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Identifying meaningful Targets for complex Lean 4.0 Manufacturing using Business Analytics: A Case Study in Biopharmaceutical Manufacturing

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Abstract

Traditional Lean manufacturing material waste and immaterial (time and effort) reduction targets may not be of significant value for complex manufacturing. A competitive advantage in complex manufacturing lies in the accumulation of process knowledge and leveraging this knowledge to improve performance metrics such as yield. The study demonstrates how Business Analytics using CRISP-DM can extract process knowledge from human experts and historical manufacturing data to provide actionable insights. The study explores how established Lean manufacturing tools such as Standard Work and 5S can be adapted to deploy the Business Analytics recommendations on the manufacturing floor leading to Lean 4.0. The proposed approach is validated on a case study in biopharmaceutical manufacturing, resulting in a 6% increase in product yield. The study discusses how the successful combination of Business Analytics and Lean manufacturing can provide useful process knowledge insights in complex manufacturing through an adapted Lean 4.0 framework to target non-traditional performance measures such as yield.

Keywords: Note; Business Analytics; Lean Manufacturing; Complex Manufacturing; Biopharmaceutical Manufacturing; Process Improvement; Yield Management;

1 Introduction

Complex process-driven manufacturing typically yields high value products such as biopharmaceuticals. However, high process complexity may lead to poor performance during initial production runs, such as failing batch release criteria or low yield. Performance improves as process knowledge is gained over time through continuous improvement. Such process knowledge is an intangible asset that can provide a critical competitive edge [1].

Business Analytics (BA) is an iterative methodical quantitative approach to optimise and enhance business performance. BA uses statistical, machine learning and mathematical optimisation to extract insights from an organization's data. A case study showing a BA application in biopharmaceutical manufacturing is described in [2]. Leveraging BA to build process knowledge offers an exciting opportunity to address gaps to implement business engineering recommendations in Lean Manufacturing (LM) standards [3].

LM is a continuous improvement framework comprised of a suite of tools such as Standard Work to detail the “One Best Way” to complete a task and ensure that all production line operators execute this task consistently [4], 5S to identify root causes of deviations and Continuous Improvement (CI) to address the causes. 5S enables identification of layout errors and parts and components out of place. The tools enable a systematic approach to enhancing efficiency while producing products at a rate that matches customer demand. Lean is "a system that uses fewer inputs to create the same outputs while delivering more value to customers" [4]. LM identifies activities that add value to the customer, while all non-value-adding activities are classified as waste and become targets reduction. Common LM targets are reducing the effort, lead time or resources to complete a task which can provide competitive advantage in high-throughput, capacity-constrained manufacturing. However, these traditional targets are less appropriate for complex manufacturing where batch lead times are fixed by the quality requirements of validated processes [5]. To realize business value in complex manufacturing, reducing effort may translate into a reduction in human resources. This goal is conflicts with Lean principles to respect and the avoid under-utilization of employee skills. Human operators can identify waste and improvement opportunities [6].

Living cells are manipulated by Biopharmaceutical Manufacturing (BM) processes to produce target proteins, which are highly valuable to both companies and patients. . BM components are sensitive to stimuli and conditions, necessitating tight process control through automated Manufacturing Control Systems (MCS), including process step durations .. For example, reaction and fermentation have validated target ranges. Therefore, reducing process step durations in complex manufacturing such as BM falls outside the remit of LM [7].

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The focus of Industry 4.0 (I4) in BM is process optimization [8]. Manipulating rather than just minimizing process step durations could improve yield while complying with regulated ranges, offering financial benefits and a competitive advantage. This is particularly important in BM as companies focus on biosimilars which require faster process knowledge creation. BM generates vast amounts of batch data for both operations management and regulatory compliance. BA can support people such as process scientists and engineers to extract insights from this data to improve process knowledge and identify more meaningful LM targets.

We present a case study of BA in BM. We leverage the organisations' manufacturing data to extract process insights on how to increase yield by manipulating process step durations within the validated range. The reduced ranges are successfully incorporated into Lean Standard Work protocols. This study specifically addresses the following research questions (RQs):

1. Can a BA approach identify refined process durations to improve biopharmaceutical manufacturing yield?
2. Can Lean manufacturing be used to deploy the BA model recommendations?
3. What implications does BA have for I4 and Lean in complex manufacturing?

The structure of the paper is as follows: Section 2 reviews the literature on the deployment of Lean, particularly in complex manufacturing. Section 3 presents the case study on integrating BA and Lean to improve yield in BM. Section 4 presents results and analysis of the case study. Finally, Section 5 discusses how our research approach using BA can bridge the gap between Lean and implementing business engineering recommendations.

2 Literature Review

Lean manufacturing principles are effective in reducing costs by eliminating tasks that do not add value to the customer [4], leading to Lean adoption beyond manufacturing into service industries like IT support [1] and financial services. A successful Lean deployment democratizes problem-solving by placing the responsibility for improving manufacturing processes in the hands of those most familiar with them: the process operators. Early Lean deployments often centralized process improvement responsibilities with project managers, which led to a concentration of Lean expertise in small groups of specialized project managers. Projects were finite and discontinuous, not lending to continuous improvement.

