Applying Statistics and Data Science to Evolving Technical and Regulatory Paradigm

Proceedings from the International Alliance for Biological Standardization (IABS) 9th Annual Statistics Workshop: A Non-Statistician's Perspective

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Summary

The 9th Annual IABS Statistics Workshop was a hybrid meeting from 7-9 November 2023 in Rockville, Maryland, USA. This event brought together regulators, statisticians, data scientists, development engineers and industry experts from several countries to explore approaches that can enable technical and regulatory innovation in biologicals development and lifecycle management. The ongoing expansion of statistical methodologies and the increased ability to mine "big data" offer new opportunities to achieve chemistry, manufacturing, and controls (CMC) regulatory requirements and by extension, to better serve the successful development and production of biologicals. Several facets of achieving harmonized statistical solutions were addressed: consensus on the scientific question, innovative techniques to guide decision making processes, addressing questions arising from yet unexplored modalities and technologies, and evolution of the regulatory framework. Recurrent themes in presentations and discussions included the paradigmatic differences between frequentist and Bayesian-based statistical approaches, the importance of ensuring that experimental design and analysis are directed at the proper research question, and the CMC challenges faced by all stakeholders with the rapid advances in treatment modalities such as mRNA vaccines, autologous cell products and gene editing based therapies. The importance of responding to guidance documents issued by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the United States Pharmacopoeia (USP) to enable a Quality by Design (QbD) framework emerged as a critical underpinning in the global acceptance and implementation of improved statistical solutions.

The goal of drug development and the objectives of CMC science were succinctly expressed by keynote speaker, Dr. Jeff Baker, a former regulator from the US Food and Drug administration (US FDA) who currently holds a position as Senior Fellow in the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL). In his talk entitled "Process Control Strategy, Residual Uncertainty, and the Myth of Fingerprints" he stated that the primary purpose of all pharmaceutical products is to provide a "positive and predictable experience to patients" and that the corresponding control strategies serve to "buffer clinically relevant variation". His recommendations gave context to the presentation topics that framed the two-day workshop agenda organized into four sessions:

[1] The Research Question: Its Importance in Achieving Successful Product Development and Regulatory Review
[2] Innovative Statistical Methodologies in CMC
[3] Application of CMC Statistics and Data Science to New Modalities and Technologies
[4] Call to Action: Implementation of Statistical Solutions for CMC

A short course entitled "Tolerance Intervals: The Bayesian Way" was offered prior to the workshop. It was a technical training seminar for statisticians and introduced applicable SAS® code needed to perform calculations. For the non-statistician audience, it served as a high-level primer to one of the central themes of the meeting— showing the target-aimed application of Bayesian statistics in addressing common CMC questions.

