Design and Implementation of Buffer Multi-batch in the 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 the 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 in 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 18 hours per batch of cycle time.*

Key Terms *— Buffer, Consumption, DMAIC, Multi-batch.*

PROBLEM STATEMENT

In the studied biopharmaceutical industry, the current manufacturing process for buffer and Formulated Bulk Products (FBP) lacks efficiency in the way time and resources are used by preparing one buffer batch for each FBP batch. With this project, manufacturing processes in 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.

RESEARCH DESCRIPTION

With this research, an analysis of buffer consumption throughout buffer and FBP manufacturing processes to determine if the current buffer batch size of 200 kg or 600kg is enough to prepare more than one (1) 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.

RESEARCH OBJECTIVES

The objective is to meet a predetermined customer service level, which is defined as the long-run percentage of time that incoming customer orders can be delivered from the finished goods stock.

It is expected to maximize plant capacity and resources by implementing the multi-batch mode.

RESEARCH CONTRIBUTIONS

Cost efficiencies are important because they facilitate ways for a company to become more profitable by maximizing the company's capability. For this, it's needed to create added value to the company's existing products and to invest in ways to innovate the organization and maximize production.

This research aims to reduce cycle time, reduce costs, and improve productivity.

LITERATURE REVIEW

Epoetin alfa is a 165-amino acid erythropoiesis -stimulating glycoprotein manufactured by recombinant DNA technology (rHuEPO) that is produced by mammalian cells into which the human erythropoietin gene has been introduced [1]. The product contains the identical amino acid sequence of isolated natural erythropoietin. [2] Erythropoietin sends a signal to our body to make more red blood cells.

This product is formulated as a sterile, colorless liquid in vials in multiple formulations and concentrations: Single Dose (SD) Phosphate in 40,000 U/mL, Multidose (MD) Citrate in 10,000 U/mL and 20,000 U/mL and Single Dose (SD) Citrate in 2,000 U/mL, 3,000 U/mL, 4,000 U/mL and 10,000 U/mL. Epoetin alfa drug substance (DS) is produced at the biopharmaceutical industry

studied and refrigerated (2° to 8°C), protected from light in 1 L Teflon container.

The manufacturing process of Epoetin alfa Drug Product (DP) starts with the buffer preparation. The formulated buffer is filtered through a 0.1 µm Posidyne filter to remove endotoxin prior DS dilution step. Then, the Human Serum Albumin (HSA) and DS are added and mixed. Subsequently, the buffer is added to complete the 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 buffers, such as pH, conductivity, and osmolality, and filtered buffers, such as Endotoxin and Bioburden.

The in-line filtration step requires that the formulated bulk is filtered twice. Following formulation, the bulk is filtered and held in a pressure vessel. The final sterile filtration is done in-line at the point of use during the filling process. The first filtration uses the same filter material as the one used in the final sterile filtration. The filter size, however, is different. For the 10-inch filter, the filtration area used in the first filtration is approximately 2.5 times larger than the 5-inch filter used in the second filtration. Currently, the maximum batch size for the examined formulation is 392 kg.

For what this research concerns, for every FBP, one buffer is formulated to be transferred to the formulation suite, as shown in Figure 1.

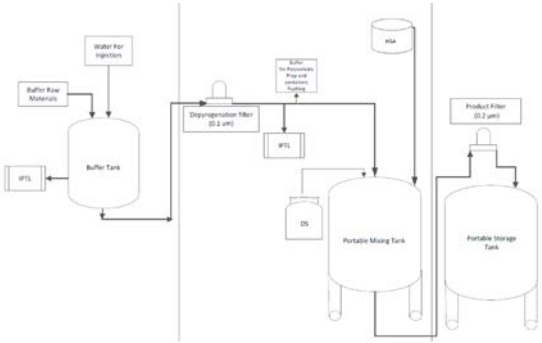

Figure 1
Formulation Process of the FBP

Figure 2 explains in a visual way the steps for the buffer process. Tank preparation is the cleaning and sterilization of the tank and transfer line, which takes approximately nine (9) hours to execute. From buffer setup through sample collection, it takes approximately two (2) hours to complete the steps, and the sample analysis takes approximately one (1) hour to obtain the desired results to execute the buffer transfer to the formulation suite.

