to longer storage times.

A key shelf life determining feature of mRNA-LNP systems is the proportion of mRNA remaining intact. In this work, two major molecular degradation mechanisms are elucidated and characterized using a mechanistic model. The model follows classical first-order kinetics, and connects to the fundamental understanding of the science of mRNA degradation. Modeling of degradation rates for mRNA-LNP products at different temperatures supports universal Arrhenius behavior independent of mRNA sequence. This allows for long-term shelf-life and storage prediction of mRNA products using accelerated stability studies. Degradation rates dependency on mRNA sequence is also investigated. Mechanistic models confirmed by data enable the prediction of shelf life for long-term storage of mRNA vaccines and therapeutics.

Biosketch

Travis R. Wolter, MSPA

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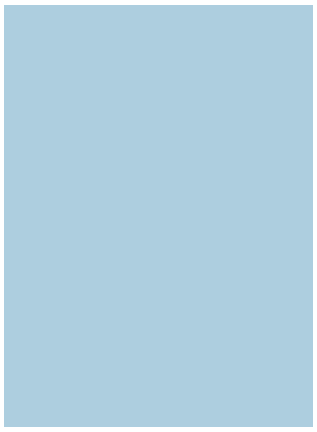
Travis R. Wolter received a masters in predictive analytics from Northwestern University and bachelors of science in statistics from the University of Wisconsin-Madison. He has held multiple positions in biotech product and process development with a focus on statistical applications to address novel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

Biosketch



Xingyi Yang

Statistician in Technical Development
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Xingyi Yang is a statistician in Technical Development department of Moderna, Inc., focusing on CMC Modeling and Statistics. She holds an M.S. in Biostatistics from the University of Arizona. She applies statistical skills to support the development and optimization of mRNA vaccines.

Abstract

Gang Wang - Xingyi Yang

Predictive Stability Modeling of mRNA Vaccines Based on Mechanisms of RNA Molecular Degradation

mRNA encapsulated in lipid nanoparticles (LNPs) is an important new platform for vaccines and therapeutics, with the demonstrated potential to be developed in record time to support public health emergencies. Characterizing drug properties during traditional long-term storage stability studies may be the slowest step in pharmaceutical development. Predictive stability models are essential to support rapid development while long-term stability studies proceed. Empirical models of stability are common and useful, but models based directly on scientific understanding of mRNA-LNP degradation mechanisms are required to enable the prediction of stability for new mRNA products with potential extrapolation of stability to longer storage times.

A key shelf life determining feature of mRNA-LNP systems is the proportion of mRNA remaining intact. In this work, two major molecular degradation mechanisms are elucidated and characterized using a mechanistic model. The model follows classical first-order kinetics, and connects to the fundamental understanding of the science of mRNA degradation. Modeling of degradation rates for mRNA-LNP products at different temperatures supports universal Arrhenius behavior independent of mRNA sequence. This allows for long-term shelf-life and storage prediction of mRNA products using accelerated stability studies. Degradation rates dependency on mRNA sequence is also investigated. Mechanistic models confirmed by data enable the prediction of shelf life for long-term storage of mRNA vaccines and therapeutics.