Industry 4.0 (I4) involves integrating equipment and devices with networked sensors and software to predict, control, and improve business. I4 equipment efficiency is enhanced by adding sensors in [9]. However, process variability rather than equipment variability is the root cause of poor performance in complex manufacturing like biopharmaceuticals. I4 generates rich data resources that can be mined for insights using BA. I4 has the potential to drive transformative performance improvements but requires changes in organizational structure and responsibilities, such as adding data scientists [10]. I4 can learn valuable lessons from the initial deployment of LM [11], such as the need to quickly expand the pool of practitioners [12]. Managing this new skill set in manufacturing presents an additional challenge for I4 adoption [12], [13]. Manufacturing companies must increase the number of BA practitioners beyond centralized teams of data scientists [14] to ensure recommendations are implemented by manufacturing teams. Presenting the benefits of implementation as mutually beneficial is crucial, and the contributions of operators must be recognized [15].

I4 can improve Key Performance Indicators for traditional LM targets such as inventory and lead times [16], and can improve predictability of operations in BM [17]. Both LM and I4 must be customized to the manufacturing environment. A case study exploring LM in complex manufacturing of Lockheed's F-22 aircraft reveals how incremental improvements identified through Lean led to quality issues in high-value products: the removal of "tool tries" resulted in final product defects [18]. This underscores the importance of accurately defining "value", understanding operators' expertise and meaningful Lean targets in complex manufacturing. The piecemeal approach to LM may stem from the influence of consulting agencies, which prioritize rapid deployment and short-term gains[9]. LM has evolved from ad-hoc to a more structures framework , and I4 must follow a similar path to achieve sustained efficiency gains .A holistic application across the business/value chain is necessary [19].

There is significant interest in the reasons for the slow uptake of I4 [20] adoption barriers may be cultural rather than technological. There is a lack of understanding of how to use analytics to improve the business in manufacturing [21], [22]. Both I4 and LM frameworks target process improvement, hence an integration of I4 and LM should be considered [2], [23] and BA could be the appropriate bridging mechanism.

A barrier to I4 uptake is capital expenditure for additional sensor equipment [11]. However, the applying BA does not require intensive capital investment [24] particularly in BM where data is already gathered by the MCS to demonstrate regulatory compliance [6]. BA extracts actionable insights from large data sets such as BM data using statistical or machine learning (ML). ML is an effective way to perform complex pattern recognition and regression analysis. The ML model outputs can be used in decision support systems to inform operations [23], [24] Neural networks (NNs) are a type of ML algorithm with excellent predictive power inspired by how the human brain's neurons link together to identify patterns from complex inputs by filtering the inputs through weighted layers and transformation functions [24]. A Multi-Layer Perceptron Neural Network (MLP-NN) is type of NN that performs well when applied to non-linear data such as manufacturing data [2.25,26].

The literature review highlights gaps integrating Lean and I4 and motivates a combined BA/Lean approach to integrate to Lean 4.0. that demonstrates value by identifying appropriate targets for Lean tools. The review shows that there is a need to increase the accessibility of the BA component of I4 and suggests that successful I4 deployment must be tailored for sectors such as BM and be part of a systematic framework rather than ad-hoc project. In the next section the study shows how BA can be combined with established LM approaches to address these gaps.

3 Case Study Methodology

Both I4 and LM frameworks target process improvement but challenges to implement business engineering improvements remain. BA could be the appropriate mechanism to leverage the data gathered by I4 to extract insights for LM improvements. The proposed combination of LM and BA is demonstrated by a successful case study in a large European Biopharmaceutical Manufacturing plant. The study follows the Cross-Industry Standard process for Data Mining (CRISP-DM) [25] shown in Figure 1 which starts at the Business Understanding step.

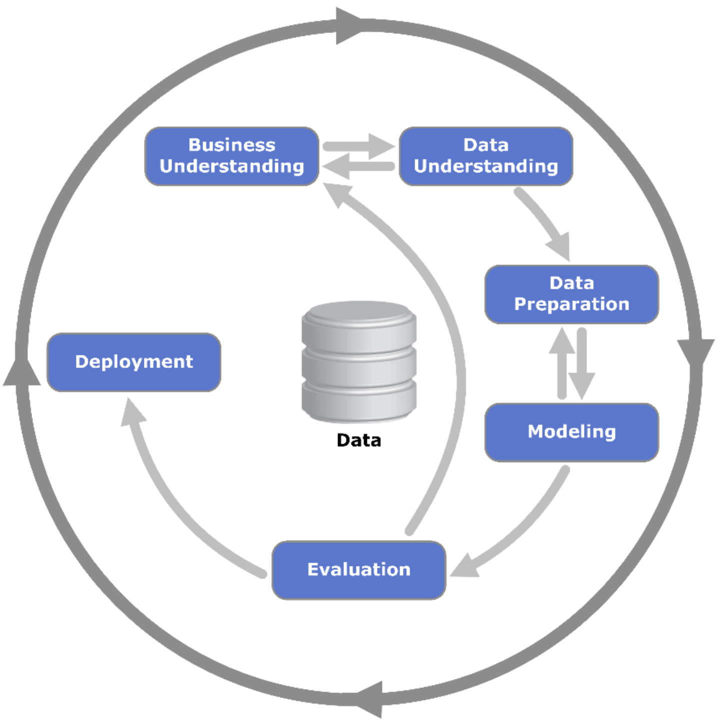

Figure 1: The CRISP-DM approach to Data Mining Source: [25]

3.1 Business Understanding: Competitive advantage in Biopharmaceutical Manufacturing

First, we collaborate with process experts to develop a deep understanding of the business requirements of senior decision-makers, and the dataset available to build the analytics models. The case study BM plant manufactures a broad portfolio of biotherapeutics which are crucial for the treatment of a wide variety of diseases. Three products that had historically demonstrated the highest variability in yield (as measured by Standard Deviation) were chosen as opposed to the products with consistently low yield. The products with the highest variability offered the most interesting opportunity to evaluate the LM/BA framework.

