Optimization of the Induction Solutions Preparation and Addition Process in Bulk Manufacturing at a Biopharmaceutical Plant

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Abstract *— An optimization of the induction solutions manufacturing and addition processes, used during the protein generation in a Cell Culture process is pursued at a Biopharmaceutical plant located in Juncos, Puerto Rico. Initiatives to improve the Cell Culture process are desired due to its extent, complexity, risks, and associated costs. The data collection for the project was segregated into two main areas: Media Preparation Area and Cell Culture Area; and focused on developing Process Flow Diagrams, Voice of the Customer (VOCs) exercises, durations analysis, and costs evaluations of the current processes. An optimized batch size of a combined induction solutions with High Temperature Short Time (HTST) treatment was implemented at the Media Preparation area; while in the Cell Culture area, a simplified addition process was implemented. The project achieved an increase in manufacturing capacity, implemented risk mitigation controls, reduced costs and man hours required for the addition process.*

Key Terms *— cell culture optimization, continuous improvement, induction solutions addition, manufacturing competitiveness.*

INTRODUCTION

Cell Culture Manufacturing is the process in which cells are cultivated to obtain a protein of interest for the purposes of developing a therapeutical medicine. Initiatives to improve the process are always desired, while maintaining the integrity of the process, due to its extent, complexity, and associated costs.

At a Biopharmaceutical plant located in Juncos, Puerto Rico there is a need to improve the induction solutions manufacturing at the Media Preparation area and addition processes at the Cell Culture area for one of its products. The induction solutions are added during the cell culture of the product to enhance the protein generation at the Production Bioreactor, stage in which the protein of interest is generated.

In alignment with the continuous improvement mindset of the Bulk Manufacturing plant, this project had the following objectives:

- Increase manufacturing capacity by achieving a 30% reduction in the time required to perform the induction solutions manufacturing at Media Preparation for the next campaign,
- Reduce risks associated to viral contaminants that may come from raw materials during the manufacturing of the solution for the next campaign,
- Achieve a $15K reduction in the manufacturing costs per Bulk batch manufactured in the next campaign, and
- Achieve a 50% reduction in the time required to perform the setup and induction solutions addition process (man hours) in the next campaign.

This paper discusses the cell culture manufacturing process, the importance on having an organizational continuous improvement mindset as new competitors, technologies and diseases emerge, while maintaining risk mitigation controls and ensuring compliance. Further discussion is focused on the development of the project: a data collection process for the induction solutions manufacturing and addition processes, the implementation of identified improvements and discussion on achieved objectives and conclusions.

LITERATURE REVIEW

Manufacturing competitiveness is defined as how an organization offers unique customer value by proving to be better than the competitor and

providing reasons as to why the customer should buy their product [1]. Throughout the years, companies have sought to develop a continuous improvement mindset, while improving their processes by eliminating waste, building quality, implementing low-cost reliable technologies, improving their processes, and building a learning culture [2]. The Biopharmaceutical manufacturing, which accounts for 20% of the total pharmaceutical revenue, with $163 billion/year, has needed to continuously improve and implement latest technologies and controls, due to their innovative treatment abilities as the process's sciences have advanced [3].

For biopharmaceuticals, the active pharmaceutical ingredient (API), the ingredient that treats the disease, is a protein usually found in an aqueous solution referred to as drug substance. This drug substance is manufactured through a cell culture process that starts with a vial thaw, flasks and bioreactors expansion process to increase cell density (i.e. cells per unit volume), and a production bioreactor step in where the protein is generated. Further processing is performed with a harvest stage and purification steps to eliminate side products, and cell debris and impurities [4]. The cell culture process is mainly conducted in batch bioreactors, which vary in size, under controlled process parameters such as agitation, gases flows, sparging rate, pressure, temperature, pH, dissolved oxygen (DO%), among others [5]. Depending on the cell culture process, nutrients are intermittently or continuously added to meet the demands of the process and help cells grow [4, 6].

With a continuous improvement mindset, there is always the desire to optimize the cell culture process of mammalian cells, due to its length, complexity, and costs; to maximize yield, efficiencies, and equipment and resources utilization [6]. Mammalian cell culture process, used to manufacture the majority of the therapies, is prone to contaminations which can result in losing a production run, requiring to implement and maintain strict sterile conditions during its manufacturing process [3, 5].

