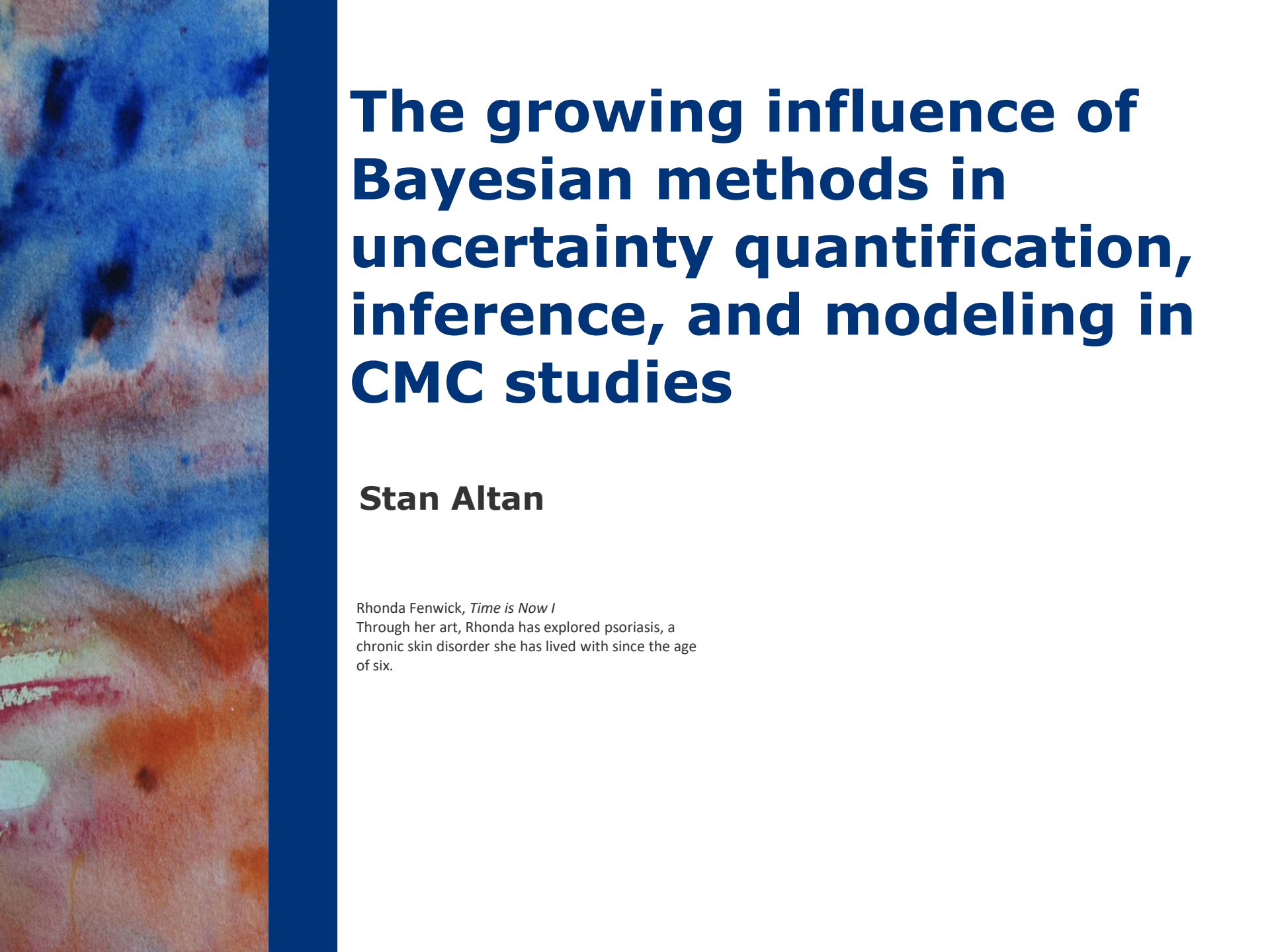




The growing influence of Bayesian methods in uncertainty quantification, inference, and modeling in CMC studies

Stan Altan

Rhonda Fenwick, *Time is Now I*

Through her art, Rhonda has explored psoriasis, a chronic skin disorder she has lived with since the age of six.

Abstract

Bayesian methods provide a coherent, probability-based framework for estimation, inference, and prediction. They are particularly valuable to CMC statisticians, who are engaged in the design of experiments, complex hierarchical (linear and nonlinear) models, and cross-sectional data collection. Bayesian methods help address the central goal of CMC studies: elucidating relationships between quality attributes and process/formulation parameters, thus ensuring safety and efficacy. Bayesian methods can be regarded as facilitating patient-centric quality considerations.

This presentation reviews the published literature on Bayesian applications in the CMC space and traces the trajectory of their increasing adoption. I will highlight the range of CMC topics where Bayesian approaches have been applied and discuss practical considerations, including prior specification, predictive distributions, interpretability, and regulatory implications. Underpinning this trend is the fundamental appeal of probability-based decision making offered by Bayesian methods.

Outline

1. Literature Review by Topic
2. Patient-Centric Drug Development and Bayesian Methods
3. Do we need CMC Bayesian regulatory guidance?
4. Prior distributions

Literature review

1. Reference books

(7 books, 2016 – 2027)