Figure 2 shows the steps in the complex BM process. The multiple (N) biological raw materials are manufactured by fermentation at a different manufacturing plant. Once onsite, the material is thawed and diluted and prepared for the conjugation process by generating an aldehyde functional group by oxidation. This mixture is purified by filtration and joined to a carrier protein that extends the molecules' in vitro half-life. The product is then reduced to the required concentration for formulation and filling. Each batch takes 54 days to complete.

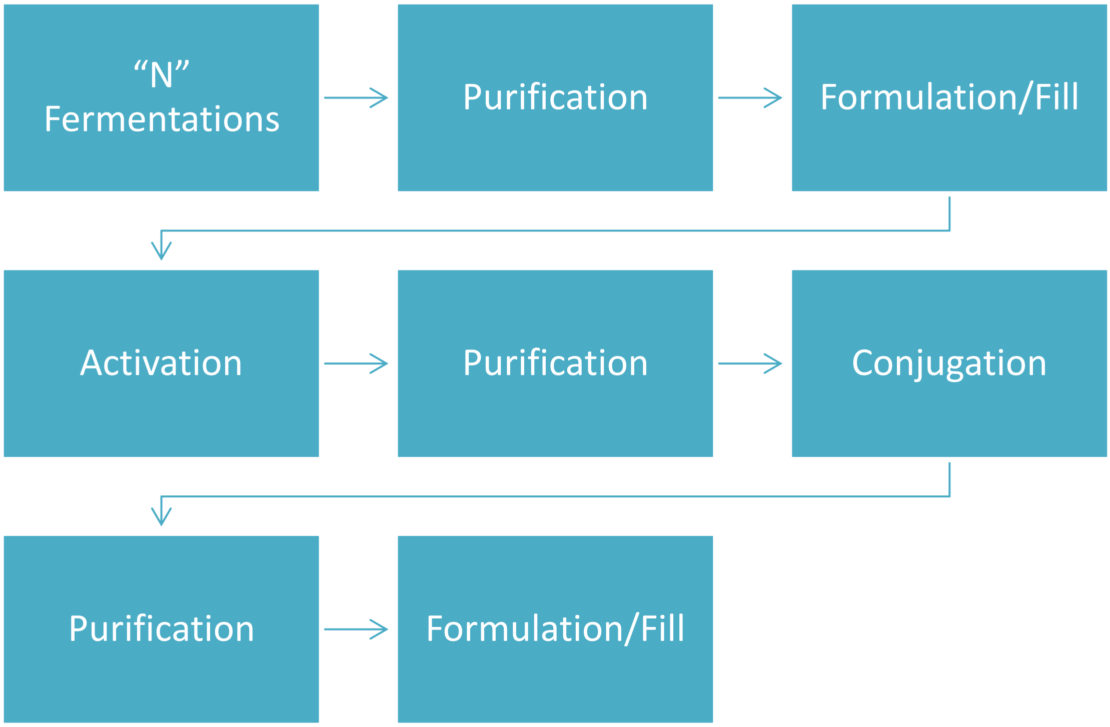

Figure 2: The BM process steps (Source: Authors own)

The interaction of the biological components during processing can result in significant variability in product yield. Process experts were consulted to prioritise which process steps were most likely to influence yield.

3.2 *Data preparation: Focusing on yield and process step durations*

Next, the data are cleaned and prepared for the analytics modelling step. This is done by identifying and correcting (or removing) errors, inconsistencies, and inaccuracies within a dataset. This crucial step in the data management and data science pipeline ensures that the data is accurate, consistent, and reliable, which is essential for effective analysis and decision-making.

The data were sourced from the MCS, which monitors process parameters via multiple network-connected sensors and controllers. This data is required to satisfy regulatory agencies. Figure 3 shows the complete data set of process parameters collected in BM. The process step durations were prioritised for analysis in the Business Understanding step for the LM/BA trial as the dataset is accessible and any insights or patterns are more readily actionable using existing Lean deployments by the operations team with no support required from external functions. The processes have been masked due to commercial sensitivity, but examples include dissolution times of biological raw materials and the duration of reactions. Three years' worth of data encompassing 52 batches with 120 processes' step durations were gathered.

