Improve the Cycle Time of Stat Testing in Quality Control Laboratory Applying Kaizen Analysis

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Abstract *— Quality Control Laboratory of Biopharma Company was selected for develop a design project, using the technique of Kaizen Project. Manufacturing area of Biotech Company produces a biological product. Biologic Bulk Drug substance must be tested for protein content. Manufacturing area needs analytical tests results to continue the Fermentation/Purification process. The main objective is reducing the cycle time for Stat Testing. The goal is identify wastes and eliminates what does not add value during analytical process. The problem is often longer of "Lab cycle time" to completed Stat testing for in-process samples. Kaizen Analysis, Value Stream Mapping, and Spaghetti diagram were executed to identify all wastes during the Sialic Testing. Quality Control Lab needs to re-design the layout of the in-process lab to eliminates the wastes and non- value activities to maintain continuous improvements in quality processes.*

Key Terms *— Kaizen Analysis, Laboratory Cycle Time, Sialic Testing, Stat Testing.*

PROBLEM STATEMENT

Biotechnology Company is a field it applied biology that involves the use of living organism and bioprocess in medicines and others fields requiring bioproducts. Manufacturing area in Biotechnology Company produces biological product. The biological product is a therapeutic product that is derived from biological processes. Biopharma laboratories have to do the analytical testing for biological product must be tested for identity, impurities, quantity, and protein content. Biopharma Laboratory should have understood the importance to get Stat Testing results because manufacturing area is waiting for these results to continue their process.

Quality Control Laboratory in Biopharma Company is selected to develop a Design Project. Manufacturing area delivery many in-process samples of Fermentation/Purification process to QC Lab to execute Stat testing. The problem is often longer lead time to complete the analytical testing.

Kaizen Analysis, Value Stream Mapping, and Spaghetti Diagram were used to perform this study. The objective for this Research was reducing cycle time in Stat testing applying Kaizen, such as identifying processes that are critical to complete the Stat Testing for biological product.

The Research demonstrated reducing cycle time in Stat testing process, it can be maximize productivity, process efficiency, improving quality, avoiding delays and errors, and speeding up the time to completed Stat testing. Simplify the testing process was improving standards and reduced Non-value added tasks and eliminate wastes.

LITERATURE REVIEW

During Bulk Drug substance manufacturing in Biopharma Company, the analytical support function provides scientific and product quality assurance to the predominantly chemical function of manufacturing activities. Analytical support involves analytical procedures and laboratory, operations, to meet the scientific, regulatory and quality expectations for product manufacture. Quality Control Laboratory (Q.C. Lab) provides expert chemical analysis for Bulk Drug Substance (BDS). The analytical testing called "Stat Testing" which means "immediately", due to manufacturing group is waiting for analytical results to continue the Fermentation/Purification process, to manufacture the biological product. Analytical techniques used to perform the Stat Testing are as

follow: HPLC UV-Vis and Purification of Protein by AKTA system.

Analytical Methods

High Performance Liquid Chromatography (HPLC) is a standard qualitative and quantitative analysis procedure used in analytical laboratory. HPLC is reliable and repeatable which makes it the preferred technique for separating, identifying and quantifying molecules from complex mixtures of both chemical and biological components.

Titer Assay by HPLC is a test for quantify of Protein A material. Sialic Assay by HPLC is a test for determination of amount of NGNA/NANA. UV-VIS method is a test for determination of Total Protein Concentration by Absorbance at 280 nanometers (nm), and Purification of Protein A by Affinity Chromatography (FPLC).

Lean

Lean thinking is a single most powerful tool available for creating value while eliminating waste in any organization. [1] Seven sources wastes: Waste of overproduction, Waste of inventory, Waste of defects, Waste of motion, Waste of processing, Waste of waiting, and Waste of transport. [2]

Currently, the Lean method is extremely important for many companies; their main objective is continuous improvements in Quality product or service. Continual Improvement is a key to long-term success and high performance. Successful managers recognize that processes must be reviewed and improved continuously to ensure that their organization stays competitive. [3]

Kaizen

The applicability of Kaizen Analysis in Quality Control Lab is to improve the cycle time of Stat testing, to create more value of procedures and processes systematically and residues reduction. Additional, Kaizen can approach to eliminating defects in any process.