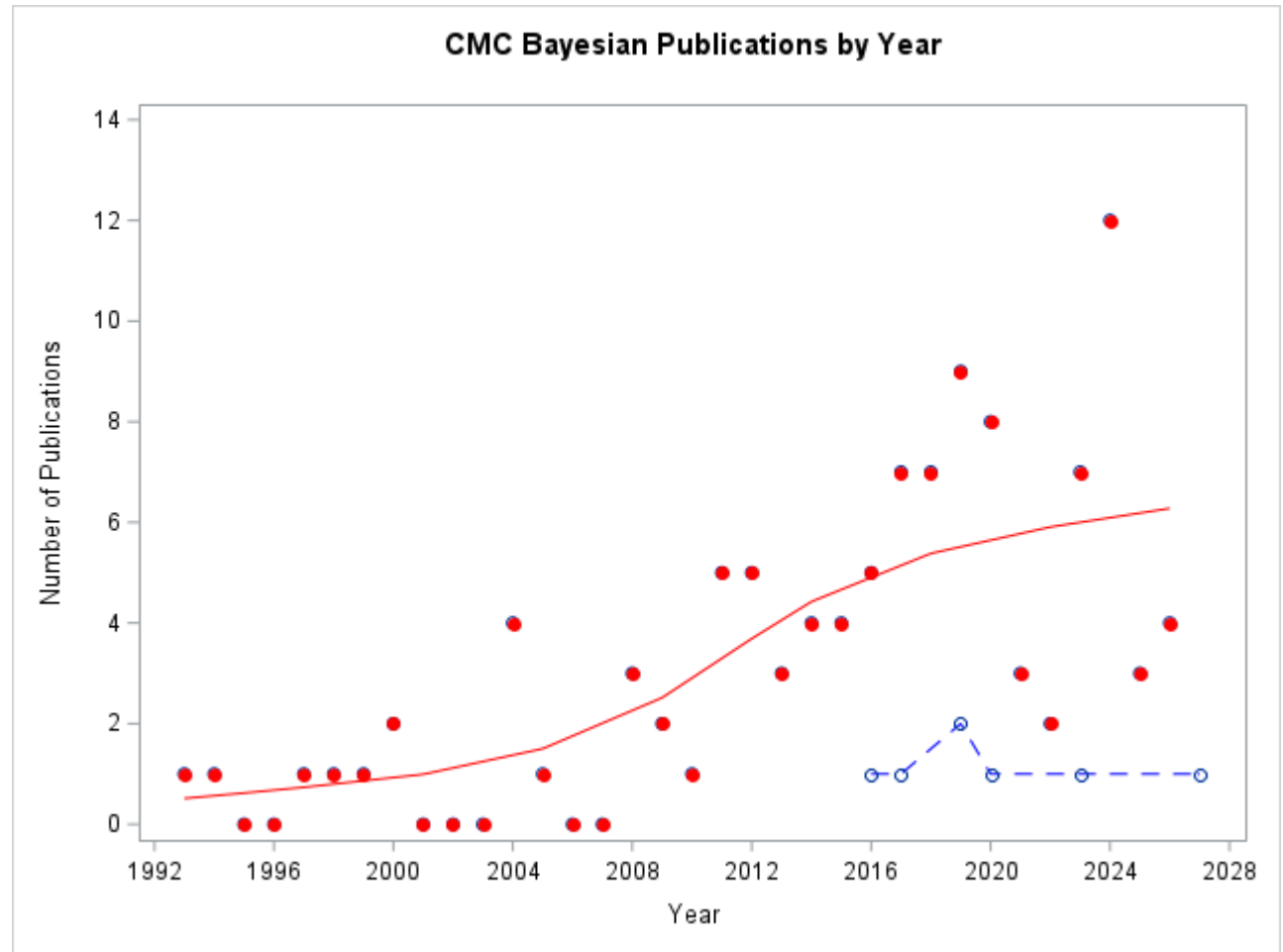
2. Journal Publications

- 110 publications across 49 journals covering the full range of CMC experimental studies

Bayesian CMC papers by subject matter

Topic	# papers	Date Range
1. Analytical Development, Compendial Testing	30	1998-2026
2. Process Validation, Sample size estimation, Tis	22	1993-2026
3. Quality by Design, DoEs	21	2000-2021
4. Bioassay	16	2000-2024
5. Equivalence Testing	8	2014-2024
6. Stability	8	2008-2025
7. Accelerated Stability	5	1994-2024
8. Regulatory related, reviews, Philosophy, Surveys	(10)	2018-2023
Total	110	1993-2026

CMC Bayesian Publications by Year



Publications by journal category

110 publications: 109 journal articles + 1 proceedings paper; 49 journals

Journal category	Journals	Papers
Statistics and biostatistics	10	41
Pharmaceutical sciences, technology and regulation	13	30
Analytical chemistry and measurement	6	13
Engineering and process development	5	8
Quality, reliability and industrial statistics	4	7
Biomedical and laboratory sciences	5	5
Bioinformatics and computing	4	4
Multidisciplinary sciences	2	2
TOTAL	49	110

Proposed grouping: each journal assigned once; proceedings paper assigned by topic. Source: literature review.

Posterior Distribution through Bayes' Rule

$$X \sim f(\cdot | \theta), \quad \Theta \sim \text{prior}(\cdot)$$

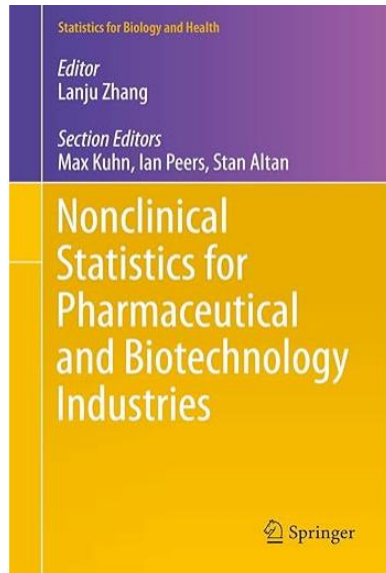
$$\begin{aligned} \text{post}(\theta | x) &= \frac{f(x | \theta) \times \text{prior}(\theta)}{\int f(x | \theta) \times \text{prior}(\theta) d\theta} \\ &\propto f(x | \theta) \times \text{prior}(\theta) \end{aligned}$$

Posterior Distribution $\sim$ Likelihood $\times$ Prior Distribution

Reference Books

Nonclinical Statistics for Pharmaceutical and Biotechnology Industries

Edited by Lanju Zhang, Max Kuhn, Ian Peers, & Stan Altan (2016)

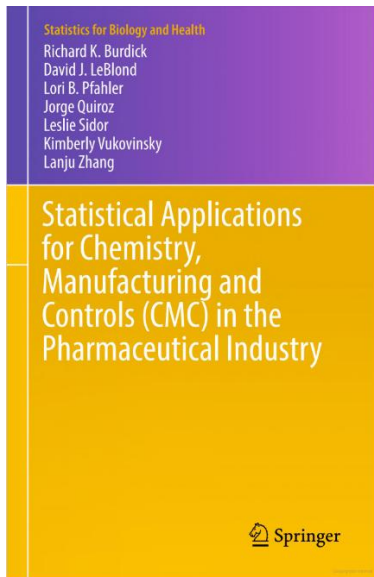


Bayesian sections

- 15.3 Bayesian application: Probability of Conformance and ICH Q8 **Design Space**
- 16.5 Bayesian predictive distribution (**Assay Validation**)
- 19.5 **Process Performance Qualification** – Sample Size
- 23.3.8 Bayesian Approach to **similarity testing**
- 24.7 Evaluating **risk** (Assessing Content Uniformity)

Statistical Applications for Chemistry, Manufacturing and Controls (CMC) in the Pharmaceutical Industry

Richard K. Burdick, David J. LeBlond, Lori B. Pfahler, Jorge Quiroz, Leslie Sidor, Kimberly Vukovsky, Lanju Zhang (2017)



Bayesian sections

2.13 Bayesian models (Stat Methods)

6.4.7 Performance Validation (Analytical Procedures)

8.4.7 Shelf-life Estimation (Stability)

8.5 Risk assessment

Bayesian Applications in Pharmaceutical Development

Edited by Mani Lakshminarayan, Fanni Natanegara (2019)



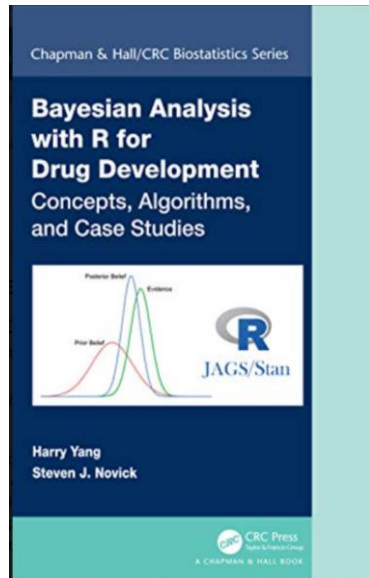
Chapter 13, 20 pages

Power Priors for Sample Size Determination in the Process Validation Life Cycle

By Paul Faya, John W. Seaman, James D. Stamey

Bayesian Analysis with R for Drug Development Concepts, Algorithms, and Case Studies