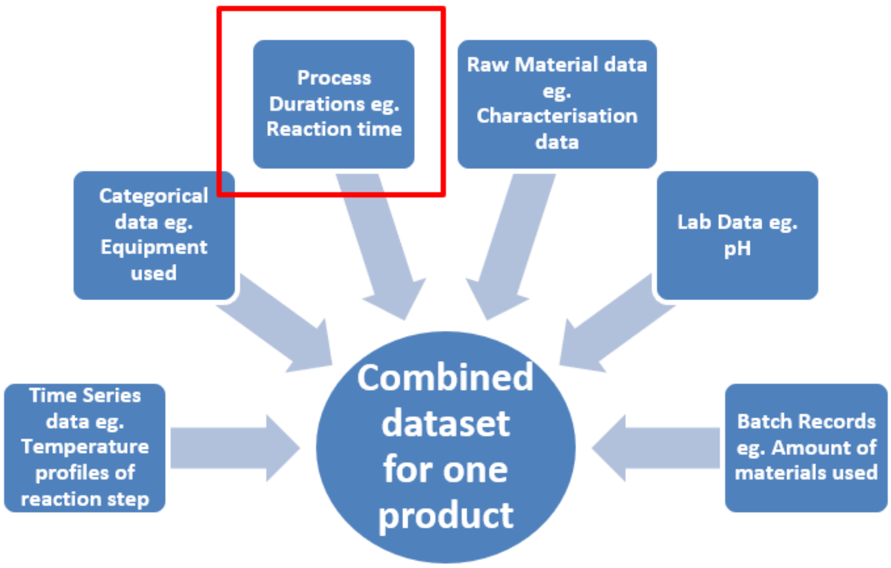

Figure 3. The manufacturing dataset – of which process step durations is a subset(Source: Authors own work)

The MCS also acts as a guide for process operators, indicating when a process step is finished or when action is required to progress the batch. These instructions are referred to as prompts. MCS batch reports include a timestamp for each prompt. The study uses the batch reports to calculate the process step durations by bookending a duration between two prompts. Other durations related to batch quality for process validation, are tracked and recorded automatically. The process step and other duration data were collated into csv files.

3.3 Modelling: Neural Network to predict manufacturing yield from process step durations

Once the dataset was assembled, the next step was to create the NN model with the best fitness parameters in the shortest amount of time. This narrowed the choice of data mining tools to code-free offerings, which can build analytics models using a Graphical User Interface (GUI). Since the study applies Lean philosophy, the customer is not concerned with how the model was created, only the accuracy of its predictions. Therefore, for the purposes of this project, investing time in coding solutions is considered waste. The study used the code-free RapidMiner GUI [3] to create a MLP-NN model. One hidden layer was found to be sufficient to identify the most influential process step durations on yield and the ideal settings within the regulated range, which would result in improved yield.

3.4 Model Evaluation

The accuracy of the NN model was evaluated to ensure no overfitting using 10-fold cross-validation with Root Mean Squared Error (RMSE) as an accuracy measure. This involves dividing the dataset into ten segments. The NN model is trained on nine segments and the accuracy is assessed on the remaining segment. The train/test process is repeated on the ten segments. This simulates how the model will perform on new unseen manufacturing data from 3 high demand products over a 12-week period utilising Standard work and %s which are described later in the paper. The test results are given in Table 1.

Product	RMSE
Product 1	11.2 ±3.5%
Product 2	10.5 ±4.2%
Product 3	8.8 ±3.8%

Table 1: Accuracy of the NN yield prediction model for each product

Considering the NN models are built on a subset of the manufacturing dataset (Figure 3) process experts deemed the NN model accuracy adequate to progress to the pilot phase where the target durations identified by the NN are to be executed on the manufacturing floor.

Product 3 showed statistically significant yield increases during the pilot which are detailed in the Section 4. Due to the limited manufacturing resources available for implementation, the team needed to respond quickly to the results of the pilot. Hence, the study dropped Products 1 and 2 from the Deployment step as no increase in yield were demonstrated after the pilot batch. These products may be revisited once more resources are secured.

3.5 Deployment: Linking Analytics to Lean Manufacturing frameworks

The last, and most challenging phase in the complex manufacturing setting, is the implementation of the NN model recommendations during the deployment phase. This is the challenge that creates the opportunity in this case study – by adapting accepted Lean tools such as Standard Work, 5S and using CI to implement the recommendations. Figure 4 shows how LM is repurposed in our study to improve yield in a complex manufacturing process.