It is important to implement controls that will minimize contamination risks associated, from sources such as bacteria and viruses that may come from donor animals, manipulations during the operations, or from contaminated media components or raw materials [7]. In the majority of the biopharmaceutical products, monoclonal antibodies (MAbs) are used, and 70% of these are manufactured using Chinese Hamster Ovary (CHO) cells [4]; hence, there is a risk of viral contaminations from rodents [3, 8]. For this and other contamination sources, several processing steps are implemented to eliminate viral contaminants to ensure that host cells and the facilities are not contaminated [3]. Nanofiltration and High Temperature Short Time (HTST) treatment are common viral load reduction steps in cell culture media raw materials [3, 8], and sterilization and aseptic steps are also common for bacterial contamination reduction [3]. Impact of contamination events can range between a lost bioreactor run (i.e. batch) to the shutdown of the entire facility [3].

To improve the robustness of the contamination mitigation controls, the biopharmaceutical facilities seek to reduce open operations by replacing manual aseptic operations with closed processing, implement pre-sterilized single-use systems (SUS) technologies, and implement proven reliable viral contamination reduction steps [5]. With these initiatives, the manufacturing facility benefits from lower operational costs, reduce cross-contamination risks, simplifies the processes, gains flexibility and agility, and runs its processes with the latest available technologies [5].

ANALYSIS

The data collection for the project was segregated into two main areas: Media Preparation Area and Cell Culture Area. The data collection process focused on developing Process Flow Diagrams, Voice of the Customer (VOCs)

exercises, durations analysis, and costs evaluations of the current processes.

Data Collection for the Media Preparation

The current Media Preparation process for the induction solutions consists of batching, and transfer and filling processes. Separate batching activities occur for each of the solutions: Solution A and Solution B; with durations in the range of one (1) hour and sixteen (16) minutes to one (1) hour and twenty-two (22) minutes for Solution A, and durations in the range of one (1) hour and four (4) minutes to one (1) hour and thirty-four (34) minutes for Solution B, as shown in Table 1.

Table 1
Durations of Induction Solution A and Solution B Batching Process at Media Preparation

Batch # Solution A	*Batching duration Solution A [hh:mm]*	*Batch # Solution B*	*Batching duration Solution B [hh:mm]*
Batch 01A	01:22	Batch 01B	01:04
Batch 02A	01:22	Batch 02B	01:23
Batch 03A	01:22	Batch 03B	00:55
Batch 04A	01:16	Batch 04B	00:52

Separate transfer and filling processes occur for each of the induction Solutions A and B, with durations in the range of fifty-two (52) minutes to one (1) hour and thirty-four (34) minutes for Solution A, and durations in the range of fifty-six (56) minutes to one (1) hour and twenty-one (21) minutes for Solution B, as shown in Table 2. Current filling processes for each of the Solutions A and B supply two (2) main Bulk batches.

Table 2
Durations of Induction Solution A and Solution B Transfer and Filling Process at Media Preparation

Batch # Solution A	*Transfer and Filling duration Solution A [hh:mm]*	*Batch # Solution B*	*Transfer and Filling duration Solution B [hh:mm]*
Batch 01A	01:34	Batch 01B	01:03
Batch 02A	01:15	Batch 02B	01:04
Batch 03A	00:55	Batch 03B	00:56
Batch 04A	00:52	Batch 04B	01:21

There is a need to optimize the batch size of the solutions, implement a combined solution manufacturing with a HTST treatment, and reduce the current manufacturing costs per solution batch of $8,400 for Solution A and $23,900 for Solution B.

Data Collection for the Cell Culture Area

The current Cell Culture addition process for the induction solutions consists of a process setup and addition process. The process setup consists of the addition assembly preparation, which includes a costly viral filter and additional components that need to be cleaned and assembled, with an average duration of five (5) hours. As shown in Table 3, the addition process duration is in the range of two (2) hours and fifty-three (53) minutes to three (3) hours and fifty-two (52) minutes.

Table 3
Duration of Induction Solution A and Solution B Addition Process at Cell Culture

Bulk Batch #	*Addition Duration [hh:mm]*	*Bulk Batch #*	*Addition Duration [hh:mm]*
Batch 01	03:52	Batch 05	03:10
Batch 02	02:45	Batch 06	03:08
Batch 03	02:56	Batch 07	03:42
Batch 04	03:08	Batch 08	02:53

The current induction solutions addition at the Production Bioreactor stage is complex due to the current addition assembly and multiple required manipulations to ensure a continuous solutions' flow through the viral filter. There is a need to simplify the addition process, reduce durations, increase reliability, and reduce the costs associated with the addition process of $21,950 per Bulk batch.

As outcome of the Data Collection process, a series of improvements were identified for the Media Preparation and Cell Culture areas, which will be discussed in the next section.