Harry Yang, Steven Novick, 1st Edition (2019)



Section III Chemistry, Manufacturing, and Control	
Chapter	Topic
8	Analytical Methods
9	Process Development
10	Stability
11	Process Control

Bayesian Methods in Pharmaceutical Research

Edited by [Emmanuel Lesaffre](#), [Gianluca Baio](#), [Bruno Boulanger](#) (2020)

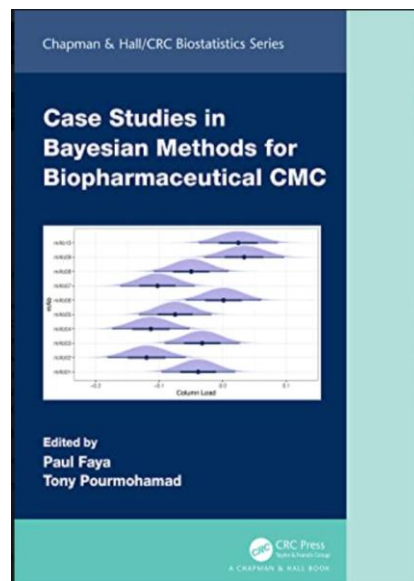


CMC sections

Section 4 Product development and manufacturing	
Chapter	Topic
18	Product Development and Manufacturing
19	Process Development and Validation
20	Analytical Method and Assay
21	Bayesian Methods for the Design and Analysis of Stability Studies
22	Content Uniformity Testing
23	Bayesian Methods for In Vitro Dissolution Drug Testing and Similarity Comparisons
24	Bayesian Statistics for Manufacturing

Case Studies in Bayesian Methods for Biopharmaceutical CMC

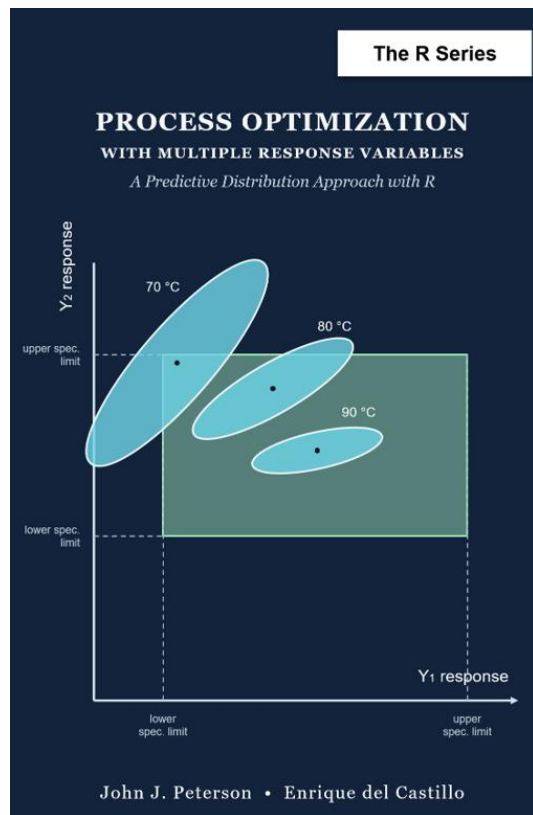
Edited by Paul Faya, Tony Pourmohamad (2023)



Chap	Title
1	Introduction
2	An Overview of Bayesian Computation
3	Basic Bayesian Model Checking
4	Quantitative Decision-Making a CMC Application to Analytical Method Equivalence
5	Bayesian Dissolution Testing
6	A Non-Normal Bayesian Model for the Estimation and Comparison of Immunogenicity Screening Assay Cut-Points
7	Application of Bayesian Hierarchical Models to Experimental Design
8	Bayesian Prediction for Staged Testing Procedures
9	A Bayesian Approach to Multivariate Conditional Regression Surrogate Modeling with Application to Real Time Release Testing
10	Bayesian Approach for Demonstrating Analytical Similarity
11	Bayesian Evaluation and Monitoring of Process Comparability
12	Bayesian Alternatives to Traditional Methods for Estimating Product Shelf-Life and Internal Release Limits
13	Application of Bayesian Methods for Specification Setting
14	Calculating Statistical Tolerance Intervals Using SAS
15	A Bayesian Application in Process Monitoring – Establishing Limits for Dosage Units in Early Phase Process Control

Process Optimization with Multiple Response Variables - A Predictive Distribution Approach with R

John Peterson, Enrique del Castillo (2027)



1. R package - multiRSM
2. Pharmaceutical applications
 - ICH Q8 design space
 - bioassay optimization

Journal Publications

Analytical Development, Compendial Testing

Analytical Development, Compendial Testing

1. Lee JC, Chen DT, Hung HN, Chen JJ. (1999). Analysis of drug dissolution data. *Stat Med.* 18(7):799-814. doi: 10.1002/(sici)1097-0258(19990415)18:7<799::aid-sim81>3.0.co;2-y. PMID: 10327528.
2. Lánský P, Lánská V, Weiss M. (2004). A stochastic differential equation model for drug dissolution and its parameters. *J Control Release.* 100(2):267-274. doi: 10.1016/j.jconrel.2004.08.021. PMID: 15544874.
3. Wilson WI, Peng Y, Augsburger LL. (2005). Comparison of statistical analysis and Bayesian Networks in the evaluation of dissolution performance of BCS Class II model drugs. *J Pharm Sci.* 94(12):2764-2776. doi: 10.1002/jps.20358. PMID: 16258987.
4. Mockus L, Láinez JM, Reklaitis G, Kirsch L. (2011). A Bayesian approach to pharmaceutical product quality risk quantification. *Informatica.* 22(4):537-558.

Analytical Development, Compendial Testing

5. Lewis RA, Novick SJ. (2012). A Generalized Pivotal Quantity Approach to the Parametric Tolerance Interval Test for Dose Content Uniformity Batch Testing. Stat Biopharm Res. 4(1):28-36. doi: 10.1080/19466315.2011.636282.
6. Novick S, Yang H. (2013). Directly testing the linearity assumption for assay validation. J Chemom. 27(5):117-125.
7. LeBlond D, Mockus L. (2014). The posterior probability of passing a compendial standard, part 1: uniformity of dosage units. Stat Biopharm Res. 6(3):270-286.
8. Novick S, Shen Y, Yang H, Peterson J, LeBlond D, Altan S. (2015). Dissolution curve comparisons through the $F(2)$ parameter, a Bayesian extension of the $f(2)$ statistic. J Biopharm Stat. 25(2):351-371. doi: 10.1080/10543406.2014.971175. PMID: 25357203.

