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Evaluation of the Impact of Buffer Management Strategies on Biopharmaceutical Manufacturing Process Mass Intensity

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Abstract: There is an increasing demand to improve the overall sustainability of the biopharmaceutical industry. A barrier to improvement has been the limited research undertaken in the area of environmental impact of key design decisions. The aim of this study was to perform a comprehensive evaluation of the impact of buffer management strategy and technology selection on overall process efficiency using process mass intensity (PMI) as a metric for comparison. The environmental impact of buffer management has yet to be fully understood, despite buffers being one of the most resource-intensive aspects of biopharmaceutical manufacturing. A detailed process model was used to evaluate the impact of buffer management on a monoclonal antibody (MAB) process at the 2000 L scale. This was achieved by means of a non-replicated full factorial design composed of six variables: product titre, quantity of unique buffers, preparation frequency, single-use threshold and equipment cleaning duration with two levels and buffer preparation strategy type with four levels. The study identified that buffer management has a critical impact on overall process mass intensity, demonstrating a possibility to achieve a reduction in PMI of up to 90% for the best scenario compared to the worst. The findings also indicated that single-use systems are greatly superior to stainless-steel systems in terms of overall process efficiency, which is consistent with established thinking. The results from this research represent a further significant step towards achieving a more sustainable biopharmaceutical industry, establishing buffer management as a critical focus area, quantifying the influence of key variables on process mass intensity and highlighting the benefits of using a process mass intensity metric as part of routine biopharmaceutical design.

Keywords: buffer management; process mass intensity; biopharmaceutical manufacturing; environmental impact

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1. Introduction

The biopharmaceutical industry is a highly regulated, patient-focused industry, providing great societal benefit through the provision of treatments for a range of illnesses and diseases [1].

Biopharmaceutical manufacturing is extremely resource-intensive, with a waste to product ratio as high as 10,000:1 [2]. This is driven by the extremely large volumes of highly purified water for injection (WFI) required for operating and then hygienically cleaning the process equipment, which is necessary given the risk of cross-contamination.

The advent of single-use technology has had a positive influence, reducing the volumes of WFI used for cleaning. While this provides an overall benefit regarding water usage, substantial quantities of plastic waste are generated per year by the industry [3]. The majority of single-use plastics used by the biopharmaceutical industry are disposed of via incineration or landfill with a relatively small proportion being recycled (mechanically and/or chemically) due to economic and accessibility concerns, as demonstrated by an ISPE industry survey, according to which less than 15% of single-use plastic waste was recycled by the respondents [4]. Additionally, large volumes of highly purified water continue to be used, particularly where limitations of scale apply for single-use technology.

There is an increasing awareness of the importance of environmental considerations within the biopharmaceutical industry, which is being driven by many factors such as corporate responsibility, legislation and the demand to lower manufacturing costs by increasing efficiency. Research relating to the environmental impact of the biopharmaceutical industry is limited, with published research primarily focused on the core process technology. Much of the published research has focused on the evaluation of single-use systems in comparison to traditional stainless-steel systems for the core production process [5–8]. Therefore, there is a relatively poor understanding of the ways in which a process may be optimised to become more sustainable.

The Impact of technology selection has also been evaluated in detail for specific core process unit operations such as the evaluation of fed batch versus perfusion bioreactors [9]. Studies such as these provide interesting insights into technology selection, with findings indicating that single-use technology is superior to traditional stainless-steel systems and that fed batch-based cell culture systems are superior to perfusion-based systems, although limited information is available overall, providing little direction to inform biopharmaceutical design and operation [1]. However, the impact of technology selection for process support areas such as buffer management has been overlooked.

Buffer management in particular offers great opportunities for improvements. Large volumes of buffer are required to support biopharmaceutical production, with 2000 L of buffer typically required for every kilogram of product [10]. Buffers are product mass-based, so as product yield increases, so does the volume of buffer required. Additionally, buffers occupy around 20% of a facility's footprint, similar to that of the entire cell culture process [11]. Given the resource-intensive nature of buffer management, there are many opportunities to increase sustainability, and to achieve this, a greater understanding of the impact of buffer management strategy is required.

Recent years have seen a move toward advanced buffer management strategies such as inline dilution and inline conditioning. Research in the area of buffer management has clearly indicated the opportunities available from both an economic and a facility flexibility perspective [10–12]. While the economic opportunities are well-documented, there has been no detailed research into the environmental impact of various buffer management strategies [13].

Process mass intensity (PMI) has been shown to be a useful metric for the biopharmaceutical industry and is defined as the total mass of materials needed to produce a specified mass of product, providing an easy-to-use, indirect measurement of environmental performance [13,14].

Although environmental performance and impact factors are not directly quantified as with some other methods (such as E-Factor, embodied energy and full life cycle assessment), PMI does provide a clear demonstration of process resource efficiency that may be correlated with environmental impact [15]. A reduction in the resources required to produce a defined quantity of product should result in a more sustainable process with a reduced environmental impact. A key advantage of PMI is the simple nature of the metric which facilities ease of application, thus making it an ideal key performance indicator (KPI) to incorporate into design decision making [16].

