Design and Implementation of buffer Multi-batch at biopharmaceutical industry.

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Abstract

In this research, an analysis of buffer consumption was performed throughout buffer and FBP manufacturing processes to determine if current buffer batch size of 200 kg or 600kg is enough to prepare more than one FBP batch or if the buffer batch size should be increased. Also, if the proposed multi-batch buffer is a viable option for the manufacturing processes at the studied biopharmaceutical industry. To execute the design and implementation of the buffer multi-batch strategy for the industry, the DMAIC methodology was used, resulting in a reduction of 18hrs per batch of cycle time.

Key Terms — DMAIC, Multi-batch, buffer, consumption.

Background

Epoetin alfa is a medication that helps your body make more red blood cells to treat anemia in patients with long-term serious kidney diseases.

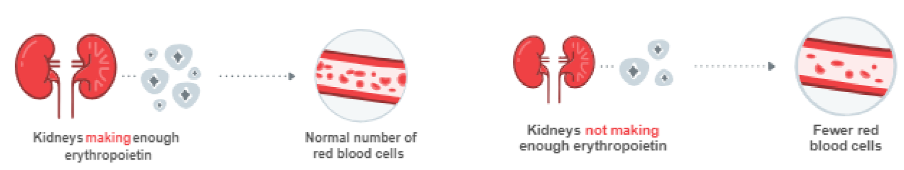

Figure 1: Healthy Kidneys vs Damaged kidneys

In the biopharmaceutical industry studied this product is formulated as a sterile, colorless liquid in vials in multiple formulations and concentrations and currently, the maximum batch size for the examined formulation is 392 kg.

The manufacturing process of Epoetin alfa drug product (DP) starts with the buffer preparation; the formulated buffer is filtered through Posidyne filter to remove endotoxin prior DS dilution step. Then, the Human Serum Albumin (HSA) and drug substance (DS) are added and mixed. Subsequent, the buffer is added to complete to Quantity Sufficient (QS) of the drug product and the mixing tank is pressurized to filter the drug product to the storage tank.

The evaluation of the buffer preparation consists of analyzing samples from unfiltered buffer, such as pH, conductivity, osmolality and filtered buffer, such as Endotoxin and Bioburden.

For what this research concerns, for every Formulated Bulk Product (FBP) one buffer is formulated to be transferred to the formulation suite as shown in Figure 2.

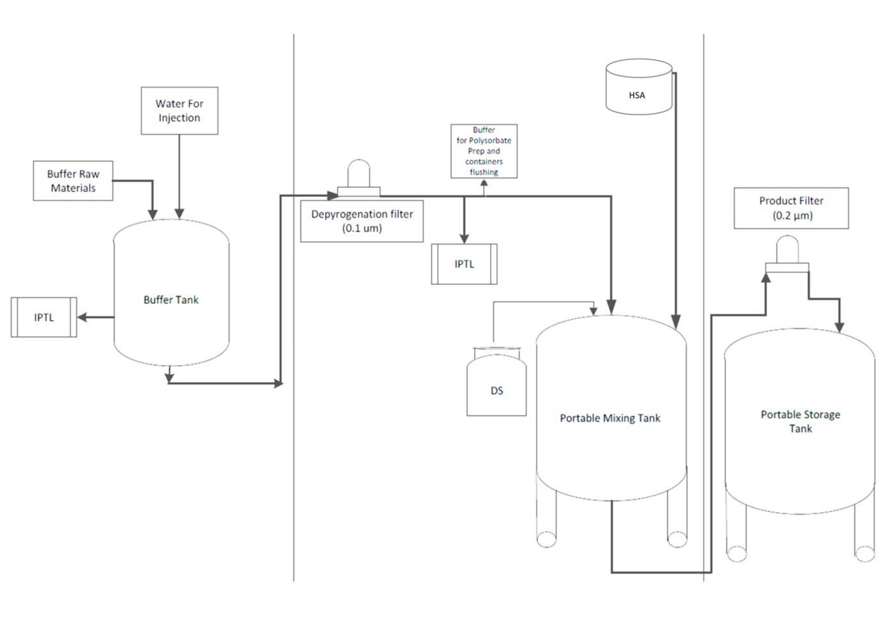

Figure 2.
Formulation process of the FBP.

Problem

Current manufacturing process for buffer and FBP lacks efficiency in the way time and resources are used by preparing one buffer batch for each FBP batch prepared.

With this project, manufacturing processes at the studied biopharmaceutical industry aim to maximize plant capacity and resources by implementing buffer multi-batch mode for the biotechnology product with the generic name of epoetin alfa.

Figure 3.
Actual Buffer Process.

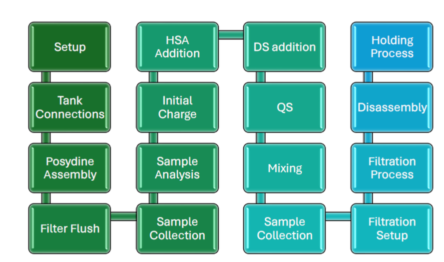

Figure 4.
Actual Steps of the Formulation Process.