Analytical Development, Compendial Testing

9. Dai SY, Xu B, Zhang Y, Li JY, Sun F, Shi XY, Qiao YJ. (2016). Establishment and reliability evaluation of the design space for HPLC analysis of six alkaloids in *Coptis chinensis* (Huanglian) using Bayesian approach. *Chin J Nat Med.* 14(9):697-708. doi: 10.1016/S1875-5364(16)30083-8. PMID: 27667516.
10. Hofer JD, Rauk AP. (2017). Use of Bayesian Methods to Analyze and Visualize Content Uniformity Capability Versus United States Pharmacopeia and ASTM Standards. *J Pharm Sci.* 106(2):554-559. doi: 10.1016/j.xphs.2016.10.003. PMID: 27837969.
11. Novick SJ, Zhao W, Yang H. (2017). Setting alert and action limits in the presence of significant amount of censoring in data. *PDA J Pharm Sci Technol.* 71(1):20-32.
12. Faya P, Stamey JD, Seaman JW Jr. (2017). A Bayesian approach to determination of F, D, and z values used in steam sterilization validation. *PDA J Pharm Sci Technol.* 71(2):88-98.
13. Yu B, Yang H, Ren P. (2017). Bayesian tolerance intervals for zero-inflated data with applications in pharmaceutical quality control. *J Valid Technol.* 23(3).

Analytical Development, Compendial Testing

14. **Novick S, Hudson-Curtis B. (2017). Content uniformity testing for stratified samples via parametric tolerance interval testing. J Biopharm Stat. doi: 10.1080/10543406.2017.1321005.**
15. **Briskot T, Stückler F, Wittkopp F, Williams C, Yang J, Konrad S, Doninger K, Griesbach J, Bennecke M, Hepbildikler S, Hubbuch J. (2019). Prediction uncertainty assessment of chromatography models using Bayesian inference. J Chromatogr A. 1587:101-110. doi: 10.1016/j.chroma.2018.11.076. PMID: 30579636.**
16. **van der Veen AMH. (2018). Bayesian methods for type A evaluation of standard uncertainty. Metrologia. 55:670-684. doi: 10.1088/1681-7575/aad103.**
17. **Banton D, Vacante D, Bulthuis B, Goldstein J, Wineburg M, Schreffler J. (2019). The use of Bayesian hierarchical logistic regression in the development of a modular viral inactivation claim. PDA J Pharm Sci Technol. 73(6):552-561.**
18. **Overstall AM, Woods DC, Martin KJ. (2019). Bayesian prediction for physical models with application to the optimization of the synthesis of pharmaceutical products using chemical kinetics. Comput Stat Data Anal. 132:126-142.**

Analytical Development, Compendial Testing

19. **Tendong W, Lebrun P, Verbist B. (2020). Controlling the Reproducibility of AC50 Estimation during Compound Profiling through Bayesian β -Expectation Tolerance Intervals. SLAS Discov. 25(9):1009-1017. doi: 10.1177/2472555220918201. PMID: 32468893.**
20. **Wübbeler G, Marschall M, Elster C. (2020). A simple method for Bayesian uncertainty evaluation in linear models. Metrologia. 57:065010. doi: 10.1088/1681-7575/aba3b8.**
21. **Avohou TH, Sacré PY, Lebrun P, Hubert P, Ziemons E. (2021). A probabilistic class-modelling method based on prediction bands for functional spectral data: Methodological approach and application to near-infrared spectroscopy. Anal Chim Acta. 1144:130-149. doi: 10.1016/j.aca.2020.11.039. Epub 2020 Dec 1. PMID: 33453790.**

Analytical Development, Compendial Testing

22. Faya P, Novick S, Seaman JW Jr, Peterson JJ, Pourmohamad T, Banton D, Zheng Y. (2022). Continuous method validation: beyond one-time studies to characterize analytical methods. Stat Biopharm Res. 15(1):225-233. [doi: 10.1080/19466315.2022.2036637](https://doi.org/10.1080/19466315.2022.2036637).
23. Pourmohamad T, Ng HKT. (2023). Statistical Modeling Approaches for the Comparison of Dissolution Profiles. Pharm Stat. 22(2):248-265. [doi: 10.1002/pst.2274](https://doi.org/10.1002/pst.2274).
24. Tamai Y, Noda A, Yamamoto E. (2023). Estimation of confidence intervals for quantitation of coeluted peaks in liquid chromatography-Photodiode array detection through a combination of multivariate curve resolution-alternating least-square and Bayesian inference techniques. J Chromatogr A. 1704:464136. doi: 10.1016/j.chroma.2023.464136. PMID: 37307637.
25. Heymann W, Glaser J, Schlegel F, Johnson W, Rolandi P, von Lieres E. (2023). Advanced error modeling and Bayesian uncertainty quantification in mechanistic liquid chromatography modeling. J Chromatogr A. 1708:464329.
26. Brunelli C, Osborne R, Yule G, Dixon T, Bruce I, Taylor M. (2024). Automated multifactorial design of experiment and Bayesian optimisation algorithm approaches to method development for the green analysis by supercritical fluid chromatography of a pharmaceutical ingredient. J Chromatogr A. 1732:465214. doi: 10.1016/j.chroma.2024.465214. PMID: 39116684.

Analytical Development, Compendial Testing

27. Faya P, Zhang T. (2024). To Dilute or Not to Dilute: Nominal Titer Dosing for Genetic Medicines. Pharm Stat. 23(6):939-944. doi: 10.1002/pst.2406. PMID: 38923802.
28. Dixon TM, et al. (2024). Operator-free HPLC automated method development guided by Bayesian optimization. Digital Discov. 3(8):1591-1601. doi: [10.1039/D4DD00062E](https://doi.org/10.1039/D4DD00062E).
29. Schach S, Eiler T, Presser B, Kunzelmann M. (2025). Bayesian Hierarchical Modeling for Variance Estimation in Biopharmaceutical Processes. Bioengineering. 12(2):193. doi: 10.3390/bioengineering12020193.
30. Tao Y, Rauk A, Gao J, De Felippis MR. (2025). Leveraging prior knowledge for process parameter classification in mAb Protein A chromatography. J Chromatogr A. 1742. doi: 10.1016/j.chroma.2024.465647.

Journal Publications

Process Validation, Sample Size Estimation, TIs

Process Validation, Sample Size Estimation, TIs

1. **Woodward PW, Naylor JC. (1993). An application of Bayesian methods in SPC. The Statistician. 42:461-469.**
2. **Berezowitz WA, Chang TH. (1997). Assessing Design Quality During Product Development. Proceedings ASQC 51st Quality Congress. pp. 907-917.**
3. **Wolfinger RD. (1998). Tolerance intervals for variance component models using Bayesian simulation. J Qual Technol. 30(1):18-32.**
4. **Raghunathan TE. (2000). Bayesian Analysis of Quality Level using simulation methods. J Qual Technol. 32(2):172-182.**
5. **Yang H. (2013). How many batches are needed for process validation under the new FDA guidance? PDA J Pharm Sci Technol. 67(1):53-62.**
6. **Mockus L, Peterson JJ, Lainez JM, Reklaitis GV. (2015). Batch-to-batch variation: a key component for modeling chemical manufacturing processes. Org Process Res Dev. 19(8):908-914.**
7. **Faya P, Seaman JW Jr, Stamey JD. (2017). Bayesian assurance and sample size determination in the process validation life-cycle. J Biopharm Stat. 27(1):159-174.**

Process Validation, Sample Size Estimation, TIs

8. Charoo NA, Durivage M, Rahman Z, Ayad MH. (2017). Sample Size for Tablet Compression and Capsule Filling Events During Process Validation. *J Pharm Sci.* 106(12):3533-3538. doi: 10.1016/j.xphs.2017.07.021. PMID: 28780393.
9. Tabora JE, Gonzalez FL, Tom JW. (2019). Bayesian probabilistic modeling in pharmaceutical process development. *AIChE J.* 65(11).
10. Sano Y, Kadowaki T, Tsuda K, Kimura S. (2020). Application of Bayesian Optimization for Pharmaceutical Product Development. *J Pharm Innov.* 15:333-343. doi: 10.1007/s12247-019-09382-8.
11. Tran H. (2021). Empirical weighted Bayesian tolerance intervals. *J Biopharm Stat.* (2):180-190. doi: 10.1080/10543406.2020.1814801. PMID: 32997587.
12. Cai Q, Mockus L, LeBlond D, Sun X, Wei H, Shah HS, Chaturvedi K, Sardhara R, Nahar K, Khalil R, Sharma A, Rutesh D, Joglekar G, Reklaitis G, Morris K. (2022). Bayesian statistical approaches to drug product variability assessment and release. *Int J Pharm.* 624:122037. doi: 10.1016/j.ijpharm.2022.122037. PMID: 35870665.