Kaizen is a system of continuous improvement in quality, technology, processes, company culture, productivity, safety and leadership.

In Japanese, kaizen means "continuous improvement". In the context of kaizen, management has to major functions: maintenance and improvement. Under its maintenance function, management performs its assigned tasks so that everybody can follow standard operating procedures (SOPs). Improvement, meanwhile, refers to activities directed toward elevating current standards. [2]

Kaizen focus on eliminating wastes (Non-value added), Standardized operations (Best Practices), and measures the standardized operation. Kaizen event are often planned using value stream mapping to target the right areas for improvement.

Value Stream Mapping

Value Stream Mapping (VSM) is a method for clearly showing in diagram form the material and information flow [4].Value Stream Map is essential to really see what's going on. VSM helps team see how a process should work (future state) once they eliminate waste.

Spaghetti Diagram

Spaghetti Diagram is a visual representation using a continuous flow line tracing the path of an item or activity through a process.

Spaghetti Diagram can be used to depict the flow information, material, or people. Spaghetti Diagram used to improve the physical layout of a workspace. [5]

METHODOLOGY

The methodology used in this project was Kaizen Analysis, Value Stream Mapping and Spaghetti Diagram. The objectives are reduce the cycle time in Stat Testing, identify constraints in a process, and identify non-value added activities (wastes) to improve process efficiency.

Sialic Kaizen Event in QC Lab

Sialic Kaizen is a multi-week effort. Kaizen often implemented through Kaizen "events-hand on and impact driven. The search for continuous incremental improvements on existing recourses: Accumulating gradual gains in small steps and sustaining performance over time. A team-based approach to problem solving to:

- Identify and evaluate problems.
- Capturing pain points and finds potential solutions.
- Implement solutions.
- Standardized of Methodology to reduce variability.why sialic kaizen.

Variety of people performed different tasks during the Stat testing and this information was recorded to trend the spent time throughout daily activities. Sialic Testing is the longest run and hands-on time of the Stat tests (see Figure 1).

Sialic Testing Kaizen aims at reducing overall time to perform activity. The objectives for Sialic Kaizen Analysis are the following:

- Record the time spent throughout Stat testing activities.
- Running activities in parallel.
- Eliminating Non-value Added tasks.
- Evaluating the multiple analyst variability of Stat testing.
- Identification of the main process steps, pain points and potential solutions.
- Standardizing methodology of Stat Testing.

Roles

Concretely, Kaizen team followed the test step by step. Main roles have been identified during the Stat testing process:

- 3 Analysts to perform a regular Sialic test.
- Someone to capture each activity on a sticky note (Capture pain points and solutions).
- Someone to time each activity.
- Others observe and note differences/comments with their methodology.

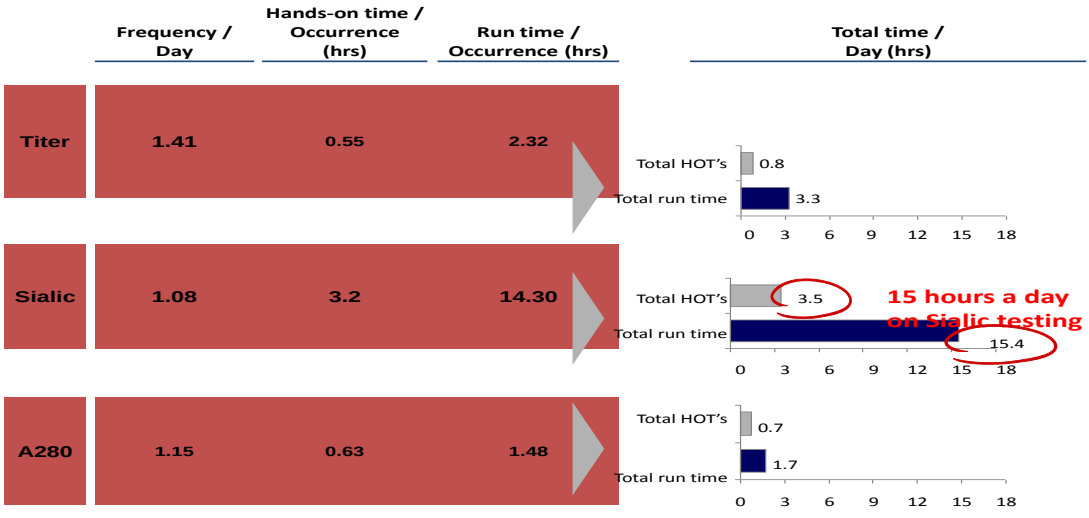

Figure 1
Total Time and Hands-On Time for Each Test of Stat Testing

Process

Different activities were performed during Kaizen events with three analysts of Quality Control Laboratory:

- Review Stat Testing process and Value Stream Mapping.
- Identify value added and Non-value added activities.
- Measure the timing of each analyst during the Stat Testing process.
- Evaluate personnel movements during Stat testing execution.
- Identify pain points.