Previous studies utilising evaluations of PMI have demonstrated the potential of the metric. Cataldo et al. [17] provided a compressive evaluation of the impact of core process technology, giving insight into the benefit of PMI. Additionally, Madabhushi et al. [15] and Budzinski et al. [16] both completed an evaluation of biopharmaceutical manufacturing processes, identifying opportunities for efficiency improvements and providing a greater understanding of resource usage. While the results demonstrated key opportunities for efficiency improvements, the studies did not consider water consumption for equipment cleaning. The exclusion of water for cleaning represents a key gap in technology evaluation given the stringent cleaning requirements of the industry. While this water does not directly contribute to the final product, its use is a resource-intensive process that has a large impact on the overall sustainability of the process.

This investigation performs a comprehensive evaluation of the impact of buffer management strategy and technology selection on overall process efficiency, considering all material inputs including buffer raw materials, consumables and WFI for cleaning. The work focuses on the area of buffer management, which has not been significantly addressed in prior literature. Buffers, as the largest constituent by volume in biopharmaceutical manufacturing, offer more accessible opportunities for optimisation compared to the core process technology, where the process and regulatory barriers to change are greater. Additionally, buffer management represents a common challenge across the industry and is not product- or facility-specific. Given the changing landscape of buffer management, it is particularly important to foster greater awareness of the environmental impact of technology and strategy selection as the industry develops.

2. Materials and Methods

2.1. Manufacturing Process

The process considered for evaluation is a typical monoclonal antibody process at the 2000 L bioreactor scale, sketched out in Figure 1.

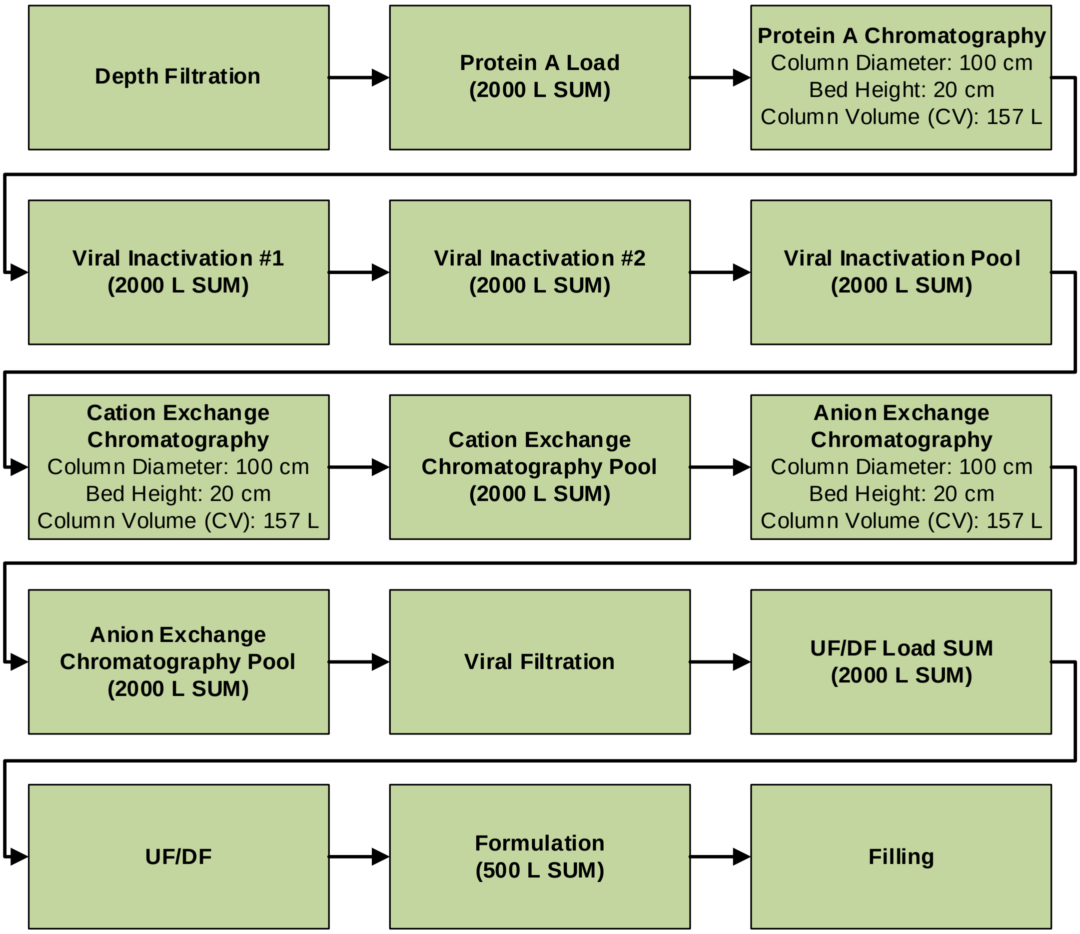

Figure 1. Overview of manufacturing process considered in the study based on standard mAb single-use (SU) BioPhorum TRM process template contained within BioSolve Process (v8.3).

2.2. Experimental Design

In the selection of a buffer management strategy for a manufacturing facility, there are a wide range of considerations and design options.

The influence of buffer management strategy on PMI was assessed by means of a non-replicated full factorial design composed of five variables which were set at two levels each and one variable which was set at four levels. The design required a total of 128 experimental runs of the process model to cover all combinations.

The variables considered included process-driven variables, namely, the product titre and number of unique solutions to be managed for a given process batch. Usually, these parameters cannot be varied independently, as they are driven by process development, but they have a significant impact given their direct influence on both the overall buffer volume required and the number of preparation and holding systems required by the process.