Process Validation, Sample Size Estimation, TIs

13. **Peterson JJ. (2023). Response Surfaces, Blocking, and Split-Plots: A Predictive Distribution Case Study. Qual Eng. 35(1):172-191.**
14. **Montes RO. (2024). Frequentist and Bayesian tolerance intervals for setting specification limits for left-censored gamma distributed drug quality attributes. Pharm Stat. 23(2):168-184. doi: 10.1002/pst.2344. PMID: 37871968.**
15. **Kilaru R, Amodio S, Li Y, Wells C, Love S, Zeng Y, Ye J, Jelizarow M, Balakumar A, Fronc M, Osterdal AS, Rolfe T, Talbot S. (2024). An Overview of Current Statistical Methods for Implementing Quality Tolerance Limits. Ther Innov Regul Sci. 58(2):273-284. doi: 10.1007/s43441-023-00598-y. Erratum in: Ther Innov Regul Sci. 58(2):285. doi: 10.1007/s43441-024-00621-w. PMID: 38148473; PMCID: PMC10850247.**
16. **Weusten J, Hu J. (2024). Predictive Ppk calculations for biologics and vaccines using a Bayesian approach - a tutorial. Pharm Stat. doi: 10.1002/pst.2380. Epub ahead of print. PMID: 38603591.**

Process Validation, Sample Size Estimation, TIs

17. Freitag AJ, et al. (2024). Use of Bayesian Modeling for Risk Assessment and Robustness Evaluation. *Org Process Res Dev.* 28(2):511-523. doi: 10.1021/acs.oprd.3c00325.
18. Chang H, Domagalski N, Tabora JE, Tom JW. (2024). Bayesian data-driven models for pharmaceutical process development. *Curr Opin Chem Eng.* 45:101034. doi: 10.1016/j.coche.2024.101034.
19. Li L, Back SI, Ma J, Guo Y, Galeandro-Diamant T, Clénet D. (2025). Bayesian optimization and machine learning for vaccine formulation development. *PLoS One.* 20(6):e0324205. doi: 10.1371/journal.pone.0324205.
20. Waibel I, et al. (2025). Bayesian Optimization for Efficient Multiobjective Formulation Development of Biologics. *Mol Pharm.* 22(11):6636-6645. doi: 10.1021/acs.molpharmaceut.5c00591.
21. *Ramírez JG, Chen F. (2026). Tolerance and prediction intervals: The Bayesian way. *J Biopharm Stat.* 36(4):600-616. doi: 10.1080/10543406.2026.2670527.
22. Pourmohamad T, Richardson R, Sansó B. (2026). Calibrated Bayesian Nonparametric Tolerance Intervals. *Technometrics.* 1-13. doi: 10.1080/00401706.2026.2699103.

*Special issue of nonclinical statistics in regulatory applications in honor of Dr. Yi Tsong

Journal Publications

Quality by Design, DoEs

Quality by Design, DoE

1. **Peterson JJ. (2004). A posterior predictive approach to multiple response surface optimization. J Qual Technol. 36(2):139-153.**
2. **Miro-Quesada G, del Castillo E, Peterson JJ. (2004). A Bayesian approach for multiple response surface optimization in the presence of noise variables. J Appl Stat. 31(3):251-270.**
3. **Peterson JJ. (2008). A Bayesian approach to the ICH Q8 definition of design space. J Biopharm Stat. 18(5):959-975.**
4. **Peterson JJ, Yahyah M. (2009). A Bayesian Design Space Approach to Robustness and System Suitability for Pharmaceutical Assays and Other Processes. Stat Biopharm Res. 1(4):441-449.**
5. **Peterson JJ, Miro-Quesada G, del Castillo E. (2009). A Bayesian reliability approach to multiple response optimization with seemingly unrelated regression models. Qual Technol Quant Manag. 6(4):353-369.**
6. **Peterson JJ, Lief K. (2010). The ICH Q8 definition of design space: a comparison of the overlapping means and the Bayesian predictive approaches. Stat Biopharm Res. 2(2):249-259.**

Quality by Design, DoE

7. Mockus L, LeBlond D, Basu PK, Shah RB, Khan MA. (2011). A QbD case study: Bayesian prediction of lyophilization cycle parameters. *AAPS PharmSciTech*. 12(1):442-448.
8. Lebrun P, Krier F, Mantanus J, Grohgan H, Yang M, Rozet E, Boulanger B, Evrard B, Rantanen J, Hubert P. (2012). Design space approach in the optimization of the spray-drying process. *Eur J Pharm Biopharm*. 80(1):226-234. doi: 10.1016/j.ejpb.2011.09.014. PMID: 21983606.
9. Maeda J, Suzuki T, Takayama K. (2012). Novel method for constructing a large-scale design space in lubrication process by using Bayesian estimation based on the reliability of a scale-up rule. *Chem Pharm Bull (Tokyo)*. 60(9):1155-1163. doi: 10.1248/cpb.c12-00340. PMID: 22976324.
10. Maeda J, Suzuki T, Takayama K. (2012). Design space construction of multiple dose-strength tablets utilizing Bayesian estimation based on one set of design-of-experiments. *Chem Pharm Bull (Tokyo)*. 60(11):1399-1408. doi: 10.1248/cpb.c12-00491. PMID: 23124564.
11. Hubert C, Lebrun P, Houari S, Ziemons E, Rozet E, Hubert P. (2014). Improvement of a stability-indicating method by quality-by-design versus quality-by-testing: a case of a learning process. *J Pharm Biomed Anal*. 88:401-409.

Quality by Design, DoE

12. Lebrun P, Giacoletti K, Scherder T, Rozet E, Boulanger B. (2015). A quality by design approach for longitudinal quality attributes. *J Biopharm Stat.* 25(2):247-259.
13. Thiry J, Lebrun P, Vinassa C, Adam M, Netchacovitch L, Ziemons E, Hubert P, Krier F, Evrard B. (2016). Continuous production of itraconazole-based solid dispersions by hot melt extrusion: Preformulation, optimization and design space determination. *Int J Pharm.* 515(1-2):114-124. doi: 10.1016/j.ijpharm.2016.10.003. Epub 2016 Oct 5. PMID: 27720874.
14. Claycamp HG, Kona R, Fahmy R, Hoag SW. (2016). Quality-by-Design II: Application of Quantitative Risk Analysis to the Formulation of Ciprofloxacin Tablets. *AAPS PharmSciTech.* 17(2):233-244. doi: 10.1208/s12249-015-0349-2. PMID: 26202064; PMCID: PMC4984889.
15. Bano G, Facco P, Bezzo F, Barolo M. (2018). Probabilistic Design space determination in pharmaceutical product development: A Bayesian/latent variable approach. *AIChE J.* 64(7):2438-2449. doi: [10.1002/aic.16133](https://doi.org/10.1002/aic.16133).