Stat Testing consists in four tests: Titer Assay to quantify of Protein A material, Sialic Assay to quantify the amount of NGNA/NANA, A-280 method for determination of Total Protein Concentration by Absorbance at 280 nanometers (nm), and Purification of Protein A by AKTA (see Figure 2).

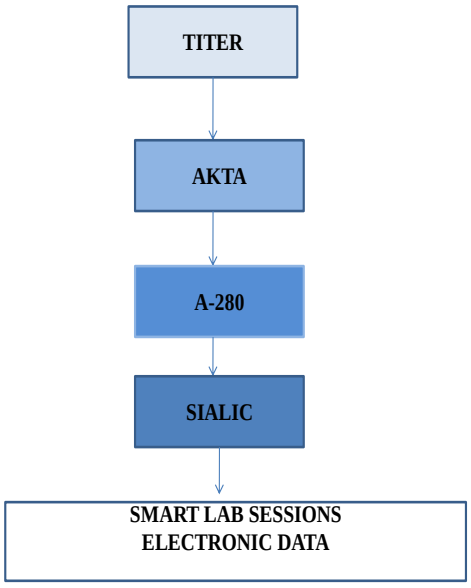

Figure 2
Value Stream Mapping of Stat Testing

SmartLab is electronic laboratory notebook. The different steps are: In-process (Initiating by Analyst), Completed (Completion of all analytical data entry by Analyst), Reviewed (Verification of all analytical data by Reviewer), and Approved (Procedure session has had final approval by Leads or Managers), see Figure 3.

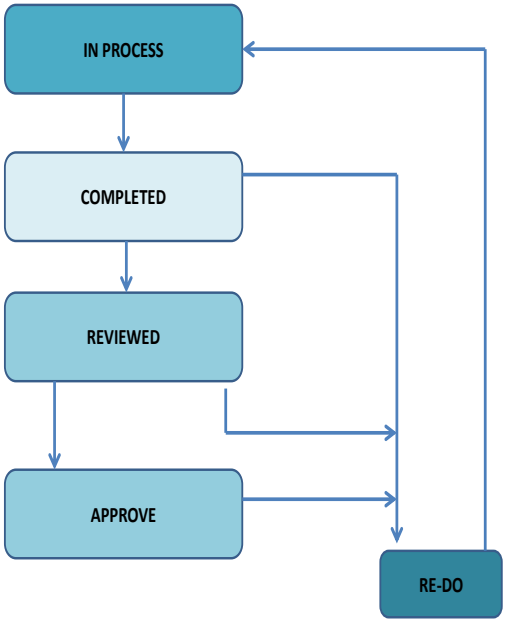

Figure 3
Value Stream Mapping of SmartLab

The first Kaizen event was performed by Analyst no. 1 to evaluate the different activities during Stat Testing and measure the cycle time for all tests. The Analyst no. 1 did not identify pain points in Stat testing process (see Table 1).

Table 1
Kaizen Event 1

Date	*11/28/2012*
Shift	First
QC Analyst	1
Tests	Sialic, AKTA, A-280
Start Time	08:30
End Time	15:50
Samples	1
Total Time (min)	440
Total Time (hr)	7.3
Total Hands-on Time (min)	189
Total Hands-on Time (hr)	3.2
Total Wait Time (min)	251
Total Wait Time (hr)	4.2

Table 2
Kaizen Event 2

Date	*01/18/2013*
Shift	First
QC Analyst	2
Tests	1 Titer, 2Sialic, AKTA, A-280
Start Time	08:55
End Time	16:36
Samples	2
Total Time (min)	378
Total Time (hr)	6.3
Total Hands-on Time (min)	216
Total Hands-on Time (hr)	3.6
Total Wait Time (min)	195
Total Wait Time (hr)	3.3

The second Kaizen event was performed by Analyst No. 2 to evaluate the different activities during Stat Testing and measured the cycle time for all tests (see Table 2). The Analyst no. 2 identified pain points in Stat testing process:

- Equipment location.
- Availability of Sample Receipt.
- AKTA sample line (elephant sound).
- Critical Reagent location.

