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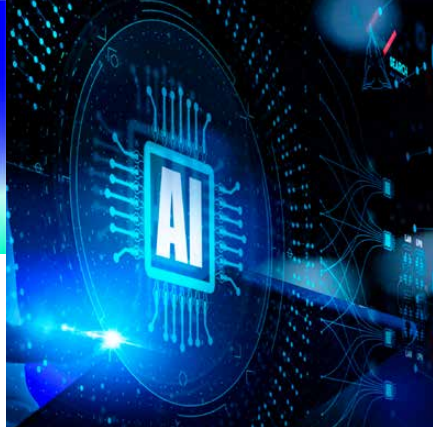

AI Algorithm Qualification for Pharma Manufacturing

How GxP-Compliant SaaS Platforms Facilitate the Process

Introduction

This paper explores a Quality by Design (QbD) approach to applying Artificial Intelligence (AI) in pharma manufacturing, and demonstrates how Aizon's GxP-compliant AI software-as-a-service (SaaS) platform can be leveraged to qualify AI algorithms for pharmaceutical product and medical device productivity chains.

AI algorithms have a valuable role to play in ensuring the quality of manufactured drugs and medical devices in the highly regulated global life sciences industry because they are able to manage multivariable analysis. However, because AI algorithms can be used to make critical decisions during manufacturing processes, they must be qualified to ensure that they enable established manufacturing goals. Until recently, a standard procedure to ensure such algorithm governance did not exist. Aizon qualified the Isolation Forest outlier detection algorithm from an agnostic perspective, enabling the resulting guidelines to be abstracted to other AI algorithms. As a result, for the first time, AI algorithms can be qualified and applied by means AI models as the foundation for decision making to leverage productivity and quality for critical processes in pharmaceutical manufacturing environments.

AI Algorithms Before Qualification

As an engineering discipline of computer science designed to create smart software to think in human-like ways, AI is capable of producing models of aspects related to human cognition. A valuable resource, AI is being adopted by the pharmaceutical industry in a limited mode; to date modest results have been published only in relation to research and clinical trial processes.

However, a new trend of AI adoption is being experimented with at the core of biopharma. Global regulatory bodies have begun examining the use of AI for pharmaceutical environment processes. When the intent is to use AI for critical decision making in drug or medical device manufacturing, the validity of the

associated algorithms require special considerations. In 2019, the FDA published a discussion paper to request feedback in regard to AI and Machine Learning (ML) usage for medical devices, and the European Medicines Agency (EMA) created a special task force to gather opinions from main pharmaceutical stakeholders regarding big data and AI-related technologies and tools.

Qualifying AI algorithms ensures that the algorithm works as expected, consolidating the defined Design of Experiment (DoE) as the evidence for the final model. Qualified AI algorithms yield AI models, which must always be validated prior to final use. However, the fact that the algorithm has been qualified presumes a ready-to-use state, which makes the model validation process easier.

Qualified AI algorithms offer tremendous potential to impact and inform biopharma manufacturing. However, without a single solution or standard procedure to ensure correct algorithm governance, there has been no assurance that AI algorithms are optimized for use.

Factoring in Process Variability

In 2009, the International Conference on Harmonisation's (ICH) second review of the Pharmaceutical Development guideline, known as Q8, described the basis to apply data science approaches in pharma manufacturing as the foundation for decision-making to leverage productivity and quality in production. Prior, in 2005, ICH had published the Quality Risk Management guideline, called Q9. The Q8 and Q9 guidelines shifted away from an assumption of process invariability – one of the main hypotheses applied in the design, implementation and control of pharmaceutical manufacturing since the early ages of this industry. Instead, Q8 and Q9 addressed the inevitability of process variability. Q8 also introduced the concept of QbD, a procedural understanding of medicine development, defining the known and expected targets and highlighting product operations expertise and process control, based on science and quality risk management principles.

The Role of Data Quality

Against this backdrop, the importance of data validity as a prerequisite for AI algorithm qualification becomes even more apparent [Gao et al., 2019]. Raw data used to test AI software must be managed with the same level of exigency as that which is applied in pharmaceutical environments. Applying life sciences verification and validation good practices to data science mechanisms can lead to robust models and solid procedures.

AI systems designed to interpret multivariable scenarios subject to safety, quality and efficacy (SQE) requirements, such as for medical devices or pharmaceutical products, must be trained with high-quality data. Data used to create models for SQE purposes must be well prepared, including a sufficient variety of use cases to cover process experts, regulators and patient expectations. Conversely, the delivery of results simulating human rationality can only meet SQE requirements when they are trained using high quality data, including positive paths, worst case scenarios, bias, and induced errors. If data do not properly cover all the potential scenarios, the training process will generate an incomplete AI model that will not be able to provide the expected accuracy. When data contain all the potential situations, the model will present robust outputs.

Applying GxP-Compliant AI Platform to Algorithm Qualification

The Isolation Forest algorithm was qualified with data generated from equipment designed specifically for this purpose. The equipment was called bigBox (Figure 1).

Fig 1: External bigBox aspect

bigBox allowed interaction between laboratory users and the engine to modify the latter's behavior. The sensors acquiring data from bigBox were connected to Aizon's platform.