Quality by Design, DoE

16. Kothari BH, Fahmy R, Claycamp HG, Moore CMV, Chatterjee S, Hoag SW. (2018). Comparing a Statistical Model and Bayesian Approach to Establish the Design Space for the Coating of Ciprofloxacin HCl Beads at Different Scales of Production. *AAPS PharmSciTech*. 19(8):3809-3828. doi: 10.1208/s12249-018-1116-y. PMID: 30280352.
17. Stamatis SD, Kirsch LE. (2018). Using Manufacturing Design Space Concepts for Stability Risk Assessment-Gabapentin NIPTE/FDA Case Study. *AAPS PharmSciTech*. 19(7):2801-2807. doi: 10.1208/s12249-018-1141-x. PMID: 30120695.

Quality by Design, DoE

18. Salvé M, Avohou HT, Monbaliu JM, Lebrun P, Lemaire C, Damblon C, de Tullio P, Hubert P, Hustinx R, Luxen A. (2018). NOTA-PRGD2 and NODAGA-PRGD2: Bioconjugation, characterization, radiolabelling, and design space. J Labelled Comp Radiopharm. 61(6):487-500. doi: 10.1002/jlcr.3613. Epub 2018 Apr 25. PMID: 29430693.
19. Kusumo KP, Gomoescu L, Paulen R, García Muñoz S, Pantelides CC, Shah N, Chachuat B. (2019). Bayesian Approach to Probabilistic Design Space Characterization: A Nested Sampling Strategy. Ind Eng Chem Res. 59(6):2396-2408.
20. Shahmohammadi A, McAuley KB. (2020). Using prior parameter knowledge in model-based design of experiments for pharmaceutical production. AIChE J. 66(11):e17021. doi: 10.1002/aic.17021.
21. Shields BJ, et al. (2021). Bayesian reaction optimization as a tool for chemical synthesis. Nature. 590:89-96. doi: 10.1038/s41586-021-03213-y.

Journal Publications

Bioassay and Related Modeling and Statistics

Bioassay, Related Modeling

1. **Miller G, Inkret WC, Schillaci ME, Martz HF, Little TT. (2000). Analyzing bioassay data using Bayesian methods—a primer. Health Phys. 78(6):598-613.**
2. **Gelman A, Chew GL, Shnaidman M. (2004). Bayesian analysis of serial dilution assays. Biometrics. 60(2):407-417.**
3. **Sivaganesan M, Seifring S, Varma M, Haugland RA, Shanks OC. (2008). A Bayesian method for calculating real-time quantitative PCR calibration curves using absolute plasmid DNA standards. BMC Bioinformatics. 9(1):120.**
4. **Feng F, Sales AP, Kepler TB. (2011). A Bayesian approach for estimating calibration curves and unknown concentrations in immunoassays. Bioinformatics. 27(5):707-712.**
5. **Rozet E, Govaerts B, Lebrun P, Michail K, Ziemons E, Wintersteiger R, Rudaz S, Boulanger B, Hubert P. (2011). Evaluating the reliability of analytical results using a probability criterion: A Bayesian perspective. Anal Chim Acta. 705(1-2):193-206. ISSN: 0003-2670. doi: 10.1016/j.aca.2011.05.028.**

Bioassay, Related Modeling

6. Klauenberg K, Ebert B, Voigt J, Walzel M, Noble JE, Knight AE, Elster C. (2011). Bayesian analysis of an international ELISA comparability study. Clin Chem Lab Med. 49(9):1459-1468. doi: 10.1515/CCLM.2011.648. Epub 2011 Jul 5. PMID: 21726164.
7. Novick SJ, Yang H, Peterson JJ. (2012). A Bayesian approach to parallelism testing in bioassay. Stat Biopharm Res. 4(4):357-374.
8. Lebrun P, Boulanger B, Debrus B, Lambert P, Hubert P. (2013). A Bayesian design space for analytical methods based on multivariate models and predictions. J Biopharm Stat. 23(6):1330-1351.
9. Fronczyk K, Kottas A. (2014). A Bayesian approach to the analysis of quantal bioassay studies using nonparametric mixture models. Biometrics. 70(1):95-102.
10. Muleme M, Stenos J, Vincent G, Campbell A, Graves S, Warner S, Devlin JM, Nguyen C, Stevenson MA, Wilks CR, Firestone SM. (2016). Bayesian Validation of the Indirect Immunofluorescence Assay and Its Superiority to the Enzyme-Linked Immunosorbent Assay and the Complement Fixation Test for Detecting Antibodies against Coxiella burnetii in Goat Serum. Clin Vaccine Immunol. 23(6):507-514. doi: 10.1128/CVI.00724-15. PMID: 27122484.

Bioassay, Related Modeling

11. Rozet E, Lebrun P, Michiels JF, Sondag P, Scherder T, Boulanger B. (2015). Analytical procedure validation and the quality by design paradigm. *J Biopharm Stat.* 25(2):260-268.
12. Novick S, Sondag P, Schofield T, Miller K. (2018). A Novel Method for Qualification of a Potency Assay through Partial Computer Simulation. *PDA J Pharm Sci Technol.* 72(3):249-263. doi: 10.5731/pdajpst.2017.008094.
13. Novick S, Yang H. (2019). A fast and reliable test for parallelism in bioassay. *J Biopharm Stat.* 29(6):1011-1023. doi: 10.1080/10543406.2019.1572615. Epub 2019 Feb 4. PMID: 30712462.
14. Novick SJ, Christian E, Farmer E, Tejada M. (2020). A Bayesian Statistical Approach to Continuous Qualification of a Bioassay. *PDA J Pharm Sci Technol.* 75(1):8-23. doi: 10.5731/pdajpst.2019.011221.

Bioassay, Related Modeling

15. Faya P, Rauk AP, Griffiths KL, Parekh B. (2020). A curve similarity approach to parallelism testing in bioassay. J Biopharm Stat. 30(4):721-733. doi: 10.1080/10543406.2020.1730875. PMID: 32163316.
16. Faya P, Zhang T, Walton W, Novick S. (2024). Non-constant mean relative potency for antibody-dependent cellular cytotoxicity assays. J Biopharm Stat. 1-12.