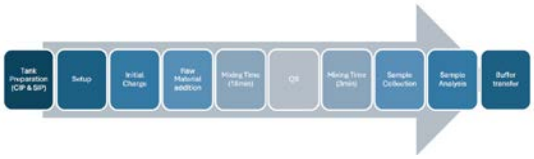

Figure 2
Actual Buffer Process

Figure 3 explains the detailed steps of the actual formulation process after the buffer preparation, from setup to the holding process. This explanation is necessary to understand how the consolidation of the process is taking place.

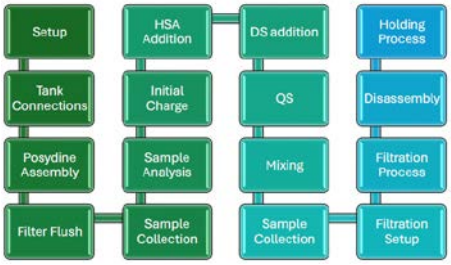

Figure 3
Complete Steps of the Actual Formulation Process

Figure 4 is the proposed strategy of one buffer for two FBPs. The diagram explains how the process is going to work with the consolidated steps. The buffer preparation process stays the same as in the formulation suite, the consolidated steps are the posydine filter assembly, filter flush, sample collection, and analysis. After these steps are executed, the formulation of the FBP 1 can be started and completed; with the completion of the FBP 1, FBP 2 is going to start in the initial charge step of the formulation process.

Figure 4
Proposed Strategy of One Buffer for Two FBP

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 (9) 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}) – the amount of buffer added into the portable mixing tank to formulate one batch of FBP
2. Buffer Losses (BUF_{loss}) – the amount of buffer lost throughout the FBP formulation process in the following process steps: Posidyne filter flush, transfer line buffer holdup (during buffer transfer from fixed tank to portable mixing tank), and Sampling (pre-filtered and post-filtered).

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. The data includes buffer tank initial and final weights, portable mixing tank weight after buffer initial charge, portable mixing tank weight after additions of drug substance and HSA, and portable mixing tank weight after FBP formulation is complete.

The number of buffer losses (BUF_{LOSS}) can be estimated based on the total buffer used in the formulation process minus the amount of buffer used in the actual product (FBP_{BUF}), as expressed in equation 1:

$$BUF_{LOSS} = \text{Total buffer} - FBP_{BUF}. \quad (1)$$

The total amount of buffer used throughout the process was determined with equation 2, the difference between the buffer preparation fixed tank initial and final weights.

$$\text{Total Buffer} = FT_i - FT_f \quad (2)$$

The amount of buffer used in the actual product (FBP_{BUF}) was calculated by adding the buffer initial charge and the quantity sufficient (QS)1 with equations 3 and 4.

$$FBP_{QS} = MT_{QS} - MT_{HSA} + DS \quad (3)$$

$$FBP_{BUF} = MT_{IC} + FBP_{QS} \quad (4)$$

RESULTS AND DISCUSSION

The current buffer batch size can vary from 200kg to 600 kg depending on 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 that the buffer batch size of 600 kg is enough to prepare up to two (2) FBP batches if batch sizes combined are equal to or less than 400 kg. However, if the combined FBP batch sizes to be prepared are greater than 400 kg, the current buffer batch size of 600 kg will not be enough. The buffer batch size of 200 kg is enough to prepare up to two (2) FBP batches if batch sizes combined are equal to or less than 30 kg. However, if the combined FBP batch sizes to be prepared are greater than 30 kg, the current buffer batch size of 200 kg will not be enough.

According to the results, the amount of buffer consumed during the preparation of two (2) 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 (2) FBPs with a batch size combined of 30kg with a dose of 2K, 3K, 4K, and 10K is approximately 154.91kg.