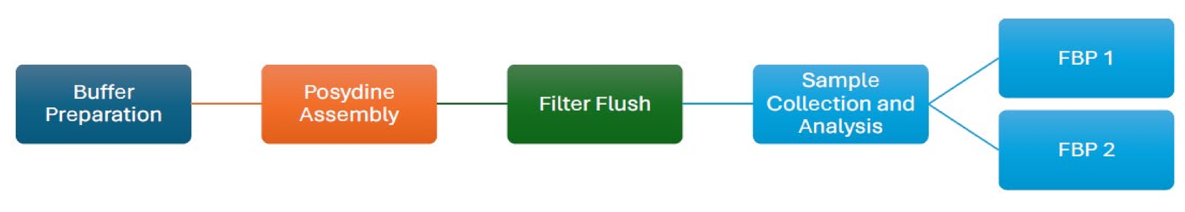

Figure 5.
Proposed strategy of one buffer for two FBP's.

Methodology

To execute the design and implementation of the buffer multi-batch strategy for the studied biopharmaceutical industry, the DMAIC methodology was used.

FBP batches with sizes ranging from 14kg to 392kg of all nine different Drug Product Bulk Potencies (DPBP), were studied to analyze buffer consumption quantities throughout FBP formulation process at the building.

As part of this research, the total amount of buffer consumed throughout the preparation of one FBP batch at the building was divided into two categories:

1. FBP Buffer (FBP_{Buf})- amount of buffer added into the portable mixing tank to formulate one batch of FBP
2. Buffer Losses (BUF_{Loss})- amount of buffer lost throughout the FBP process

The amount of Buffer Losses was also calculated using data retrieved from Data Historian for commercial batches with batch sizes ranging from 14 kg to 392 kg.

Results and Discussion

Current buffer batch size can vary from 200kg or 600kg depending of the original FBP batch size and concentration. A total of 68 buffer batches were formulated in 2023, in the studied biopharmaceutical industry.

In this research it was found, with the buffer batch size of 600 kg is enough to prepare up to two FBP batches if batch sizes combined are equal or less to 400 kg. However, if the combined FBP batch sizes to be prepared is greater than 400 kg, the current buffer batch size of 600 kg will not be enough.

With the buffer batch size of 200 kg is enough to prepare up to two FBP batches if batch sizes combined are equal or less to 30 kg. However, if the combined FBP batch sizes to be prepared is greater than 30 kg, the current buffer batch size of 200 kg will not be enough.

According to results, the amount of buffer consumed during the preparation of two FBP formulations, if batch sizes combined are equal or less to 400 kg with a dose of 40K is approximately 436.87 kg.

The buffer consumed during the preparation of two FBP with the batch size combined of 30kg with a dose of 2K, 3K, 4K and 10K of is approximately 154.91kg.

•Measure: For a FBP Batch size of 14 Kg of the Doses 2K, 3K, 4K, and 10K, the buffer consumption for one FBP and two FBP's is depicted in table 1.1. This shows that 2 FBP's with a Batch size of 14kg consume a maximum of 154.91 Kg of buffer, supporting the theory that a buffer of 200Kg can be used for two formulations of 14 Kg each.

FBP Batch size: 14 Kg								
Dose	DPBP	Kg_{DS}	Kg_{HSA}	Kg_{BUF}	$Kg_{Buffer\ losses}$	$Kg_{Safety\ factor}$	1FBP $Kg_{total\ BUF}$	2 FBP $Kg_{total\ BUF}$
2K	0.01250	0.14	0.48	44.38	46.15	20	90.53	154.91
3K	0.01875	0.21	0.48	44.31	46.15	20	90.46	154.77
4K	0.02500	0.28	0.48	44.24	46.15	20	90.39	154.62
10K-SD	0.06250	0.70	0.48	43.82	46.15	20	89.97	153.78
10K-MD	0.06250	0.70	0.48	43.82	46.15	20	89.97	153.78

Table 1.1 Buffer Consumption of FBP Batch size 14Kg

For a FBP Batch size of 80 Kg of the Doses 2K, 3K, 4K, and 10K, the buffer consumption for one (1) FBP and two (2) FBP's is depicted in table 1.2. This shows that 2 FBP's with a Batch size of 80kg consume a maximum of 227.88Kg of buffer, supporting the theory that a buffer of 600Kg can be used for two formulations of 80 Kg each.

FBP Batch size: 80 Kg								
Dose	DPBP	Kg_{DS}	Kg_{HSA}	Kg_{BUF}	$Kg_{Buffer\ losses}$	$Kg_{Safety\ factor}$	1FBP total BUF	2 FBP total BUF
2K	0.01250	0.26	0.88	80.87	46.15	20	127.02	227.88
3K	0.01875	0.38	0.88	80.74	46.15	20	126.89	227.63
4K	0.02500	0.51	0.88	80.61	46.15	20	126.76	227.37
10K-SD	0.06250	1.28	0.88	79.84	46.15	20	125.99	225.83
10K-MD	0.06250	1.28	0.88	79.84	46.15	20	125.99	225.83

Table 1.2 Buffer Consumption of FBP Batch size 80 Kg

For a FBP Batch size of 392 Kg of the Dose 10K and 20K, the buffer consumption for one (1) FBP and two (2) FBP's is depicted in table 1.3. This shows that 2 FBP's with a Batch size of 392kg consume a maximum of 829.5112 Kg of buffer, supporting the theory that a buffer of 600Kg cannot be used for two formulations of 392 Kg each.