Conclusions

1. Bayesian statistics have emerged as a school of thought that contrasts philosophically to frequentist statistics. Although Bayes theorem was developed in 1763, the computing power needed to apply it effectively has only come about in the last two decades. Currently, there are growing groups of CMC statisticians who are eager to promote the Bayesian methodology. One of their goals is to increase exposure to those unfamiliar with the power of Bayesian approaches to support CMC applications. Clinical statisticians at the FDA are actively paving the way for Bayesian approaches and the expectation is that CMC statisticians will also become more interested in advancing these tools.
2. Regulatory ambiguity and uncertainties validate industry's perceived risk aversion to changing practices that have been successful historically (termed traditional approaches) and are still considered acceptable even if not ideal. One of the main catalysts for industry action is responding to what regulators ask for rather than a genuine commitment to continuous improvement and willingness to be adaptive in response to increased knowledge and availability of new tools.
3. Novel product modalities such as mRNA vaccines and cell and gene therapy treatments are presenting new questions to CMC scientists and in turn, motivating development and implementation of novel statistical solutions. This environment is providing opportunities to advance Bayesian approaches and big data analyses and highlighting efficiencies that can be gained when leveraging platform-based control strategies.
4. The statistical and data science toolkits should be widely inclusive; the suitability of any given technique is context dependent. Selection and use of specific strategies must be scientifically and statistically defensible and lead to high quality decisions –specifically choices that enable consistently positive patient experiences.
5. Successful development of biologics and their broad accessibility is an outcome of collective stakeholder synergy. It can only be achieved through effective and efficient use of resources, interdisciplinary collaboration, open exchange of important information and a shared commitment to continuous improvement toward optimal patient outcomes. Uncertainty is a fact and statisticians are needed to evaluate risk and design effective experimental strategies. However, they must work with other stakeholders to accomplish this.
6. Defining and detailing the appropriate scientific research question is the most critical step in developing a valid statistical strategy. Statistics serves to quantify and communicate uncertainty and allows for evaluation and interpretation of data in light of the risks associated with decision making. If the question is not appropriately developed, then the solutions are unlikely to solve the actual question that matters.
7. QbD is a philosophical framework that can be applied to manufacturing and analytical processes. It forces biologicals development to focus on identifying the critical quality attributes of the outputs to create a target profile upfront. A process or test method is fit for purpose if the measured metrics meet the corresponding established requirements associated with the target profile. Continuous learning and ongoing performance verification distinguish a flexible approach to achieving desired outcomes from using studies which are performed at a single point in time and only investigated for special case excursions.
8. It is not uncommon for bench scientists to avoid interacting with statisticians or to treat them as a service to provide analyses and report writing at the end of an experiment or study. In some instances, scientists can still make good decisions because of the vast experience and training that provides them with a database of information from which they derive intuitive expectations and conclusions. The Bayesian framework is seen as a way to translate, quantify and incorporate the extensive platform and molecule specific data that exists into the advantages of a full probability

model. However, in addition to aversion to change, gaps in understanding on fundamental statistical concepts from the non-statistician side and failure to adequately address this through more effective education, ultimately impair the ability to communicate across disciplines and advance more complex ideas.

9. Standard setting organizations can fill the gap in regulation and guidance by providing detailed procedures and techniques that have been derived by thought leaders across the ecosystem of biologicals development and lifecycle management. Inviting stakeholder input early and sharing plans for prospective topics have been identified as critical factors for receptiveness and implementation by end users. It was noted that for ideas and frameworks such as QbD that emerge from small molecule or other industry applications, special considerations must be given to biological products which may require enhancements or alternatives to accommodate their complexity and unique modes of manufacture.
10. FDA reviewers provided insight into the agency's perspective indicating that specific goal needs to be clearly stated before "fitness for purpose" can be demonstrated for an assay. Also, that ICH, USP, and FDA guidance documents, are recommendations not intended to serve as a how-to guide on assay validation. Furthermore, validation is only one point in the lifecycle and an entire quality control system is needed to ensure appropriate product quality.

Recommendations

1. Bench scientists should actively seek collaboration with CMC statisticians in the formulation of the research question and the design of studies to support conclusions to be drawn. To this end, statisticians must actively and openly listen to the constraints, concerns and specifics of the CMC issues being described. All stakeholders should collectively identify effective ways to improve education and engagement in discussions about how statistics are being used to support CMC development and lifecycle management. This includes statisticians and non-statisticians and for the latter, ensuring sufficient comprehension through highly relevant and clearly conveyed examples. Gaps should be prioritized where training can facilitate faster changes towards better practices for biologicals overall.
2. Increase representation from disciplines outside of statistics and data science to elevate the discussions related to the quality of the underlying research questions and corresponding approaches to address them appropriately. This includes discussions held internally at organizations, conversations between regulators and sponsors and attendance and participation at future CMC Statistics Workshops and other conferences.
3. Industry should be encouraged to take the lead in advancing innovations in statistical and data science tools by engaging early and often with regulators and sharing available data to build knowledge that eventually benefits the field.
4. Regulators should be encouraged to facilitate the paradigm shift towards patient centric specifications by uncoupling process consistency and clinical relevance and working with their global counterparts to achieving greater consensus and certainty for novel approaches that would benefit patients.
5. Reserve Bayesian conferences for exploration and advancement of tools and techniques for statisticians, software developers, etc. and merge Bayesian applications into other industry conferences to increase exposure and advance implementation and acceptance of Bayesian-based strategies by bench scientists and regulatory reviewers (both statisticians and non-statisticians)