The titre range was selected to represent extremes in process efficiency. Although the process is based on a 2000 L production scale, the higher titre of 10 g/L is representative of a larger stainless-steel process at a lower titre (e.g., 2 g/L at 10,000 L scale). The number of unique buffers was varied to provide a typical quantity difference between two equivalent processes. These were set at two levels, as the process variation is generally linear.

The remaining variables were selected to represent key design decisions made in the development of a buffer management strategy. These are not directly process-related and may be varied independently during the design process.

The single-use threshold, the volume below which preparation and holding systems utilise single-use technology rather than fixed stainless systems, is one of the key facility design criteria. In this instance, a value of 0 represents complete stainless-steel usage for buffer systems (i.e., zero single-use), and 3000 is the threshold volume below which single-use technology is used (i.e., buffers with a volume of 0 to 3000 L are prepared in single-use systems). The value of 3000 L as an upper bound was selected due to limitations in scale of single-use systems.

Additionally, preparation frequency and level of equipment cleaning (rinse time), both have a direct impact on facility design, impacting both preparation and holding systems as well as utility system design. These were set at two levels, given their generally linear impact in all cases. A preparation frequency of 1 relates to a single preparation per batch, with 0.2 representing a single preparation covering a series of five batches. In the case of rinse time, this represents the cleaning time of stainless-steel vessels, with a longer cleaning time resulting in greater WFI consumption.

The sixth variable considered represents the four main buffer management strategy types: traditional, buffer concentrates, inline buffer prep with a buffer kitchen and inline buffer prep on demand.

These four options cover the main technological approaches to buffer management. Traditional buffer preparation is the preparation of a multi-component buffer solution through the hydration of powders at the final required concentration ready for delivery to the process. Traditional buffer preparation can take place using both single-use and stainless-steel systems. Buffer concentrates follows a similar process, except the solution is prepared at a higher concentration than that which is required by the process, and the buffer must subsequently be diluted prior to use. Inline buffer preparation (also known as inline conditioning (ILC) or buffer stock blending (BSB)) is the preparation of buffers in line from concentrated single-component stock solutions. This can take place ahead of time in a buffer preparation area such as a buffer kitchen or can take place on demand with delivery directly to the process with no need for an intermediate buffer hold.

2.3. Calculation of Process Mass Intensity

The BioSolve Process (v8.3) software application from Biopharm Services Ltd. (Chesham, Buckinghamshire, UK) was used to construct a process model to assess the relative performance of buffer management strategies in terms of process mass intensity. BioSolve Process is a user-configurable, Excel-based modelling tool which is widely used within the biopharmaceutical industry. The software includes a full database of equipment, consumables and raw materials used in the industry with information provided directly from suppliers and manufacturers, which means that the underlying information impacting the process mass intensity can be relied upon. Advanced scenario analysis was used to complete the model.

Using the standard mAb single-use (SU) BioPhorum TRM process template contained within BioSolve, the PMI was calculated for each scenario built by all possible combinations of the options detailed in Table 1, taking into account the total mass of the materials needed to produce a specified mass of product. The template process used is available as standard within the software application and is based on the BioPhorum Biomanufacturing Technology Roadmap which includes the basis and assumptions underpinning the template process [18]. The model considered all process materials, including product, media and buffer solutions, and all raw materials, consumables and solutions (primarily WFI) for equipment cleaning. The PMI calculated represents the overall PMI for the process; thus, the determination of an impact of buffer strategy represents the overall impact on the manufacturing process and is not restricted solely to buffer preparation and holding.

Table 1. Investigated variables and levels.

Variable	Factor	Level 1	Level 2	Level 3	Level 4
X1	Strategy Type	Traditional	Buffer Concentrates	Inline Buffer Prep On Demand	Inline Buffer Prep Kitchen
X2	Product Titre (g/L)	2	10		
X3	Single-Use Threshold	0	3000		
X4	Rinse Time (min)	5	15		
X5	Preparation Frequency	1	0.2		
X6	Unique Buffers for Process	11	14		

2.4. Data Analysis

Analysis of the experimental data was completed using JMP v. 16.2. A factorial analysis of variance (ANoVA) was applied to identify main and interactive effects with significant impact on PMI. As there is no error caused by white noise with a set of model data (if the model is run twice, the results are exactly the same), only the effects providing significant portions of the decomposition of the sum of squares were then retained, with the pool of all others then providing an estimate of error for the statistical testing.

3. Results

3.1. Impact of Buffer Management on PMI

The impact of buffer management on PMI was very significant, as shown in Figure 2, which provides a summary of the results obtained in all 128 model runs. For a given product titre, which represents the process scale/yield, there was a large variation in the PMI results observed. This demonstrates the criticality in selecting an appropriate buffer management philosophy for a facility in terms of realising a resource-efficient process. Comparing the minimum and maximum observed PMI values for a given process, there was an approximate 90% reduction in overall PMI in the case of a 2 g/L process and an 80% reduction in PMI in the case of a 10 g/L process between the most efficient and the least efficient management strategies.

The buffer required by the process had a significant impact on the process mass intensity. At the 2 g/L scale, the batch size corresponded to 2.8 kg of product with 4093.4 L of buffer required. As the product titre increased to 10 g/L, the product yield per batch increased to 14.1 kg, with the buffer required increasing to 20,127.6 L. For every 1 kg of product, over 1400 L of buffer was consumed by the process, demonstrating the importance of the buffer in terms of the process mass intensity.