The third Kaizen event was performed by Analyst No.3 to evaluate the different activities during Stat Testing and measured the cycle time for all tests (see Table 3).

Table 3
Kaizen Event 3

Date	*02/04/2013*
Shift	Second
QC Analyst	3
Tests	Sialic, AKTA, A-280,
Start Time	18:09
End Time	18:24 next day
Samples	1
Total Time 2nd Shift (min)	256
Total Time 2nd Shift (hr)	4.3
Total Hands-on Time 2nd Shift (min)	223
Total Hands-on Time 2nd Shift (hr)	3.7
Total Time 1st Shift (min)	124.0
Total Time 1st Shift (hr)	2.1
Total Hands-on Time (min)	33
Total Hands-on Time (hr)	0.6
Total wait Time (min)	118
Total Wait Time (hr)	2.0
Total time 1st Shift and 2nd Shift (hr)	24.3

The Analyst No. 3 identified pain points in Stat testing process:

- Multiple sample prep area.
- AKTA sample line (elephant sound)

Spaghetti Diagram in the Figure 4, Figure 5 and Figure 6, reflects all personnel movements by each Analyst during Stat testing execution.

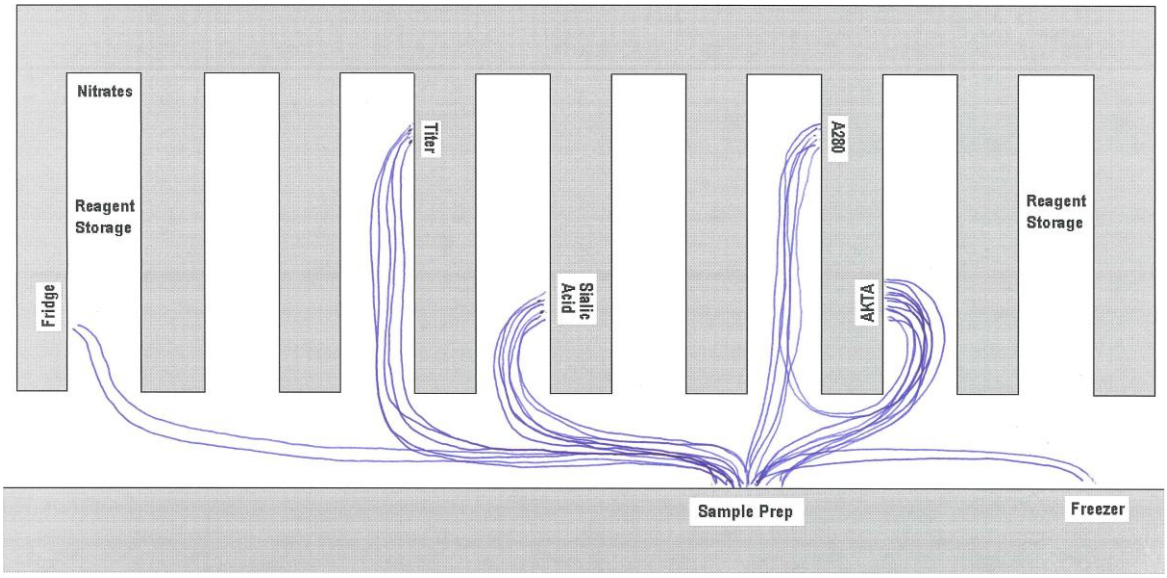

Figure 4
Actual Flow of Stat Testing Process from Analyst 1

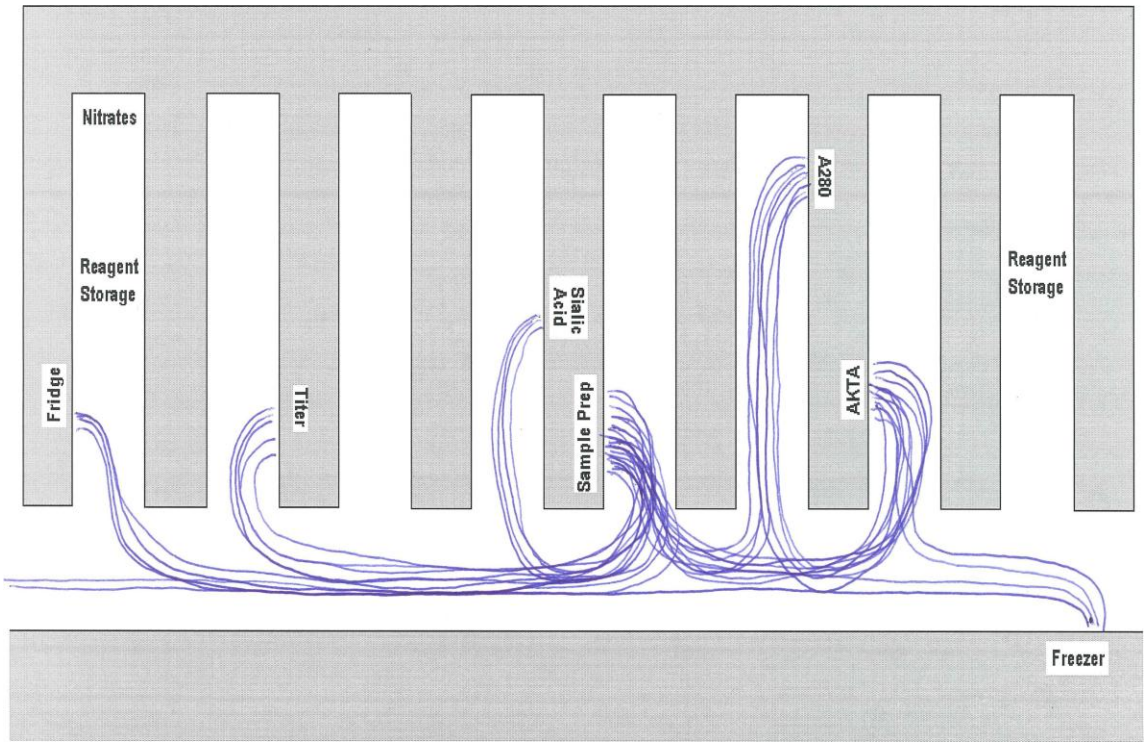

Figure 5
Actual Flow of Stat Testing Process from Analyst 2

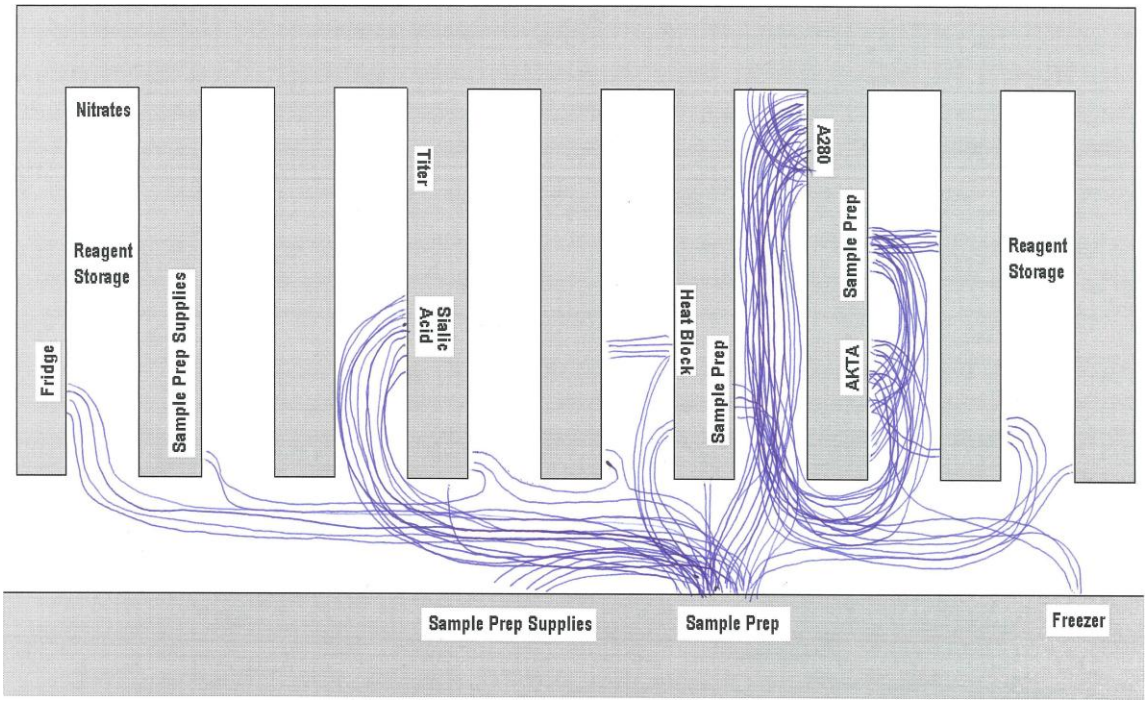

Figure 6
Actual Flow of Stat Testing Process from Analyst 3

RESULTS

Three Kaizen events were performed in Quality Control Laboratory. The target time in QC Lab to complete Stat Testing is 12 hours. The timing starts when the sample is available in LIMS for testing. The Kaizen Analysis results are the following:

- The total cycle time of Analyst no. 1 was 7.3 hours. Analyst No. 1 can reduce the cycle time of Stat Testing at 4.7 hours.
- The total cycle time of Analyst no. 2 was 6.3 hours. Analyst No. 2 can reduce the cycle time of Stat Testing at 5.7 hours.