Journal Publications

Comparability, Equivalence Testing and Similarity

Comparability, Equivalence, Similarity

1. Chiu ST, Liu JP, Chow SC. (2014). Applications of the Bayesian prior information to evaluation of equivalence of similar biological medicinal products. J Biopharm Stat. 24(6):1254-1263. doi: 10.1080/10543406.2014.941982. PMID: 25032488.
2. Yang H, Novick S, Burdick RK. (2016). On Statistical Approaches for Demonstrating Analytical Similarity in the Presence of Correlation. PDA J Pharm Sci Technol. 70(6):547-559. doi: 10.5731/pdajpst.2016.006551. PMID: 27325594.
3. Zeng L, Novick S, Yu B, Yang H. (2019). General framework for equivalence testing over a range of linear outcomes with CMC applications. Stat Biopharm Res. 11(2):182-190.
4. Sondag P, Lebrun P. (2020). Risk-Based Similarity Testing for Potency Assays Using MCMC Simulations. Stat Biopharm Res. 13(3):303-312. doi: [10.1080/19466315.2020.1764864](https://doi.org/10.1080/19466315.2020.1764864).

Comparability, Equivalence, Similarity

5. Pourmohamad T, Oliva Avilés CM, Richardson R. (2021). Gaussian process modeling for dissolution curve comparisons. J R Stat Soc Ser C Appl Stat. 71(2):331-351. doi: 10.1111/rssc.12535.
6. Pourmohamad T, Lee HKH. (2024). Equivalence Testing for Multiple Groups. Stat. 13(1):e645. doi: [10.1002/sta4.645](https://doi.org/10.1002/sta4.645).
7. Weusten J, Kim JY, Giacoletti K, Vázquez J, De Los Santos P. (2024). A Bayesian approach for evaluating equivalence over multiple groups, and comparison with frequentist TOST. J Appl Stat. 51(12):2382-2401. doi: 10.1080/02664763.2023.2297150. PMID: 39267716; PMCID: PMC11389643.
8. Kim JY, Altan S, Banton D, Eilert T, Faya P, Hui G, Novick S. (2026). Comparability Assessment for Changes to Manufacturing Processes: Industry Recommendations on Bayesian Practices. Stat Biopharm Res. 1-12. doi: 10.1080/19466315.2026.2677711.

Journal Publications

Stability Modeling, Release, Risk Assessment

Stability Modeling, Release

1. **Chen J, Zhong J, Nie L. (2008). Bayesian hierarchical modeling of drug stability data. Stat Med. 27(13):2361-2380.**
2. **Yu B, Zeng L, Yang H. (2018). A Bayesian approach to setting the release limits for critical quality attributes. Stat Biopharm Res. 10(3):158-165.**
3. **Montes RO, Burdick RK, LeBlond DJ. (2019). Simple approach to calculate random effects model tolerance intervals to set release and shelf-life specification limits of pharmaceutical products. PDA J Pharm Sci Technol. 73(1):39-59.**
4. **Mockus L, Reklaitis G, Morris K, LeBlond D. (2020). Risk-Based Approach to Lot Release. J Pharm Sci. 109(2):1035-1042. doi: 10.1016/j.xphs.2019.10.011. PMID: 31610180.**

Stability Modeling, Release Limits

5. **Chen XG, van der Vaart AW. (2023). Setting the control limit at release for stability assurance. Pharm Stat. 22(1):45-63. doi: 10.1002/pst.2259. PMID: 36637243.**
6. **Altan S, Faya P, Rauk AP, LeBlond D, Seaman JW Jr, Banton D. (2023). Stability analysis using mixed models: A critique of tolerance interval methods and a probabilistic solution. Pharm Stat. 22(5):784-796. doi: 10.1002/pst.2305. PMID: 37164770.**
7. **Cordero M, Meinfelder F, Eilert T. (2024). A Modern Approach to Stability Studies via Bayesian Linear Mixed Models Incorporating Auxiliary Effects. J Pharm Sci. 113(7):1779-1793. doi: 10.1016/j.xphs.2024.02.020. PMID: 38417792.**
8. **Ferrari F, et al. (2025). Bayesian hierarchical model predicts biopharmaceutical stability indicators and shelf life with application to multivalent human papillomavirus vaccine. Sci Rep. doi: 10.1038/s41598-025-99458-y.**

Journal Publications

Accelerated Stability Modeling

Accelerated Stability Modeling

1. **Su XY, Li Wan Po A, Yoshioka S. (1994). A Bayesian approach to Arrhenius prediction of shelf-life. Pharm Res. 11(10):1462-1466. doi: 10.1023/a:1018956209236. PMID: 7855053.**
2. **Faya P, Seaman JW Jr, Stamey JD. (2019). Using accelerated drug stability results to inform long-term studies in shelf life determination. Stat Med. 37(17):2599-2615. doi: 10.1002/sim.7663. PMID: 29766536.**
3. **Nakai Y, Noda A, Yamamoto E. (2023). Algorithm for the early prediction of drug stability using Bayesian inference and multiple measurements: Application for predicting the stability of silodosin tablets. J Pharm Biomed Anal. 233:115442. doi: 10.1016/j.jpba.2023.115442. PMID: 37182365.**
4. **Chau J, Altan S, Burggraef A, Coppenolle H, Kifle YW, Prokopcova H, Van Daele T, Sterckx H. (2023). A Bayesian Approach to Kinetic Modeling of Accelerated Stability Studies and Shelf Life Determination. AAPS PharmSciTech. 24(8):250. doi: 10.1208/s12249-023-02695-5. PMID: 38036798.**
5. **Francq BG, Giannelos N, Sanchez R, Paludi M. (2026). Accelerated Stability Studies: A Frequentist–Bayesian Hybrid Simulation Approach Implemented in the AccelStab R Package. Pharm Stat. 25(5):1-17. doi: 10.1002/pst.70116.**

Journal Publications

Regulatory-Related, Survey, Review and Philosophy

Regulatory-Related, Survey, Review and Philosophy

1. **Bland JM, Altman DG. (1998). Bayesians and frequentists. BMJ. 317(7166):1151-1160. doi: 10.1136/bmj.317.7166.1151. PMID: 9784463; PMCID: PMC1114120.**
2. **Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR. (1999). Methods in health service research. An introduction to Bayesian methods in health technology assessment. BMJ. 319(7208):508-512. doi: 10.1136/bmj.319.7208.508. PMID: 10454409; PMCID: PMC1116393.**
3. **Gupta SK. (2012). Use of Bayesian statistics in drug development: Advantages and challenges. Int J Appl Basic Med Res. 2(1):3-6. doi: 10.4103/2229-516X.96789. PMID: 23776799; PMCID: PMC3657986.**
4. **Irony T. (2018). The value of Bayesian approaches in the regulatory setting: lessons from the past and perspectives for the future. BSWG KOL Lect Series. January.**
5. **Peterson JJ, Kramer TT, Hofer JD, Atkins G. (2019). Opportunities and challenges for statisticians in advanced pharmaceutical manufacturing. Stat Biopharm Res. 11(2):152-161.**

Regulatory-Related, Survey, Review and Philosophy

6. Faya P, Sondag P, Novick S, Banton D, Seaman JW Jr, Stamey JD, Boulanger B. (2021). The current state of Bayesian methods in nonclinical pharmaceutical statistics: Survey results and recommendations from the DIA/ASA-BIOP Nonclinical Bayesian Working Group. *Pharm Stat.* 20(2):245-255. doi: 10.1002/pst.2072. Epub 2020 Oct 6. PMID: 33025743.
7. Destro F, Barolo M. (2022). A review on the modernization of pharmaceutical development and manufacturing – Trends, perspectives, and the role of mathematical modeling. *Int J Pharm.* 620. doi: 10.1016/j.ijpharm.2022.121715.
8. Ionan AC, Clark J, Travis J, Amatya A, Scott J, Smith JP, Chattopadhyay S, Salerno MJ, Rothmann M. (2023). Bayesian Methods in Human Drug and Biological Products Development in CDER and CBER. *Ther Innov Regul Sci.* 57(3):436-444. doi: 10.1007/s43441-022-00483-0. Epub 2022 Dec 2. PMID: 36459346; PMCID: PMC9718464.

