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.

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. As shown in Figure 1, this cell culture process starts with a vial thaw, continues with flasks and bioreactors expansion processes 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 (i.e. centrifugation and filtration) and purification steps using chromatography columns, to eliminate side products, cell debris, and impurities [1].

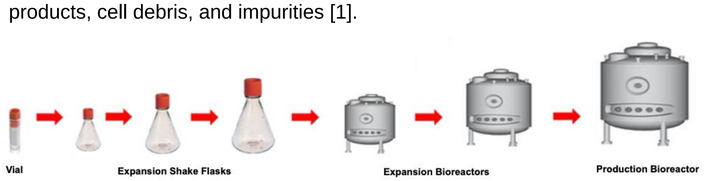

Figure 1: Cell Culture Process Overview [2]

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 manufactured at the Media Preparation area and 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.

Initiatives to improve the cell culture process are always desired, while maintaining the integrity of the process, due to its extent, complexity, risks, and associated costs, following a continuous improvement mindset.

Project's Objectives

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,
- Achieve a 50% reduction in the time required to perform the setup and induction solutions addition process (man hours) in the next campaign.

Methodology

The data collection for the project was segregated into two main areas: Media Preparation Area and Cell Culture Area, as shown in Figure 2. The data collection process focused on developing Process Flow Diagrams, Voice of the Customer (VOCs) exercises, durations analysis, and costs evaluations of the current solutions preparation and additions processes.

The current Media Preparation process for the induction solutions consists of batching, and transfer and filling processes for two separate Solutions A and B, and for Cell Culture, consists of process setup and addition process.

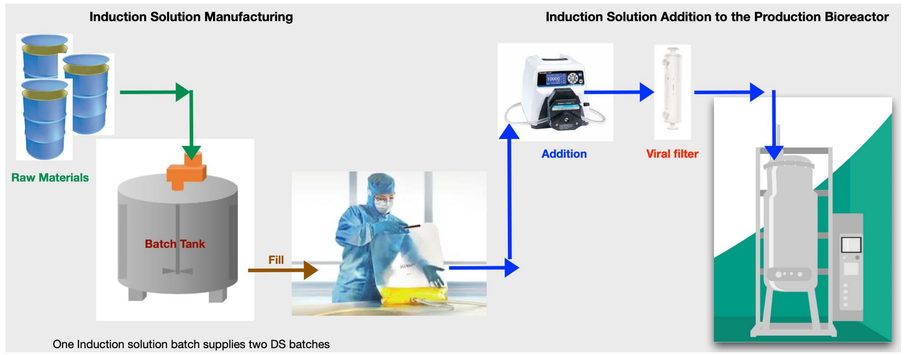

Figure 2: Media Preparation and Cell Culture areas overview for the data collection process

Batching Process

- Solution A with average batching duration of 1 hour and 20 minutes.
- Solution B with average batching duration of 1 hour and 18 minutes.

Transfer and Filling Process

- Solution A with average transfer and filling duration of 1 hour and 9 minutes.
- Solution B with average transfer and filling duration of 1 hour and 16 minutes.
- Each Solution batch supplies 2 Bulk batches.

Addition Setup 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.

Addition Process

- The average addition process duration for Solutions A and B is 3 hours and 11 minutes.

Results

Media Preparation Area

	Current State	Proposed State
Batching	• Separate batches are manufactured for each Induction solution • Batch size: 300L for each solution	• A **combined** (both solutions) batch will be manufactured • Batch size: **2,000L**
Transfer and Filling Process	• One batch of each solution supplies 2 Bulk batches	• One batch of a combined solution will supply **5 Bulk batches** • Implement a **High Temperature Short Time (HTST) treatment**

Cell Culture Area

	Current State	Proposed State
Process Setup	• Complex addition assembly uses expensive viral filter per addition • Cleaning and preparation of assembly components takes a significant amount of time	• **Eliminate viral filter usage** due to the HTST treatment at Media Preparation • Implement the usage of **Single Use Systems (SUS)** for the addition assembly
Addition Process	• Addition process is complex due to addition assembly and required manipulations to maintain a continuous flow through	• Addition process is **simplified** due to the viral filter removal. Manipulations are significantly reduced during the addition.

Figure 3: Media Preparation and Cell Culture proposed and implemented improvements for the induction solutions

Discussion

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 1. The new optimized batch will supply five (5) Bulk lots, instead of two (2) Bulk lots achieved with the previous process and will be manufactured with a risk mitigation HTST treatment.

Table 1: 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			

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 2. 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.

Table 2: Comparison of Durations for Induction Solutions A and B Addition Process versus new Combined 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

Conclusions

An optimization in the induction solutions manufacturing and addition process was successfully completed in the Media Preparation and Cell Culture areas by implementing an optimal batch size of a combined Induction solution with HTST treatment, and a simplified addition process at the Production Bioreactor stage with the removal of the costly viral filter and the usage of SUS assemblies.

References

[1] Lori Herz. Development and Manufacture of a Cell Culture Process for a Phase 1 Biopharmaceutical Product, Case-study (2020). https://ezproxy.pupr.edu:2053/content/case-study/CS0003_Herz_Case_Study_Cell_Culture_text_figures

[2] Mario Sinani, et al. ATF Perfusion Technology: Improved Fed-Batch Throughput and Reduced Seed Train Expansion. https://www.repligen.com/application/files/6115/3928/5014/2015_BPI_ATF_Poster.pdf