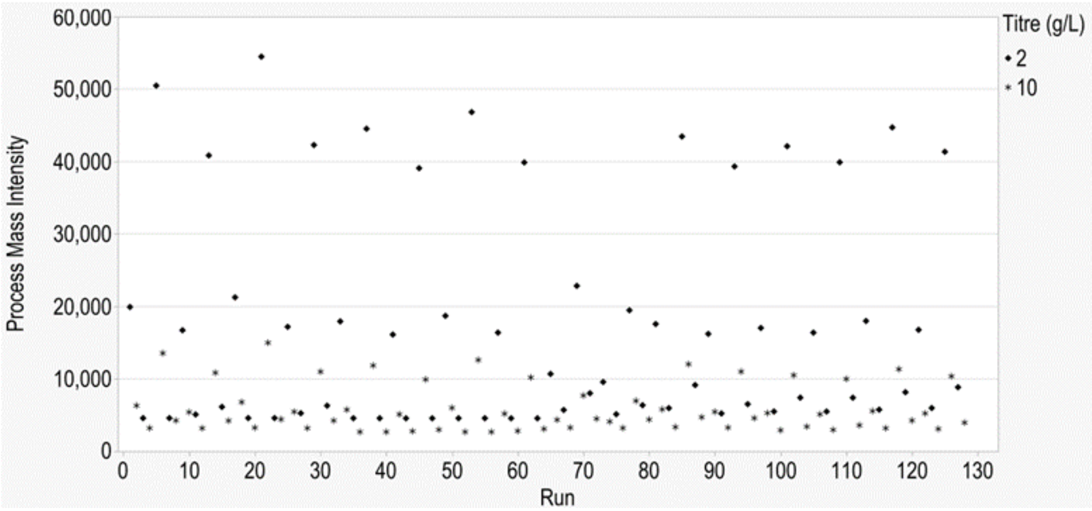

Figure 2. Impact of buffer management philosophy on PMI, demonstrating variation in observed results across all collected data, with outcomes distinguished by product titre.

When preparation and holding systems are included, the importance of buffer management with respect to the process mass intensity increased even further. To prepare and deliver buffers to the process, a higher volume of buffer is required than that which will be consumed by the process. This percentage is known as overage and will vary by facility and preparation system, but an overage in the region of 10–15% is common for traditional buffer preparation systems [19]. In addition, resources are required to support the preparation and storage of buffer systems including plastic associated with single-use systems and WFI associated with the cleaning of fixed stainless-steel systems.

A breakdown of the contributions to PMI is given in Figure 3, with equipment cleaning being by far the biggest factor. This is reflective of the rigorous cleaning requirements of the biopharmaceutical industry and demonstrates the importance of this factor's inclusion within an overall evaluation of PMI.

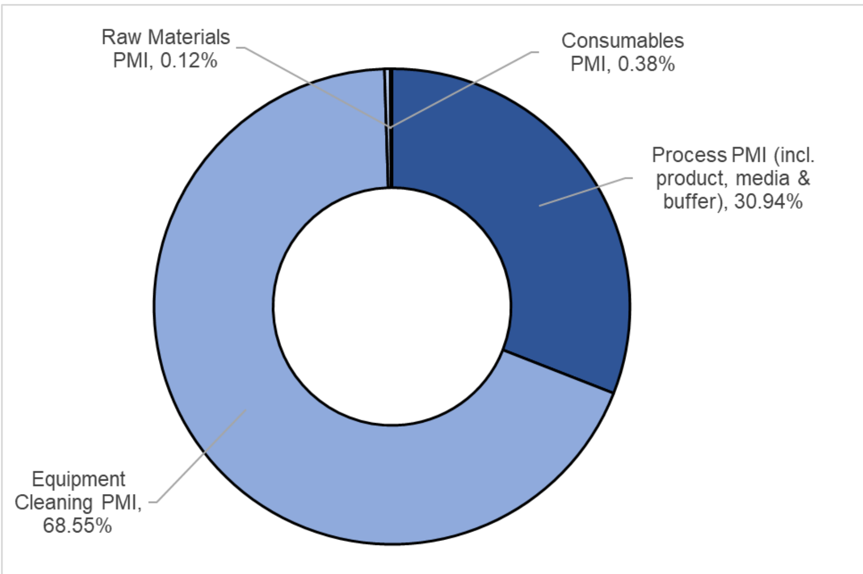

Figure 3. Breakdown of contributions to process mass intensity based on average results from all model runs, demonstrating significance of water required for equipment cleaning.

3.2. Influence of Variables on PMI

Figure 4 provides a summary visualisation of the factorial ANoVA with a pie chart of the decomposition of the sum of squares. As can be seen, the impact on PMI is dominated by the main effects of SU threshold, titre and rinse time, and the two-way interactions between these three variables—jointly, these six effects explained 89% of the total variance of the data. If one were to also consider their third-order interactive effects, these three variables explained 92% of the variance of the data. All other variables, including all interactive effects with them, had a much lower impact compared to these.