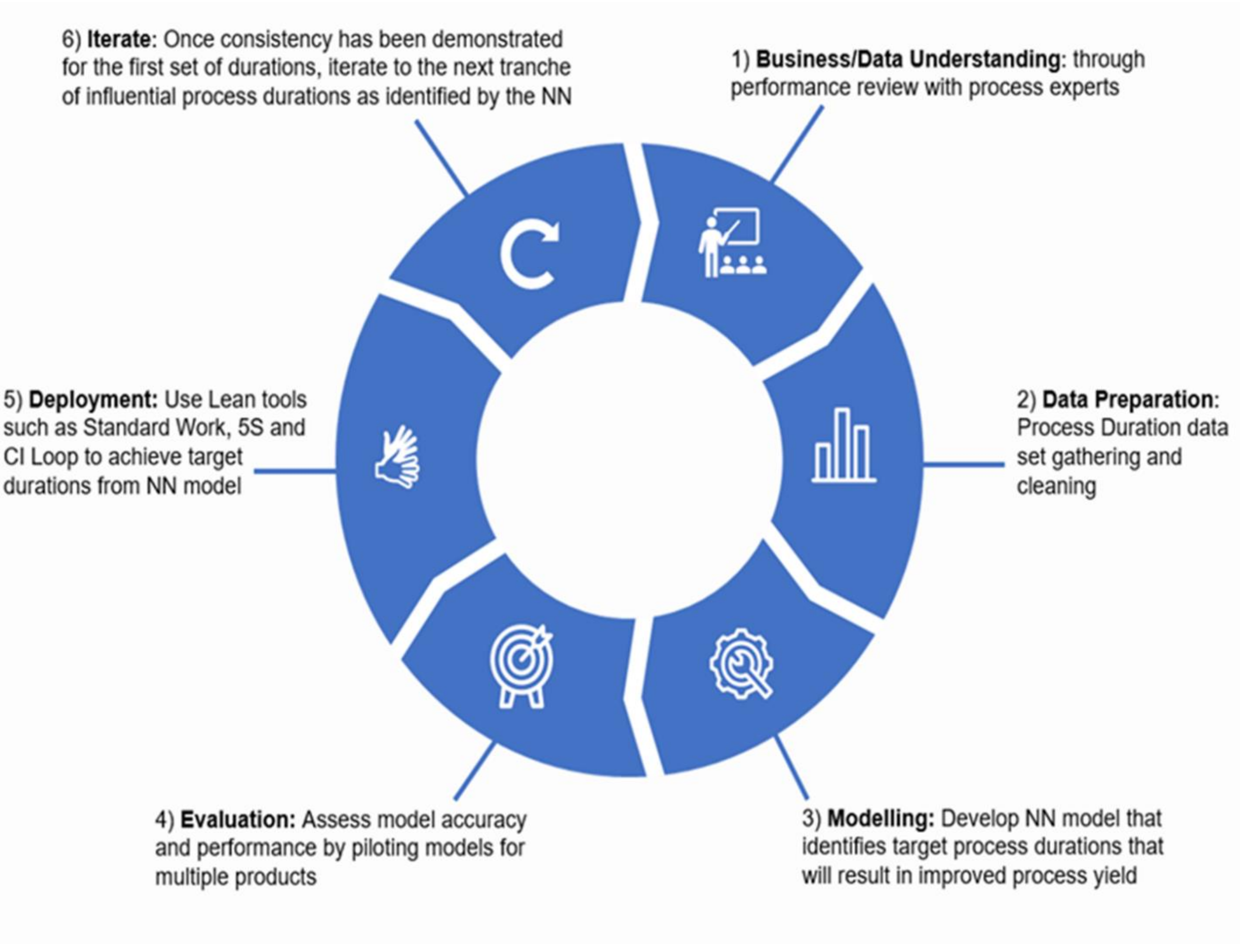

Figure 4: Adapting Lean tools: deploying a BA model to improve process yield in a complex manufacturing process (Source: Authors own work)

A meaningful measure of performance for Standard Work in complex manufacturing is often difficult to identify. Figure 5 shows how the traditional Deming Cycle can be amended to target the recommended process step durations identified by the NN model. Currently, each task is mapped to a process step duration agreed by the team and approved by the regulatory authority for the Standard Work plan,. Our BA approach produces NN model recommendations for modified process step durations that are now are considered the “Plan”.

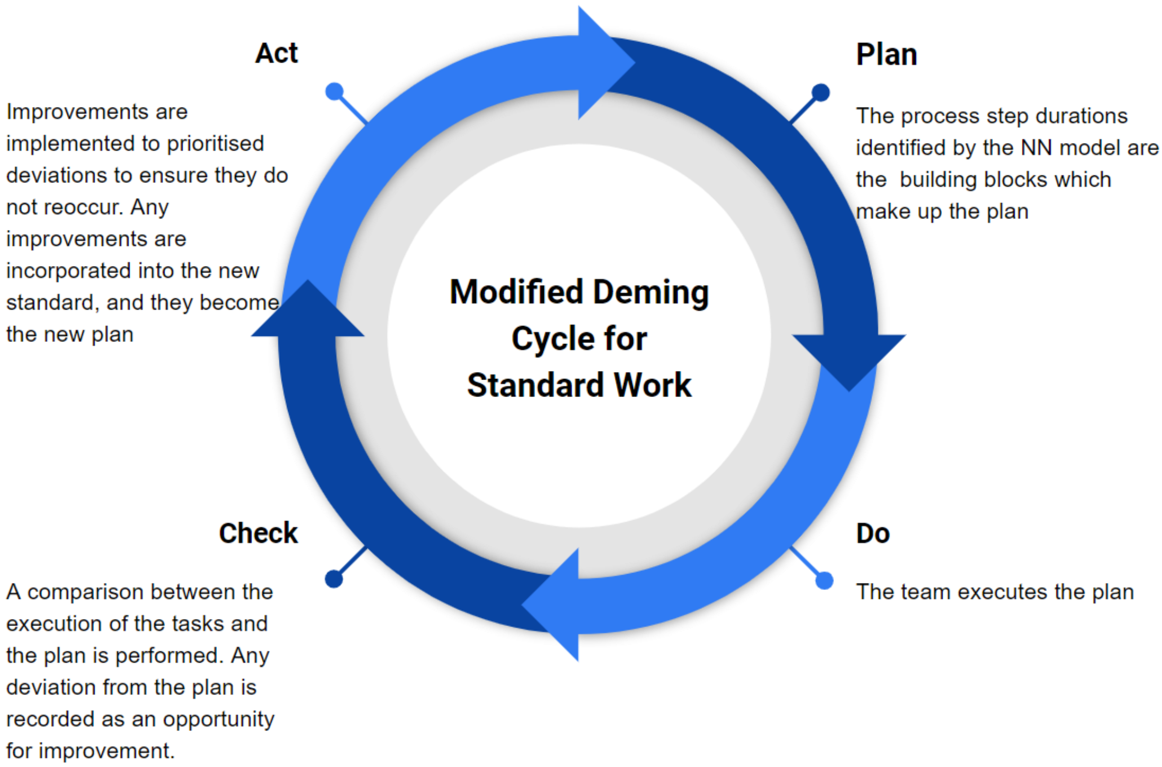

Figure 5: The modified Deming Cycle for Standard Work used to attain the process step durations recommended by the NN model (Source: Authors own work).