FBP Batch size: 392 Kg								
Dose	DPBP	Kg_{DS} (E2)	Kg_{HSA} (E3)	Kg_{BUF} (E4)	$Kg_{Buffer\ losses}$	$Kg_{Safety\ factor}$	1FBP total BUF	2 FBP total BUF
10K-SD	0.06250	6.13	4.19	381.68	46.15	20	427.83	829.5112
10K-MD	0.06250	6.13	4.19	381.68	46.15	20	427.83	829.5112
20K-MD	0.12500	12.25	4.19	375.56	46.15	20	421.71	817.2612

Table 1.3 Buffer Consumption of FBP Batch size 392 Kg

For a FBP Batch size of 200 Kg of the Dose 40K, the buffer consumption for one (1) FBP and two (2) FBP's is depicted in table 1.4. This shows that 2 FBP's with a Batch size of 200Kg consume a maximum of 436.87 Kg of buffer, supporting the theory that a buffer of 600Kg can be used for two formulations of 200 Kg each.

FBP Batch size: 200 Kg								
Dose	DPBP	Kg_{DS} (E2)	Kg_{HSA} (E3)	Kg_{BUF} (E4)	$Kg_{Buffer\ losses}$	$Kg_{Safety\ factor}$	1FBP total BUF	2 FBP total BUF
40K	0.25000	12.50	2.14	185.36	46.15	20	231.51	436.87

Table 1.4 Buffer Consumption of FBP Batch size 200 Kg

•Analyze: The multi-batch approach is expected to result in more lots and shorten the formulation process' cycle time. The procedure was challenged following implementation, and the outcomes showed a high percentage of multi-batch approach viability, supporting the validity of the hypothesis.

•Improvement: With the implementation of the multi-batch strategy, a reduction of 18 hours to start the second batch will be seen. Regarding to costs, with a reduction of 20 buffers in the year, a total of $19,269.43 will be saved.

Process	Time (Hours)
Rinse/CIP	3
SIP-TK	3
SIP-TL	3
Buffer	2
IPTL	3
LAL sample	1
LAL test	3
Total	**18**

Table 2: Repeated steps to start second batch

Buffer size		Costs	Savings	
200	SD-200	$ 140.68	12	$ 1,688.16
600	SD-600	$ 353.92	2	$ 707.84
	MD-200	$ 788.49	3	$ 2,365.47
	MD-600	$ 2,363.11	2	$ 4,726.22
	SD_{PO4} - 200	$ 263.94	1	$ 263.94
	Filters	$ 634.26	10	$ 6,342.60
	Hoses	$ 158.76	20	$ 3,175.20
			Total	$ 19,269.43

Table 3: Savings in cost

•Control: Following the creation of the change control, the new recipe was developed to meet all the requirements, including SOP revision, system optimization, associate training, and new recipe production. To incorporate the information that has been validated without affecting the validation process, the recipe was built considering every risk assessment and critics parameter. Following implementation, a standard work was developed to assess the enhancement and ensure that the operator continued to follow the standard work.

Conclusions

In this research, a new buffer multi-batch strategy was introduced, to reduce cost and improve efficiency in the Formulation area for the problem stated. With this approach, plant capacity and resources were maximized in the area making the project successful. The area profits from project improvement in terms of decreased cycle time, greater labor usage, and accessibility to equipment. The advantages related to process and area agility and efficiency. We can come to a successful conclusion by completing all the phases that the DMAIC approach demands.

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References

1. Arafeh, M., Barghash, M. A., Haddad, N., Musharbash, N., Nashawati, D., Al-Bashir, A., & Assaf, F. (2018). Using Six Sigma DMAIC Methodology and Discrete Event Simulation to Reduce Patient Discharge Time in King Hussein Cancer Center. *Journal of healthcare engineering*, *2018*,3832151. https://doi.org/10.1155/2018/3832151
2. Dammacco, F., Castoldi, G. and Rödjer, S. (2001), *Efficacy of epoetin alfa in the treatment of anaemia of multiple myeloma. British Journal of Haematology*, 113: 172-179. https://doi.org/10.1046/j.1365-2141.2001.02715.x
3. Graduate School. (n.d.). Retrieved from http://www.pupr.edu/academics/graduate-school/ Maverickjiang. (2012, Mar 13). Learn how to write scientific papers in under 4 minutes. [video file] Retrieved from https://www.youtube.com/watch?v=Soit1wG_GCQ
4. Timothy Littlewood & Graham Collins (2005) Epoetin alfa: basic biology and clinical utility in cancer patients, Expert Review of Anticancer Therapy, 5:6, 947-956, DOI: 10.1586/14737140.5.6.947