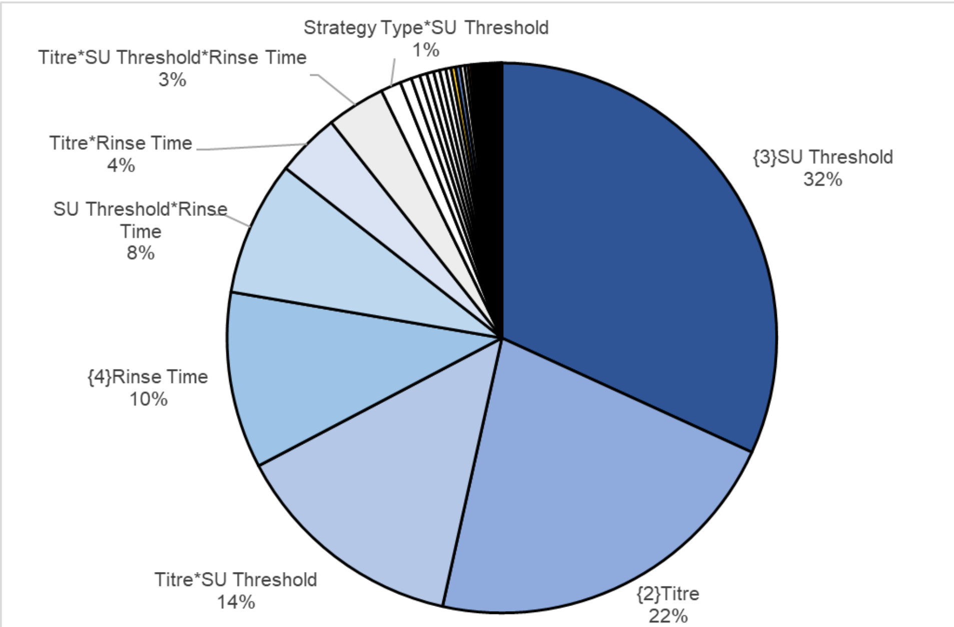

Figure 4. Raw sums of squares explained by all effects shown as percentages of the total sum of squares obtained with all model data (3.62×10^{10}).

While the product titre will be a fixed parameter for a given process, the significance of the single-use threshold demonstrates the importance of maximising the utilisation of single-use technology.

There is a significant correlation between the single-use threshold, rinse time and product titre in the operation of a facility. The quantity of a buffer is directly related to the product titre. As the product titre increases, the volume of buffer increases. As the volume of buffer increases, the necessity of stainless-steel systems increases, as the volumes may not be manageable in single-use systems given the maximum size of commercially available systems. At the point where single-use systems are no longer viable, the rinse time becomes a critical parameter, as the quantity of WFI for cleaning directly contributes to the PMI.

3.3. Single Use vs. Stainless Steel

The single-use threshold was the most influential parameter, with its main effect accounting for almost one-third of the variance of the data. It showed significant interactions with the titre and the rinse time, and therefore its effect is better assessed with the means plots that visualise the two-way interactions shown in Figures 5 and 6. These plots show that while there were significant differences due to titre and rinse time already with the higher SU threshold (3000), the influence of those two variables was much smaller at the higher threshold than it was with the single-use threshold of 0. Thus, a higher PMI corresponded to an SU threshold of 0 primarily and then further increased with the use of the lowest titre and the highest rinse time.

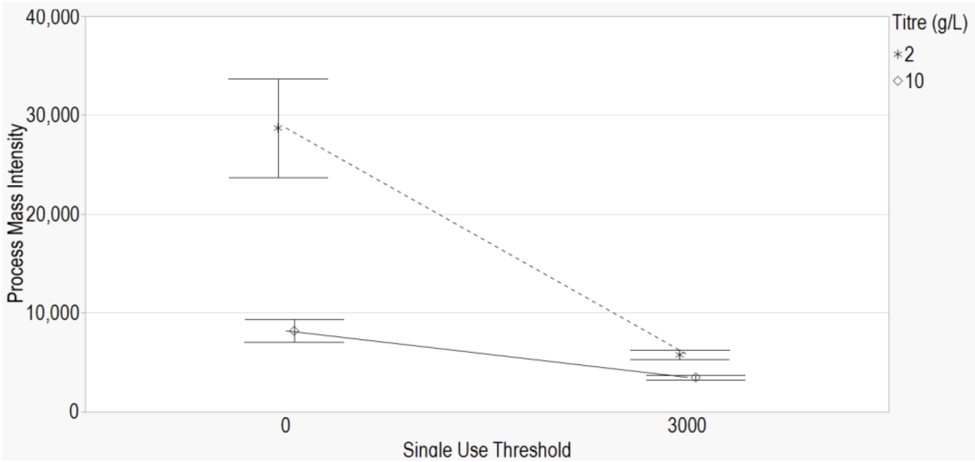

Figure 5. Means plots showing the influence of the single-use threshold at varying product titres on PMI. The error bars show the 95% confidence interval of the means.