3.5.1 Deployment: Visual Management

Performance should be clearly communicated to ensure the improvements resulting from LM are understood by all and hence sustained. Once the Standard Work protocol has been refined, Visual Management is used to monitor and communicate performance against the target durations.. Figure 6 shows a target duration of 90 mins +/- 10 mins for the dissolution time of a raw material. There are a number of deviations from the target in the red section. The reasons for these deviations are recorded and mitigated through the CI loop.

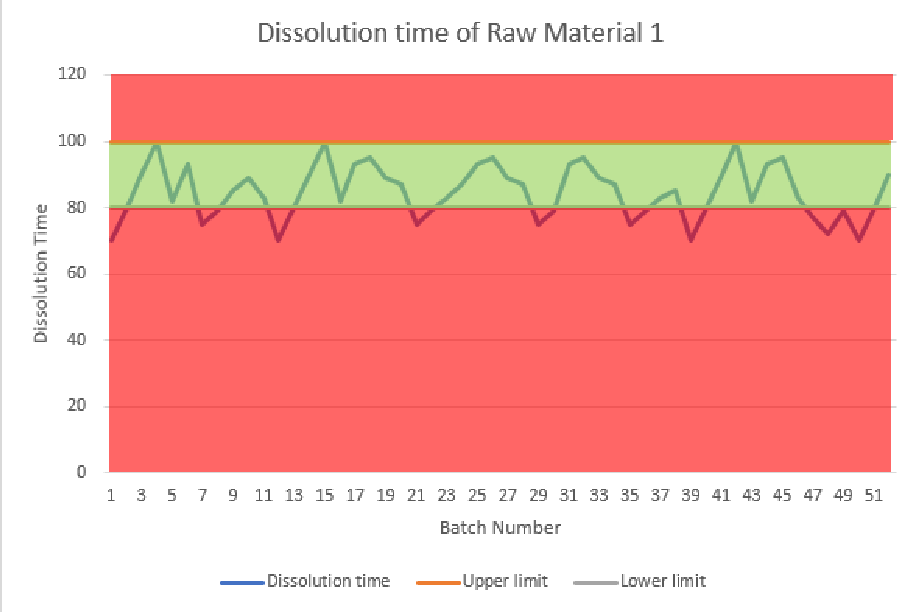

Figure 6: Visual Management of a process duration recommended by the NN model

(Source: Authors own work)

3.5.2 Deployment: Continuous Improvement Loop

Disruption and delays to the production schedule are inevitable in complex manufacturing. The CI Loop strives to the gather, prioritise and mitigate the reasons for disruptions to ensure they do not reoccur.. An example in this study is a member of the operations team not achieving a recommended target duration due to a piece of equipment not being available when required. 5S can address this issue, in this case, tidying the work area to ensure the appropriate piece of equipment is available to allow the durations recommended by the NN model to be set.

3.6 Iterate

Issues preventing the team from achieving the desired process step durations can be identified and addressed through the CI loop. Once consistency is demonstrated, the Standard Work protocols are updated and applied to the next production batch.

4 Results and Discussion

The three research questions answered by our BA/Lean framework are discussed next.

4.1 Can a BA approach identify refined process durations to improve biopharmaceutical manufacturing yield?

A NN model successfully recommended process durations to encode in a modified Standard Work protocol. Note that once the process duration is within its validated range, there is no impact on product quality. Deviations from these target duration ranges affect process efficiency, not product quality. The model can only recommend process step durations from within the dataset used to train it, all of which were within the approved range. No improvement in yield was observed for products 1 or 2 in the pilot and they were de-prioritised. . Improvements were noted for Product 3 and the protocol was used on a further 11 batches as shown in Figure 7. the protocol was evaluated for batches 13 – 26 (between the two red dashed lines). Batches 13 – 15 demonstrate an increase in yield. In order to test the effect, the protocol did not run on batch 16. Figure.7 shows a decrease. The protocol was reintroduced, and a yield increase was observed. This cadence was repeated a further two times. Batches labelled "No Protocol" did not have the modified Standard Work protocol implemented. The highest yield within the study of 78.9% was achieved when applying the NN process duration recommendations through the modified Standard Work protocol.