Table 1

68 Buffers Formulated in 2023 with their Consumption Information

Dose	Batch size	DS Qty	Buffer qty	Initial charge	HSA + DS	Final QS	Buffer para QS	Total Buffer used	Buffer Loss
40000	183	17206	600	155.6	175.6	183	7.4	163	437
10000	163.23	3819	600	138.8	145.2	163.3	18.1	156.9	443.1
10000	392	9214	600	333.2	347.5	391.9	44.4	377.6	222.4
4000	19	178	200	16.2	17.6	19	1.4	17.6	182.4
10000	390	9167	600	331.5	345.7	390	44.3	375.8	224.2
10000	30	702	200	25.5	27.5	30.1	2.6	28.1	171.9
20000	204	9590	600	173.4	186.1	204	17.9	191.3	408.7
10000	392	9214	600	333.2	347.4	392	44.6	377.8	222.2
10000	22.68	533	200	19.3	21.1	22.7	1.6	20.9	179.1
3000	15	106	200	12.9	14.1	15	0.9	13.8	186.2
10000	390	9167	600	331.5	345.7	390	44.3	375.8	224.2
10000	390	9167	600	331.5	345.7	390	44.3	375.8	224.2
2000	25.61	120	200	21.9	23.3	25.7	2.4	24.3	175.7
10000	390	9167	600	331.4	345.7	390	44.3	375.7	224.3
10000	392	9214	600	333.2	347.5	392	44.5	377.7	222.3
20000	313	14714	600	266.1	284.9	313	28.1	294.2	305.8
10000	390	9167	600	331.5	345.7	390	44.3	375.8	224.2
4000	19	179	200	16.1	17.5	19	1.5	17.6	182.4
10000	392	9214	600	333.2	347.3	392	44.7	377.9	222.1
3000	44	310	200	37.4	39.3	44.1	4.8	42.2	157.8
10000	163	3831	600	138.6	145.6	163	17.4	156	444
40000	183	17090	600	155.6	175.5	183	7.5	163.1	436.9
10000	79	1851.4	600	67.1	70.8	79	8.2	75.3	524.7
40000	183	17090	600	155.6	175.5	183	7.5	163.1	436.9
3000	79.31	557	600	67.5	69.8	79.4	9.6	77.1	522.9
2000	79	371	600	67.2	69.4	79	9.6	76.8	523.2
10000	44	1033.8	200	37.4	39.9	44	4.1	41.5	158.5
20000	79	3714	600	67.1	72.6	79	6.4	73.5	526.5
4000	42	395	200	35.6	37.6	42	4.4	40	160
10000	30	705	200	25.5	27.6	30	2.4	27.9	172.1
20000	313	14615	600	266.1	284.9	313	28.1	294.2	305.8
4000	79.31	746	600	67.5	70	79.4	9.4	76.9	523.1
3000	33	233	200	28.1	29.6	33	3.4	31.5	168.5
2000	79	371	600	67.2	69.3	79	9.7	76.9	523.1
4000	44	414	200	37.4	39.2	44	4.8	42.2	157.8
3000	34	240	200	28.9	30.7	34	3.3	32.2	167.8
4000	44	414	200	37.4	39.2	44	4.8	42.2	157.8
10000	44	1034	200	37.4	39.9	44	4.1	41.5	158.5
2000	32	150	200	27.2	28.7	32	3.3	30.5	169.5
20000	203.60	9554.5	600	173.1	185.7	203.7	18	191.1	408.9
3000	44	310	200	37.4	39.1	44	4.9	42.3	157.7
4000	44	411	200	37.4	39.3	44	4.7	42.1	157.9
10000	162.81	3801	600	138.3	144.8	162.9	18.1	156.4	443.6
2000	14	65	200	11.9	13.2	14	0.8	12.7	187.3
40000	183	17090	600	155.6	175.4	183	7.6	163.2	436.8
10000	390	9105	600	331.5	345.6	390	44.4	375.9	224.1
10000	392	9152	600	333.2	347.3	392	44.7	377.9	222.1
10000	392	9152	600	333.1	347.3	392	44.7	377.8	222.2
10000	392	9152	600	333.2	347.4	392	44.6	377.8	222.2
20000	170.49	7961	600	145	155.6	170.5	14.9	159.9	440.1
10000	392	9152	600	333.2	347.5	392	44.5	377.7	222.3
2000	29.85	139	200	25.5	27	30	3	28.5	171.5
10000	30	700	200	25.5	27.6	30.1	2.5	28	172
40000	183	17186	600	155.6	175.6	183	7.4	163	437
20000	115.79	5437	600	98.4	106.1	115.8	9.7	108.1	491.9
4000	31.1	290	200	26.6	28.1	31.1	3	29.6	170.4
10000	392	9152	600	333.1	347.4	392	44.6	377.7	222.3
10000	163	3826.9	600	138.6	145	163	18	156.6	443.4
10000	163	3827	600	138.6	145.1	163	17.9	156.5	443.5
20000	82	3850	600	69.7	75.3	82	6.7	76.4	523.6
10000	392	9152	600	333.1	347.4	392	44.6	377.7	222.3
3000	14	99	200	11.9	13.2	14	0.8	12.7	187.3
20000	204	9579	600	173.4	186	204	18	191.4	408.6
10000	390	9157	600	331.5	345.7	390	44.3	375.8	224.2
20000	197.82	9289	600	168.1	180.4	197.9	17.5	185.6	414.4
10000	390	9157	600	331.5	345.6	390	44.4	375.9	224.1
4000	22.43	211	200	19.1	20.5	22.5	2	21.1	178.9