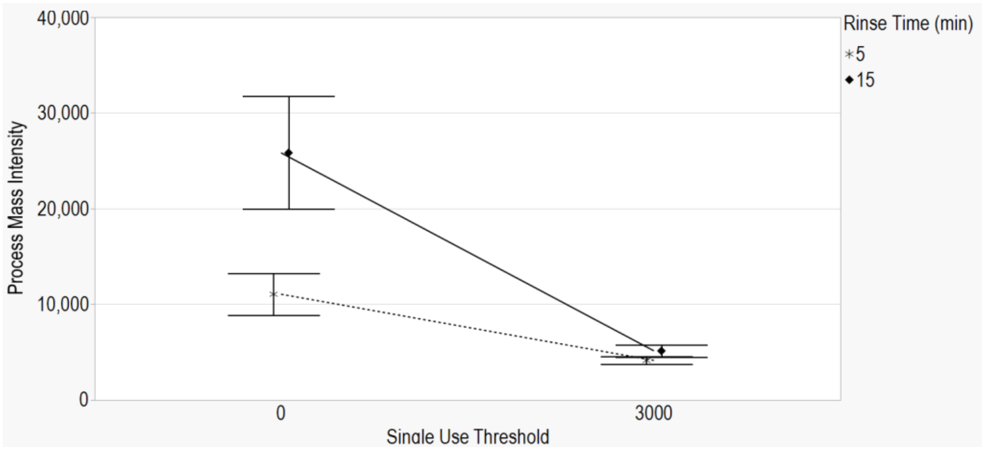

Figure 6. Means plots showing the influence of the single-use threshold at varying rinse times on PMI. The error bars show the 95% confidence interval of the means.

The interactive effects did not cause any flipping (no crossing of the lines in the means plots); the lowest titre and highest rinse time always corresponded to a higher PMI; however, as the SU threshold increased, the overall PMI for the facility decreased, and all the more so the lower the titre and the higher the rinse time. In all cases, a greater utilisation of single-use technology resulted in a lower PMI. The impact of single-use technology increased further as the rinse time for stainless-steel systems increased. This relates to the mass of WFI required for vessel cleaning being much greater than the mass of single-use plastic associated with a mixer or holding bag.

3.4. Single Use vs. Stainless Steel

The SU threshold and the titre on their own explained over two-thirds of the variance of the data (the two main effects and their two-way interaction); thus, the titre was the most important factor after the SU threshold. The volumetric demand for buffer and the quantity of unique solutions required are process-driven variables, influenced by process development. The volumetric demand is directly correlated to the product titre being realised in the production bioreactors, and the quantity of buffers will be identified through the development of the purification process. These process-related parameters are generally not influenced by facility design, as they are fixed parameters for a given process. They do however have a big impact on the overall process efficiency throughout the life cycle of a facility, as shown in Figures 5 and 6.

As the product titre increased, the overall PMI decreased, which resulted in a more resource-efficient process. There is a general industry trend towards increased upstream productivity, which is being realised in the form of increasing product titres. The drive to improve upstream productivity is a result of the need to increase yield and reduce the cost of manufacturing. While an increase in the product titre results in a greater volumetric demand for buffer and presents several challenges for buffer management, it represents an overall improvement in resource efficiency.

The quantity of unique buffers required by a process is of lesser consequence, having shown a negligible impact compared to the three main factors, although it remains an important parameter. As the number of solutions required by a process increases, the quantity of preparation and holding systems also increases, which results in a higher PMI, even if this impact is rather small compared to the impact of the main three variables.

Therefore, during process development the aim should be to maximise the product titre and minimise the number of unique solutions required by the process. This would have a two-fold impact. Firstly, the PMI would be optimised, resulting in a more efficient process, and separately, the cost of manufacture would be reduced as a result of fewer solutions needing to be managed (i.e., less equipment required to support the process and fewer preparations resulting in reduced labour requirements).

3.5. Impact of other Factors

Given the dominance that the single-use threshold and titre had on the results, to fully evaluate the relative importance of the effects caused by the other factors, Figure 7 shows a pie chart with the main and interactive effects of those factors excluded.