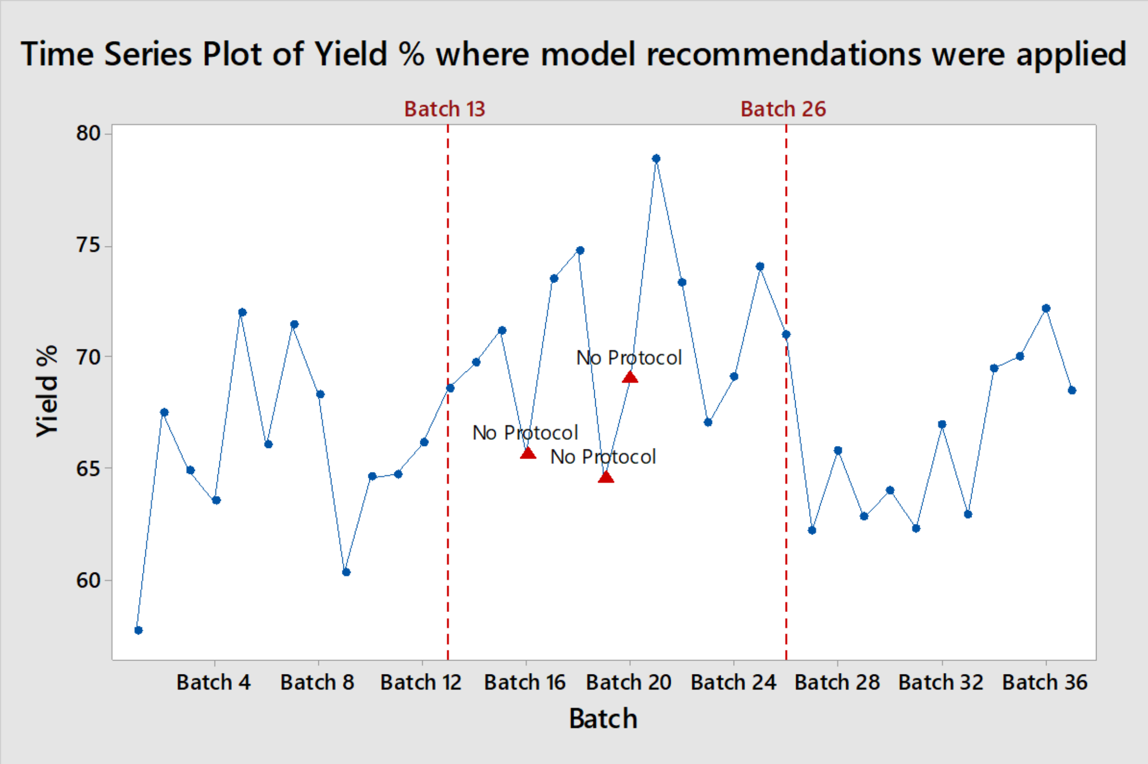

Figure 7: The yield for Product 3 as the experiment progressed. The modified Standard Work protocol was evaluated for 11 batches between the dashed red lines (Source: Authors own work)

An Anderson-Darling test confirmed the yield data followed a normal distribution, see Figure 8. A two-sample t-test confirmed that implementing the NN model recommendations resulted in a statistically significant difference in yield.

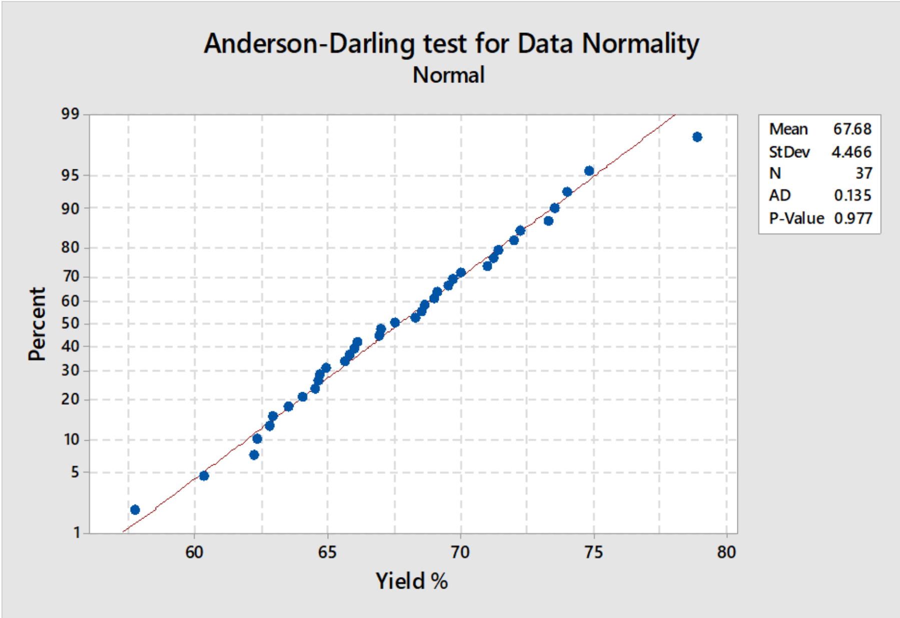

Figure 8: The Anderson-Darling test for data normality showing a p-value above the 0.05 threshold (Source: Authors own work)

Figure 9 and Table 2 show a 95% confidence interval of the mean improvement in the mean yield is 8.6-3.4%. A 6% yield increase of a high-value biopharmaceutical product is a significant economic return. This highlights a very real competitive advantage and shows that a BA approach can identify refined process step durations to improve yield in a complex manufacturing process.

