IMPROVEMENTS TO PERFUSION SKIDS 66501/66502/66503 OPERATIONS USED FOR ENBREL PRODUCT IN AML-06.

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AMGEN

Enbrel etanercept

Abstract

Amgen AML-06 Drug Product Plant, it is a multi-product facility where therapies for chronic diseases are manufactured. Its systems are designed for the continuous improvement of the processes, in order to comply with the supply requirements for medications.
The project to be worked will impact the manufacturing process specifically for the Perfusion process of Enbrel product. The perfusion process is carried out in Bioreactor N-1, a previous step to Bioreactor N where the protein is finally produced. The team will be working with symptoms in the Perfusion equipment, which cause the process time to exceed the validated limits.
To achieve this, we will use the DMAIC methodology, with the intention of improving an implemented process. The goal is that we can implement improvements to the process and that the time of the process is within the established ranges, and thus not impact the integrity of the cells or the schedule of the lots. To meet the goal, it is necessary to achieve a reduction of at least 6% of the processing time.

Project Description

During this project we will investigate problems associated with the Perfusion process for Enbrel product. Using the DMAIC methodology, we will find the root causes and find improvements for this process that is a very important and crucial step in the overall manufacture of Enbrel.

Objectives

•Identifying the downtime problem root causes.
•Suggest the improvements to be applied to achieve at least 6% time reduction.
•Establish responsibilities and scheduling of resources.
•Implement the improvements through the Change Control System.
•Compare final state with the initial state.

Methodology

The methodology to be used in this project will be the DMAIC process. DMAIC is an acronym for Define, Measure, Analyze, Improve, Control. DMAIC is the process improvement methodology of Six Sigma that's used for improving existing processes.

Results and Discussion

Define Phase

The Perfusion process have a validated duration of 120 hrs. ± 12 hrs. For the last 10 batches, the average duration time was 140 hours. This is unacceptable due to compromise the complete bio-reactor train schedule. This situation causes that the bio-reactor N-1 (Perfusion), can't be ready for the next batch on time due to others preparation activities like cleaning and sanitization.
The improvement proposal only impact perfusion skids 66501/66502/66503 and cleaning skid 40508 operations used for Enbrel product in AML06.The following are the problems detected in the perfusion skid operation:
1. Pump Mechanical Seal damage.
2. Batch microbial contamination.
3. Leaks observed in the flexible hoses.

Define Phase Cont.

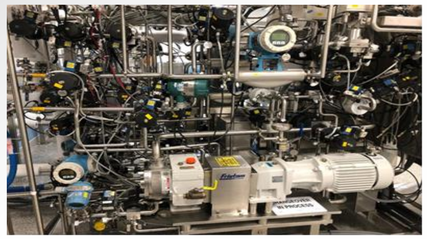

Figure 1: Perfusion Skid 66501

Table 1: Project Schedule

Phase	Duration	Start Date	Finish Date
Define	2 days	03/23/2020	03/24/2020
Measure	3 days	03/25/2020	03/27/2020
Analyze	2 days	03/30/2020	03/31/2020
Improvements	24 days	04/01/2020	04/24/2020
Control	5 days	04/27/2020	05/01/2020

Measure Phase

• Process Time validated: 120 hrs. ± 12 hrs.
• Actual average process time: 140 hrs. (Last 10 batches)
• Hour above Process upper limit of 132 hrs are considered downtime.

Table 2: Process Time per Batch

Batch	Time (hrs)
1	155
2	139
3	145
4	125
5	134
6	146
7	142
8	125
9	152
10	137

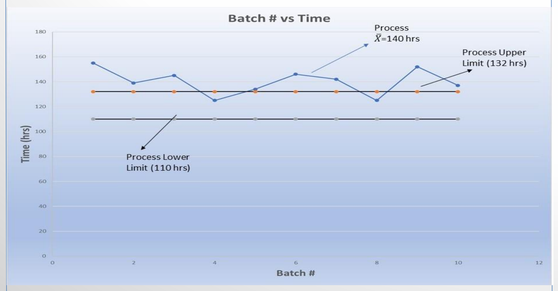

Figure 2: Actual Process Trend

Analyze Phase

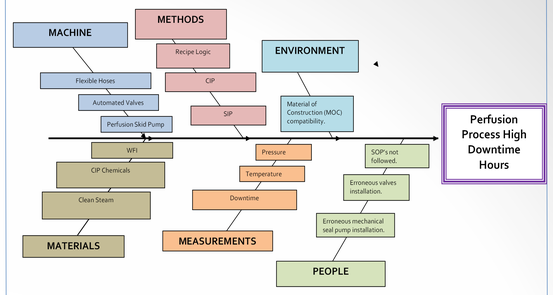

Figure 3: Fishbone Diagram

Root Causes:
1. Mechanical seal pump is affected due to high temperature operations.
2. Mechanical seal pump is affected due to pressure operation of CIP, SIP, WFI flush and Perfusion process.
3. Possible microbial growth due to low sterilization efficiency.

Improvement Phase

Improvements suggestions:
1. Install a Temperature and Pressure interlock for the Perfusion pump to protect the mechanical seal.
2. Improve Logic Control for SIP to increase sterilization efficiency. By this improvement, all the automated valves will be sterilized and the vacuum condition will be eliminated.
3. Set a Logic Control to the Pump heat exchanger to control the temperature at mechanical seal side.
4. Replacement of flexible hose by a stainless-steel spool. Possibility of microbial growth and leaks will be eliminated

Control Phase

Change Controls records were closed and systems were returned to manufacturing. Manufacturing procedures (SOP's) were revised to include instructions to monitoring the process. Data of temperature and pressure will be documented in official manufacturing documents (Forms). Alarms were included in the Process Control System (PCS), to alert the manufacturing associates.

Data was obtained for the first 5 batches after the improvement's implementation. It is important to note that the first 5 batches were free of microbial contamination. The data is presented in the Table 3 and Fig. 4.

Table 3: Process Time per Batch After Improvements

Batch	Time (hrs)
1	126
2	125
3	128
4	121
5	127

Control Phase Cont.

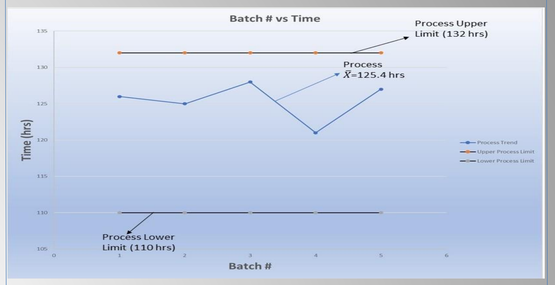

Figure 4: Process Trend After Improvements

Conclusion

The DMAIC methodology results very effective to analyze the problem, investigate the root causes and establish the improvements needed. Five enhancements were implemented to improve the perfusion process in a short period of time. In summary, the following improvements were performed:

1. Sterilization for all components of the skid equipment were optimized.
2. The logic of the SIP recipes and the transfer of the media to the Bio-reactor were optimized.
3. The possibility of leaking and contamination was decreased by replacing the flexible hose.
4. Interlocks were established to protect the mechanical seal of the pump and thus avoid contamination and equipment down situations.

After analyzing the data of the first 5 batches after the improvements, we can see that the average process time was 125.4 hrs. Fourteen (14.6 hrs.) less for an equivalent of a time reduction of a 10.43%. This achievement allowed that the batches not be discarded and the equipment for the perfusion process to be ready to receive the next batch after the required cleaning and sanitizing processes.

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