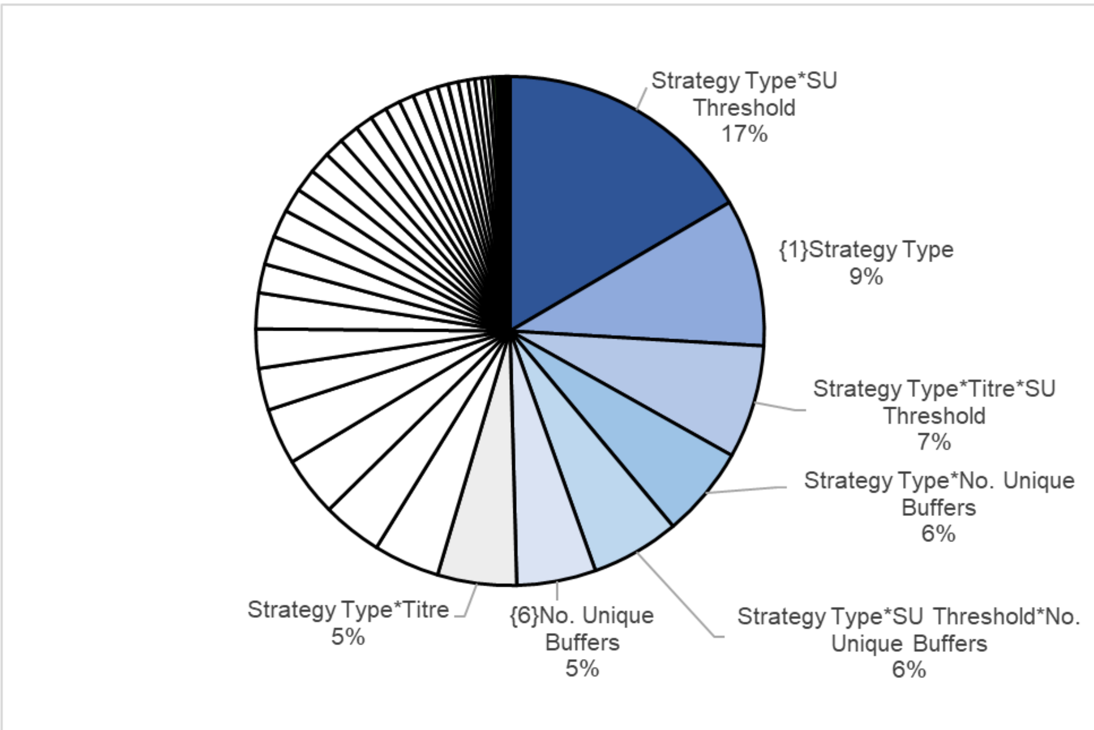

Figure 7. Raw sums of squares explained by all effects shown as percentages of the total sum of squares obtained with all model data, excluding main and interactive effects between SU threshold, titre and rinse time (1.39×10^9).

As shown in Figure 7, which of the four options regarding the strategy type is chosen is the most relevant of the other variables, given its main effect and interactions with the three dominant factors (especially SU threshold). Over one-third of the variance of the data, excluding the portions already explained by the main and interactive effects between the three most influential factors, is explained by the main effect of the strategy type and its interactions with the SU threshold, titre and rinse time. This is of particular importance given that buffer management strategy is one of the key design considerations for a facility.

The means plots of the strategy type and titre given in Figure 8 show that for the highest titre where higher PMI values were achieved, the inline buffer preparation options (whether buffer kitchen or on-demand) led to the highest PMI results. At both the 2 g/L and 10 g/L product titres, the use of buffer concentrates resulted in the lowest PMI values. The use of buffer concentrates reduces the preparation volume of buffer solutions, resulting in a greater utilisation of single-use technology as greater numbers of preparations fall below the single-use threshold. At the 2 g/L scale, traditional buffer preparation resulted in a lower PMI compared to inline buffer preparation, predominantly due to the volumes of WFI required for cleaning of the ILC system. As the product titre increased to 10 g/L, inline conditioning on demand resulted in a slightly lower PMI than traditional buffer preparation. This slight flip between the two options can be explained by the increased buffer volumes associated with the product titre increase, which results in greater utilisation of stainless steel and thus increased cleaning volumes.

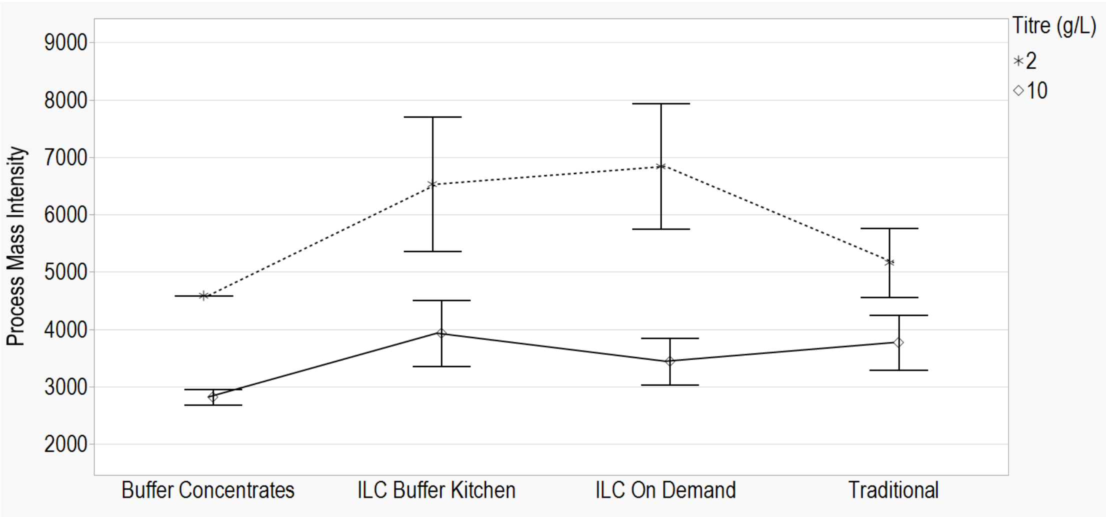

Figure 8. Means plots showing the influence of the buffer management strategy at varying product titres on PMI. The error bars show the 95% confidence interval of the mean.

4. Discussion

The overall PMI results observed in this research are broadly in line with the published literature when relevant exclusions are accounted for. Budzinski et al. [16] pre–ented PMI values in the region of 5000 kg/kg, with one outlier having a PMI of 17,000 kg/kg. These PMI results were for similar-scale processes with bioreactors in the 2000–5000 L scale and with product titres in the range of 2.2–3.8 g/L. Given that water for cleaning was excluded from those reported figures, the comparative results in this research would apply for scenarios with a 2 g/L titre and maximised single-use technology (which limits the water required for cleaning). Where single-use technology is maximised, the PMI results in this study presented an average PMI of 5776 kg/kg, which is comparable.