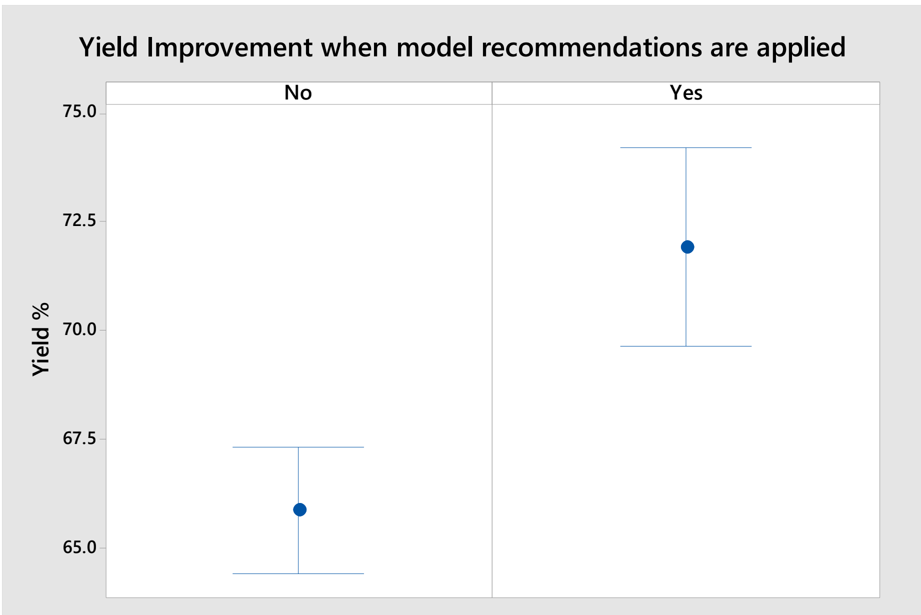

Figure 9: Comparison of batches implementing the protocol recommending the optimal process step durations vs batches without the protocol (Source: Author own work).

Modified Process step durations applied	Number of batches	Mean Batch Yield (%)	StDev	SE Mean
No	26	65.89	3.59	0.70
Yes	11	71.92	3.39	1.0

Table 2: Descriptive statistics showing the difference in Yield (Source: Authors own work)

4.2 Can Lean manufacturing be used to deploy the BA model recommendations?

Section 2 shows that traditional Lean targets might not apply to complex manufacturing. Our study customizes LM in a complex process-driven manufacturing case using BA to identify meaningful Lean targets. Standard Work is a cornerstone of Lean. Modifying process step durations is prioritised over traditional LM goals. Modified durations were successfully encoded in standard work protocols. Issues for failing to achieve target durations are addressed through the Lean Continuous Improvement loop. Examples included bottlenecks of resource capacity and sub-optimal workplace layout. The study shows that LM tools are a ready-made vehicle for BA model deployment. The integration of BA and LM is not a stand-alone project, but rather an iterative framework to address the most persistent process issues. After barriers to achieving one target process duration are addressed using the CI loop, the team progresses to the next significant duration. The combined BA and Lean approach may also spark other ideas from the operations team on how to improve processes.

4.3 What implications does BA have for I4 and Lean in complex manufacturing?

Section 2 explores how Lean and I4 co-exist. Our novel study shows how they can be combined. Manufacturing companies are unsure of I4 first steps. This study shows how value can be achieved without additional costly I4 infrastructure in a complex manufacturing setting. BM is highly regulated, and the sector is understandably conservative in approaches to process improvement [7]. Well-intentioned changes can have unforeseen consequences. By including process experts from the start can mitigate this situation. This case study was implemented by a small team with BA and manufacturing expertise embedded in the manufacturing unit. This provided the analytics team with access to crucial tacit process knowledge and improved the probability of an appropriate BA model. The study shows that BA can combine with Lean to leverage MCS data and demonstrate value for I4.

5 Conclusion

The study proposes a BA informed Lean Standard Work protocol or methodological to rapidly demonstrate the effectiveness of analytics to BM. Each biopharmaceutical production batch is of high value, and low yield is costly. Traditional LM targets are suitable for low-complexity manufacturing. This study demonstrates the combination of BA and LM achieves value in complex manufacturing where there are a high number of interacting biopharmaceutical processes. It shows how BA can extract valuable insights from human operators and historical manufacturing data and successfully adapt LM tools to implement the BA recommendations. This accessible approach to applying analytics to historical data is a key step towards adoption of I4. As with any complex manufacturing sector, the biopharmaceutical industry expends significant resources to capturing large amounts of data. It required no additional I4 infrastructure, improved yield by 6% and maintained regulatory compliance.

This study has implications for the Pharma industry, without approaches such as BA, the process of knowledge residing in people and data remain untapped. To our knowledge, this project is the first to directly improve biopharmaceutical manufacturing yield incorporating insights extracted by BA from a subset of the available data. into Lean Standard Work tools.

A limitation of the study was that small scale of the pilot and test phases. The performance tapered off in the final batches. A future solution is to perform small scale studies before the recommendations are applied to the commercial-scale manufacturing process.

Finally, it should be recognised that although the NN algorithm was deployed using the code free platform RapidMiner, some level of expertise in data science is required to deploy the approach. Other manufacturing projects involving sensor data satisfy the definition of big data and may require deep learning. An important direction for further research is the application of Multi-objective optimisation taking critical quality attributes (CQAs) into account. Solely targeting process duration times to improve yield could potentially result in a deterioration of other CQAs. A BA model which explores the design space of the manufacturing process to return process parameter settings to improve yield while maintaining all CQAs in a desired range is the focus of our next study.

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