- The total cycle time of Analyst no.3 and Analyst no. 4 was 24.3 hours. Analyst No. 3 and Analyst No. 4 cannot reduce the cycle time of Stat Testing due to the third shift is not available to perform and complete analytical testing (see Table 4)

Table 4
Total Cycle Time of Stat Testing

Analyst	Cycle Time of Stat Testing (hrs)
No. 1	7.3
No. 2	6.3
No. 3/No. 4	24.3

Non-Value Added (Wastes)

Non- value added is all activities that do not contribute to the Stat Testing process. Non-value added tasks are wastes. Kaizen Team had been identified different wastes during the Sialic Kaizen Analysis:

- Every Analyst has variability during equipments set up.
- Some SOP's are not clear about equipments set up before start testing.
- Elephant sound of AKTA system. This sound indicates that the Analyst has to change the AKTA line to complete the elution process for each step: Reference Material and samples.
- Pick up samples in other Lab.
- Ineffective schedule and Stat testing sequence.
- Excessive personnel movements during Stat testing execution.
- Lack communication between manufacturing and the QC Lab group.
- Critical Reagent Location.
- Timing of Aliquoting of samples.
- Reviewer is not available to approve the chromatograms.
- Poor Team work skills.
- Number of samples to analyze.

CONCLUSION

Kaizen Analysis has been a dramatic effect on reducing cycle time and significant improvements in efficiency and productivity. During the Sialic Kaizen process performed in Quality Control Lab, it was evident that there are areas of opportunity for improvements. Spaghetti Diagram by analyzing the waste was identified by delaying unnecessary movements