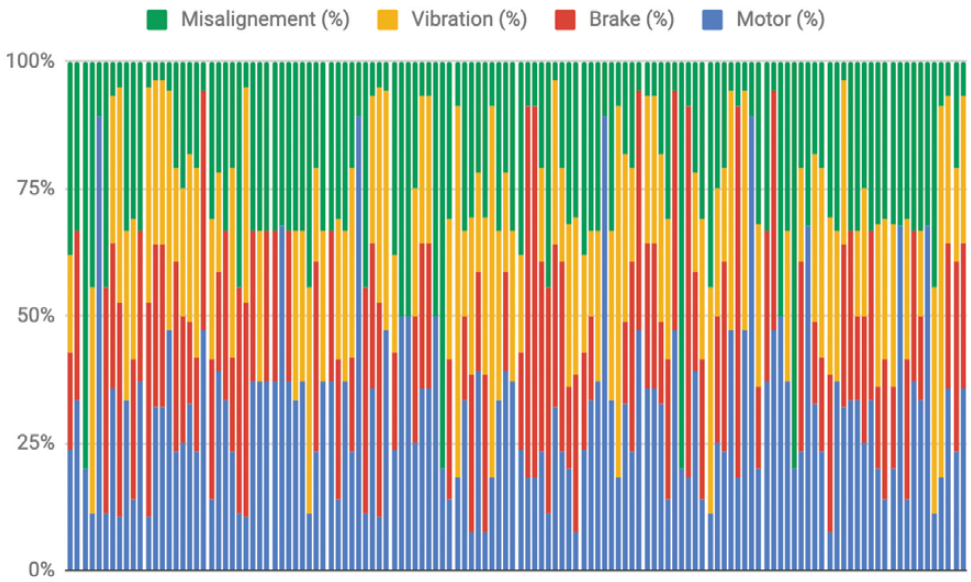

Fig 2: DoE with the 128 replicas (X-axis) corresponding to the 29 categories of experiments where all the meaningful combination of values assigned to each signal (Y-axis) have been configured in order to cover a meaningful spectra of use cases

Real-time data related to four parameters (MS Main, MS Brake, MS Misalignment, MS Imbalance) was sent from bigBox every five seconds. The number of experiments was fairly distributed for each set of values, as shown in Table I and Figure 2, but it is important to note that the research focused on the process itself rather than the data set.

	Fixed value (%)		
Signal	**I**	**II**	**III**
MS Main	25	62	100
MS Brake	0	50	100
MS Unbalance	0	50	100
MS Misalignment	0	0	100

Table I: Distribution of experiments by value ranges organized in three intervals I, II and III. Notice that the misalignment presents a Boolean behavior during the experiment and it only gets two values.

From an experimental point of view, a structured DoE was performed using all the operational ranges of bigBox. Four main elements were considered in relation to describing a standard methodology for qualifying AI algorithm usage:

- → Logic implemented through source code
- → Variables that provide the input and output values (predictors and predicted factors)
- → Data set used during the qualification process
- → Final model or outcome generated by the execution of the algorithm
- → Figures of merit associated with the model

Use of QbD allowed characterization of the algorithm and identification of which designed space areas built into the synthetic data sets performed better.

A New Era

The devised DoE and experiment strategy resulted in a valid qualification for the AI algorithm.

In this case, the DoE was created to include outliers in the experiments because the algorithm being qualified was the Isolation Forest, which is intended to identify outliers from a collection of values using an iterative mechanism of data isolation. Therefore, the conclusions derived from the results could be summarized in Table II.

Input variable	Capacity to detect outliers	Comments
Speed variation	Very high	All the replicas including only speed variation are categorized as outliers
Vibration introduction	Very high	All the replicas including only vibration variation are categorized as outliers
Misalignment	High	2 out of 3 replicas clearly categorized as outliers
Brake	Low	All replicas are below 85% of outliers but above 60%

Table II: Conclusions derived from the abstraction exercise after the results analysis generated by the DoE applied to the Isolation Forest algorithm.

However, since Isolation Forest was used only as an agnostic example in this research, the resulting qualification guidelines can be abstracted to other AI algorithms, opening the door for AI algorithms to be leveraged by pharma manufacturers in relation to productivity and quality decisions.

Conclusion

Data science provides innovative tools to interrogate, analyze and manage data sets generated by complex systems in science. The required accuracy and thoroughness that must be applied within AI model creation has to ensure the expected quality of the results. Though this research specifically qualified the Isolation Forest algorithm, the applied methodology can be extrapolated for the purpose of general AI algorithm qualification to regulated manufacturing environments.

To learn more about qualifying additional AI algorithms, visit https://connect.aizon.ai/ai-algorithm-qualification.html.

References

i. Frankish, K. and Ramsey, W. M. (2014). The Cambridge handbook of artificial intelligence. Cambridge University Press.

ii. AstraZeneca (2017). Artificial intelligence and machine learning: revolutionising drug development. Case study, IMED Annual Review.

iii. Herwig, C., Wölbeling, C., and Zimmer, T. (2017). A holistic approach to production control: From industry 4.0 to pharma 4.0.

iv. ICH, editor (2005). Quality Risk Management Q9, volume Step 4. ICH Harmonised Tripartite Guideline, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

v. Price, W. N. (2014). Making do in making drugs: Innovation policy and pharmaceutical manufacturing. Boston College Law Review, 55(2).

vi. Witjas-Paalberends, E. R., van Laarhoven, L. P. M., van de Burgwal, L. H. M., Feilzer, J., de Swart, J., Claassen, E., and Jansen, W. T. M. (2018). Challenges and best practices for big data-driven healthcare innovations conducted by profit–non-profit partnerships – a quantitative prioritization. International Journal of Healthcare Management, 11(3):171– 181.

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