Regulatory-Related, Survey, Review and Philosophy

9. Campbell G, Irony T, Pennello G, Thompson L. (2023). Bayesian Statistics for Medical Devices: Progress Since 2010. *Ther Innov Regul Sci*. 57(3):453-463. doi: 10.1007/s43441-022-00495-w. Epub 2023 Mar 3. PMID: 36869194; PMCID: PMC9984131.
10. Travis J, Rothmann M, Thomson A. (2023). Perspectives on informative Bayesian methods in pediatrics. *J Biopharm Stat*. doi: 10.1080/10543406.2023.2170405.
11. Altan S, Faya P, Kim JY, LeBlond D, Novick S, Pourmohamad T, Thompson C. (2024). Call for a regulatory guidance on Bayesian methods in the statistical support of drug development studies. *Biopharmaceutical Report*. 31(1):6-9.

Methodological references

Methodological References

- **General References**

- Gelman, A. et al. (1995). *Bayesian Data Analysis*, Chapman & Hall.
- Box, G. and Tiao, G. (1973). *Bayesian Inference in Statistical Analysis*, Wiley.
- Breslow, NE. (1990). Biostatistics and Bayes, *Statistical Science* 5, 269-298.

- **Gibbs Sampling Methodology, Numerical Methods and Examples**

- Casella, G. and George, E. I. (1992). Explaining the Gibbs Sampler, *The American Statistician*, 46(3), 167-174.
- Gelfand et al. (1990). Illustration of Bayesian Inference in Normal Data Models using Gibbs Sampling, *JASA* 85(412), 972-985.
- Givens, GH and Hoeting, JA. (2005). *Computational Statistics*, Wiley.

Summary of published applications

- Analytical method performance metrics
 - Probability a reportable result is within a desirable interval of true value
- Risk Assessments
 - Comparability, Biosimilars
 - Acceptance Criteria Assessments
 - Tolerance Intervals
- Stability shelf life estimation, long term and accelerated studies
- QbD design space construction
- Dissolution profile comparisons
- PPQ sample size estimation
- Bioassay – similarity testing, potency estimation

Patient-Centric Drug Product Development



Patient-Centric Drug Product Development

- The 2016 Cures Act led to the regulatory coining of the term “patient focused” to capture the notion of making decisions based on patient needs.
- CMC scientists modified the term and aligned it with the earlier term “clinically relevant”.
- A changing regulatory landscape and industry technical advancements imply a new paradigm for the development of “patient-centric” specifications by achieving the vision of QbD.
 - Causal linkages of CQAs to clinical outcomes
 - Acceptance Criteria (AC) defined by multivariate relationships between CPPs and CQAs within a Design Space
- Control of quality through risk-based specifications that relate directly to patient outcomes. Quality statements that provide interpretable risk to the patient.

Frequentist vs. Bayesian Shelf-Life Quality Statements

Frequentist (Q1E model)

- Fixed effects model
 - inference restricted to those 3 batches
 - Complicated pooling rules
- Quality statement: The dosage unit you are about to take comes from a manufacturing process whose first 3 batches were shown to conform to the shelf life claim with 95% confidence.

Bayesian (Mixed model)

- Prior distribution assumptions, data, MCMC Algorithm $\Rightarrow$
 - Shelf life derived directly from future batch mean posterior distribution

$$T_m^* = (LSL - \beta_{0m}) / \beta_{1m}$$

- Distribution of Batch Shelf Life (DBSL) is based on future batch means
- Choose appropriate percentile value (lower 95th quantile) of the posterior of future batch means.
- Quality statement translates to a direct probability as a risk statement: The dosage unit you are about to take comes from a batch whose mean has a 95% probability of meeting the shelf life claim.

Need for Regulatory Guidance pertinent to CMC Bayesian applications

CMC statisticians are ready to adopt Bayesian approaches

- Patient-centric considerations
- Regulatory impetus:
 - Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance <https://www.fda.gov/media/71012/download>
 - Manufacturing process understanding
 - Critical sources of variability are identified and explained
 - Variability is managed by the process
 - Product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, manufacturing, environmental, and other conditions.
 - ICHQ6(R1) draft
 - ... specifications should be justified by thorough understanding of molecular attributes, **clinical relevance**, evidence derived from nonclinical (in vitro, in vivo, and in silico) models (e.g., ... and use of **prior knowledge** as applicable.
- Bayesian methods map to regulatory decision questions (risk statements, release criteria, and design-space construction)

Guidance topics important to industry

- Methods for choice of priors
 - conjugate vs nonconjugate, improper and proper priors, sensitivity analysis
 - degree of informativeness (flat, weak, less weak, etc.)
 - What should the default prior be for different settings related to stage of drug development or amount of information, power prior approaches
- Convergence Diagnostics
 - Heidelberger–Welch, Geweke, Raftery–Lewis, ESS
- CMC applications where Bayesian approaches have met regulatory scrutiny
- Bayesian correspondence to the use of p-values in decision making
- Considerations
 - At a high level
 - Lightly technical
 - Vetted references to the literature
 - Workshops

Prior distribution considerations

Prior Distributions

- Variance components
 - Batch – Batch (manufacturing) variability
 - Residual Error
 - Dosage unit – Dosage unit variability (manufacturing)
 - Measurement error
- Fixed Effects
 - Process Mean at Time 0
 - Time covariate
- Choosing a prior distribution
 - Elicitation - Scientific Judgment
 - Literature sources
 - Currently existing data – update, or use as empirical estimates to suggest a prior
 - Formulation studies
 - Early phase and Accelerated stability studies
 - Experience from similar molecules/platform
 - Pros and cons of Jeffreys' prior, uniform, appropriateness of power priors
 - Christiansen (2011) described in Stroup (2021)

Summary

Growing Influence of Bayesian Methods in Pharmaceutical Studies

- Bayesian methods provide a coherent probability-based framework for estimation, inference, and prediction across pharmaceutical development.
- Literature review: 106 articles across 46 journals — main application areas: stability and shelf-life estimation, QbD design-space construction, dissolution and bioassay similarity testing, process validation and sample-size planning.
- Practical strengths: flexible hierarchical models, direct probability statements for risk, principled borrowing of prior knowledge, and predictive distributions for design and release decisions.
- Regulatory considerations: need clear guidance on prior choice, sensitivity analysis, convergence diagnostics, and examples where Bayesian approaches have been accepted.

Thank you

Acknowledgements

- ASA Biopharm section Nonclinical Bayesian WG
- Don Berry
- Paul Faya
- Dave LeBlond
- John Peterson

Questions for the panel

- How to translate prior knowledge into a probability distribution?
- How to justify the choice of a prior in regulatory submissions?
- Do CMC statisticians need regulatory guidance on Bayesian methods?
If so, what should it cover?