cause long set up time. Analysts performed Stat Testing in different sequential order. Therefore, it has a huge variability in the analytical process and it causes inefficient process and delay in the cycle time of testing. Looking the Lab layout, analysts employed a number of movements through the equipments bays and sample preparation station, produced waste of time and effort, increase operational costs, and there may a greater distraction causing errors in different processes: sample analysis, analytical data entry, verification and approval of Smart Lab sessions.

Finally, Kaizen Analysis obtained positive results using the Value Stream Mapping and Spaghetti Diagram. The cycle time of Stat Testing was improved from 12 hours to 6.3 hours. The benefits of this Research include increase productivity; improve cycle time and quality of Analytical Lab services. In addition, it can improve organization and input on decisions impacting the company strategies, coordinated and sustainable approach. A continuous improvement is the main objective for leading Operational Excellence.

FUTURE WORK

During the Kaizen events, Quality Control Team evaluated potential improvements and identified three main projects:

- Standardize Stat Testing: Identify methodology sequencing that improves testing timing predictability and efficiency. Standardize best practices and ensure that everyone does it the same way to reduce variability in results.
- Re-configure in-process Lab: Change layout (U-shape workstation). Remove unnecessary equipments. Implement, review, and approval qualification of equipments (IQ/PQ/OQ).
- Review and approval standardization.

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