RESULTS AND DISCUSSIONS

A staggered approach was followed to implement all identified improvements for the Media Preparation and Cell Culture areas, and obtained results are described below.

Improvements for the Media Preparation Area

The following improvements were implemented for the Media Preparation area following the data collection process:

- A combined (both Solutions A and B) batch manufacturing process with an increased batch size of 2,000L
- Implement a HTST treatment during the transfer process from batch tank to hold tank

These two improvements required generating a new Bill of Materials (BOM); new Automation recipes for the batch, transfer and filling processes; update applicable procedures and Electronic Batch Records (EBR) and perform a Cleaning Validation process for the new batch and hold tanks used.

Improvements for the Cell Culture Area

The following improvements were implemented for the Cell Culture area following the data collection process:

- Eliminate the viral filter usage due to the implementation of the HTST treatment at Media Preparation
- Implement the SUS technology for the addition assembly

These two improvements required generating a new BOM, new Automation recipe for the addition process at the Production Bioreactor and update applicable procedures and EBR.

Summary of Results and Comparison Against Project's Objectives

The implementation of a combined induction solutions and optimized batch manufacturing process in the Media Preparation Area provided an increase in the manufacturing capacity by achieving a reduction of 68% in the batching time and 42% in the transfer/filling times during the induction solutions' manufacturing per Bulk batch, as shown in Table 4. The new optimized batch will supply five (5) Bulk lots, instead of two (2) Bulk lots achieved with the previous process. Hence, the previous batching average duration was of forty (40) minutes for Solution A (per Bulk batch) and of thirty-nine (39) for Solution B (per Bulk batch). The new batching average duration per Bulk batch is twenty-five (25) minutes. For the transfer and filling process, the previous average duration was of 39 minutes for Solution A (per Bulk batch) and of thirty-eight (38) for Solution B (per Bulk batch). The new transfer and filling average duration per Bulk batch is one forty-five (45) minutes. In addition, a risk mitigation initiative was implemented by including the HTST treatment as part of the combined induction solutions' manufacturing.

Table 4
Duration of Induction Solutions A and B Manufacturing versus new Combined Solution Manufacturing

Batch #	*Batching duration [hh:mm]*	*Transfer and Fill duration [hh:mm]*	*Batch #*	*New Batching duration [hh:mm]*	*New Transfer and Fill process [hh:mm]*
01A	01:22	01:34	01C	02:08	03:41
02A	01:22	01:15	02C	02:08	04:00
03A	01:22	00:55	03C	01:59	03:40
04A	01:16	00:52	Avg.C	02:05	03:47
Avg.A	01:20	01:09			
01B	01:04	01:03			
02B	01:23	01:44			
03B	01:12	00:56			
04B	01:34	01:21			
Avg.B	01:18	01:16			

Batching and Transfer/fill durations are for two (2) Bulk batches. New durations are for five (5) Bulk batches.

Due to implementation of the HTST treatment, the viral filtration is no longer required during the solutions' addition process at the Production Bioreactor in Cell Culture. This allowed simplifying the assembly setup and addition process, representing a 57% reduction in the time required for the addition setup and process, as shown in Table 5.

Table 5
Comparison of Durations for Induction Solutions A and B Addition Process versus New Addition Process

Bulk Batch #	*Solution A and B Duration [hh:mm]*	*Bulk Batch #*	*New Duration [hh:mm]*
Batch 01	03:52	Batch 01	01:18
Batch 02	02:45	Batch 02	01:29
Batch 03	02:56	Batch 03	01:35
Batch 04	03:08	Batch 04	01:17
Batch 05	03:10	Batch 05	01:14
Batch 06	03:08	Batch 06	01:20
Batch 07	03:42	Batch 07	01:28
Batch 08	02:53	Batch 08	01:09
Avg.	03:11	Avg.	01:21

A $14,586 reduction was achieved per Bulk batch manufactured due to the elimination of the viral filter and implementation of a simplified assembly using SUS technologies.

CONCLUSIONS

An optimization in the induction solutions manufacturing and addition process was achieved in a Bulk manufacturing facility. The project implemented a combined induction solutions' manufacturing with an optimized batch size, and with a HTST treatment as a risk mitigation initiative for the Media Preparation area. In the Media Preparation area, a 68% reduction was achieved in batching activities durations and of 42% in transfer/filling activities durations. For the Cell Culture addition process, a simplified addition process was implemented, which led to a 57% reduction in setup and addition durations and a $15K reduction in associated costs due to the elimination of a viral filter and implementation of SUS assemblies. All the project's objectives were met.

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