When single-use technology is not utilised, the average PMI in this research increases to 17,239 kg/kg, with the primary difference being attributable to the water for cleaning. Given that the average PMI increases by over 66% when accounting for water for cleaning, this further emphasises the criticality of including water for cleaning in the research. This also likely explains the conclusion by Budzinski et al. [16] that single-use technology did not have a significant impact on PMI, which contradicts the results of this study and other published life cycle assessments [5–8]. The importance of cleaning is also demonstrated by

Cataldo et al. [17], who found a PMI of up to 10,000 kg/kg at a smaller 1000 L scale, with cleaning representing over 50% of the overall PMI.

The exclusion of cleaning solution in the assessment becomes more impactful at a larger production scale, represented by the 10 g/L case in this research. For a production scale of 500 L, as presented by Madabhushi et al. [15), the utilisation of single-use technology would be expected to be high, and thus the effect of excluding cleaning is lower. As the production scale increases beyond the limitations of scale for single-use systems, the importance of considering cleaning solutions increases further. A failure to account for cleaning solutions may lead to misleading conclusions such as that stainless steel is more efficient than single-use technology, which would contradict the results presented in this research and other detailed life cycle assessments [5–8].

The importance of the buffer management strategy to the PMI has been demonstrated, with opportunities existing to achieve a reduction in PMI of up to 90% when an optimum design is implemented, compared with what would be the worst choice.

The findings reported suggest that the potential benefits of optimising buffer management are of greater significance when compared with previous initiatives such as increasing the product titre, transitioning from fed batch to perfusion, reducing the number of chromatography steps, etc., which presented improvements on the order of 19–40% [13,16]. While it remains essential to optimise the core production process, it has been clearly demonstrated that improvements in buffer management should not be overlooked. A greater focus is required towards the area of buffer management in order to maximise the potential efficiency improvements for the industry.

The impact of buffer management on PMI is influenced by both process-driven variables and facility design considerations. While generally not within the scope of a facility design, initiatives to increase the product titre and reduce the number of unique solutions should continue due to the benefits associated with both the PMI and economic considerations whereby increasing the product titre and reducing the quantity of buffers has been shown to reduce the cost of buffer manufacturing [10]. This illustrates the alignment of economic considerations with increased manufacturing efficiency and reductions in PMI.

The results demonstrate that single-use systems offer the greatest opportunity to reduce water consumption, and consequentially, they vastly outperform stainless-steel systems when used for buffer management. The maximised implementation of single-use systems at a 2 g/L process scale resulted in a PMI reduction of approximately 80% compared to stainless-steel systems. At the 10 g/L scale, the potential reduction associated with single-use systems dropped to 57%, given that greater levels of stainless-steel systems are required to support larger buffer volumes; however, the potential reduction remains noteworthy. Where stainless steel systems are utilised, efforts should be taken to optimise cleaning cycles and reduce the quantity of WFI required for cleaning.

The finding that single-use systems outperform stainless-steel systems aligns with the conclusions of other studies using alternative approaches such as life cycle assessment, where the benefits of single-use systems have been documented [6,20,21]. This is of particular importance, as these studies were focused on the core process, where cleaning requirements are more stringent than those of buffer systems due to the presence of proteinaceous waste, which is more challenging to remove; there is thus a routine requirement for sterilisation. Even with reduced volumes of water for cleaning and a complete absence of steam-in-place sterilisation, it remains valid that single-use systems are superior to stainless steel.

The economic impact of buffer management strategy has been evaluated at length in the literature [10–12]. Buffer management strategy has a significant impact on the capital and operating cost of buffer manufacture. Advanced buffer manufacturing strategies result in considerable reductions in the cost of buffer, with inline conditioning providing the lowest overall life cycle costs. The effect of buffer strategy on PMI is not as impactful as it is from an economic perspective. There is, however, a marginal improvement in PMI with the utilisation of advanced buffer manufacturing strategies, demonstrating the synergy between economic improvements and process efficiencies. The process considered was a 2000 L scale single-use process. For larger scales of manufacture, the use of inline conditioning and buffer concentrates reduces the volumes of buffer to be handled considerably, thus increasing the potential applications of single-use systems, which further increases the PMI potential.

5. Conclusions

PMI as a metric provides an excellent opportunity for incorporation into biopharmaceutical design with relatively little effort to determine it. The outcomes from the PMI assessment may be used to complete a quantitative assessment of the impact of design decisions on process efficiency. There are a number of barriers to the adoption of more sustainable design which include a perception that environmental analysis is highly time-consuming and thus does not lend itself to being a routine design tool. The adoption of indirect metrics such as PMI would go some way to overcoming this barrier.

PMI provides an indirect measurement of environmental performance, and the outcomes generally align with the outcomes of previously published life cycle assessments, comparing single-use and stainless-steel systems. Given that PMI is an indirect indicator of environmental performance, further research is currently underway into the direct environmental impact of buffer management philosophy, which would be of great benefit to further validate the correlation between PMI and environmental performance, particularly because research related directly to buffer management is limited.

This research has provided a comprehensive evaluation of the area of buffer management, which has been overlooked previously. The tremendous optimisation potential of buffer management has been demonstrated, with a reduction in PMI of up to 90% being achievable. The importance of increased single-use technology utilisation in place of stainless-steel systems continues to be valid for buffer systems, even though the cleaning and sterilisation requirements are not as stringent as for core process technologies. This further emphasizes the criticality of considering WFI demands for equipment cleaning as part of any future research.

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Conflicts of Interest: The authors declare no conflict of interest.

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