Measure: The baseline of the present process, data collection, system validation, and process capability assessment are all part of the measure phase. For this research, a total of 68 buffer batches formulated in 2023 were studied. The dose, batch size, DS quantity, buffer quantity, initial charge, HSA + DS, final QS, buffer for QS, total buffer used, and buffer loss are presented in Table 1. The buffer losses in every FBP are depicted in Table 2.

For an FBP batch size of 14 Kg of doses 2K, 3K, 4K, and 10K, the buffer consumption for one (1) FBP and two (2) FBPs is depicted in Table 3. This shows that 2 FBPs with a Batch size of 14kg consume a maximum of 154.91 Kg of buffer, supporting the theory that a buffer of 200 kg can be used for two formulations of 14 Kg each.

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 4. This shows that 2 FBPs with a Batch size of 80kg consume a maximum of 227.88Kg of buffer, supporting the theory that a buffer of 600 kg can be used for two formulations of 80 Kg each.

Table 2

Buffer Losses in Every FBP Quantity

Buffer Transfer Quantity	
Filter Flush	25.35 Kg[1]
Transfer Line Losses	18 Kg
Sampling	0.8 Kg
Buffer collection	2 Kg
Total	**46.15 Kg**

[1] Filter Flush time 6.5 min with filtration rate of 3.9 Kg/min

Table 3

A FBP of a Batch Size of 14 Kg

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 4

A FBP of a Batch Size of 80 Kg

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

For an FBP batch size of 392 Kg of the dose 10K and 20K, the buffer consumption for one (1) FBP and two (2) FBPs is depicted in Table 5. This

shows that 2 FBPs with a Batch size of 392kg consume a maximum of 829.5112 Kg of buffer, supporting the theory that a buffer of 600 Kg cannot be used for two formulations of 392 Kg each.

Table 5

A FBP of a Batch Size of 392 Kg

FBP Batch size: 392 Kg								
Dose	DPBP	Kg_{DS} (E2)	Kg_{WSA} (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

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 6. This shows that 2 FBPs 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.

Table 6

A FBP of a Batch Size of 200 Kg

FBP Batch size: 200 Kg								
Dose	DPBP	Kg_{DS} (E2)	Kg_{WSA} (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

Analyze: Using statistical tools like hypothesis testing, the analyze phase involves identifying significant components and inputs that have a significant impact on the output, identifying potential root causes, and analyzing the process to optimize efficiency.

The multi-batch approach is expected to result in more lots and shorten the formulation process cycle time. Using the data gathered as part of the measures, hypothesis testing of reducing the formulation process cycle time and increasing the number of lots produced was interpreted. 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 buffer multi-batch strategy, a reduction of 18 hours to start the second batch will be seen because the steps in Table 7 will not be necessary, resulting in a reduction in the cycle time.

Table 7

Steps Repeated in the Beginning of a New Formulation

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

Regarding costs, with a reduction of 20 buffers in the year, a total of $19,269.43 will be saved (Table 8).

Table 8

Costs Saved in the Reduction of 20 Buffers in the Year

DATOS				
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

After applying the multi-batch method, we were able to assess the findings and find a considerable improvement. By consolidating each step, the formulation cycle time was shortened, improving labor utilization and equipment availability.

Control: The multi-batch approach was developed as a more efficient way to achieve both more lot production and schedule adherence. 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. This control

is crucial because we must maintain that the project optimization succeeds after implementation and monitor it.

Because standard work measures the time for each step after the average determined for the execution of coworkers and the evaluation of any task, it is a highly common tool in the production regions. Budget cuts and shortened project timelines are desirable to the industries.

CONCLUSION

In this research, a new buffer multi-batch strategy was introduced, to reduce costs 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.

To sum up, process optimization is an essential component of cost-cutting plans for companies in a range of industries. Through the analysis and enhancement of critical processes, companies can gain a competitive advantage, improve efficiency, and save a substantial amount of money. Through process improvement, the area was able to locate redundant tasks, bottlenecks, and other productivity-straining issues. Through the application of best practices and workflow optimization, the region increased output overall and enhanced efficiency.

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