Clean Room Differential Pressure Monitoring Improvements

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Abstract *— Manufacturing of oral solid dosage (OSD) forms, such tablets and capsules, is performed in a highly regulated environment. One of the guidelines used to provide the minimum requirements that a manufacturer must meet to assure that their products are safe for their intended use is the Good Manufacturing Practice (GMP). This practice gathers the data of the agencies that control the authorization and licensing of the manufacture and sale of food & beverages, pharmaceutical products, and others. A case study will be developed from a European Regulatory Agency recommendation to a Pharmaceutical Company to improve clean rooms differential pressure monitoring strategy, in order to meet the agency standard. Aspects and tools from Process, Automation, and Quality Engineering were used in order to comply with the standard. Additionally, a potential time saving project was identified.*

Key Terms *— Clean Rooms, Data Historian, Differential Pressure Monitoring, Pharmaceutical.*

INTRODUCTION

In pharmaceuticals and medicine industries, clean rooms are used when it is necessary to ensure an environment free of bacteria, viruses, or other pathogens. In addition, the temperature and humidity may be controlled and monitored [1]. Some important definitions during this article are:

- *Cleanrooms* are designed to maintain extremely low levels of particulates, such as dust, and airborne organisms. Typically, they have a cleanliness level quantified by the number of particles per cubic meter at a predetermined molecule measure. One of the techniques used in clean spaces is the room pressurization (or depressurization) to create the desired flow patterns from less clean rooms to cleaner rooms and to minimize airborne particle contamination. The air flow patterns are achieved by mechanically creating air pressure differences between rooms to cause intentional air movement through room leakage opening [2].
- *Differential Pressure Monitor (DPM)* is an electronic device used to monitor the difference in pressure between two areas (see Figure 1). DPMs are typically used in the pharmaceutical industry to monitor or control air flow between rooms and prevent the product cross-contamination or foreign particle contamination.

Figure 1
Differential Pressure Monitor

The existing model of DPM device that is installed in the site are Siemens 547-103A. This model is designed for critical low differential pressure applications that require stringent pressure monitoring and alarming. In terms of communication protocol, the P1 or classic 4-20mA can be used.

- *Building Management System (BMS)* is a computer-based control system installed in buildings that controls and monitors the building's mechanical and electrical equipment such as heating, ventilation, air conditioning (HVAC), lighting, power systems, fire systems, and security systems.
- *Data Historian* refers to a complementary set of time-series database applications that are

developed for operational process data. Historian software is often used in conjunction with standard BMS to provide enhanced data capture, validation, and compression capabilities.

JUSTIFICATION

In 2018, a European Regulatory Agency, recommended to a Pharmaceutical Company located in Puerto Rico to improve their clean rooms differential pressure monitoring strategy. The current European Quality Standard states "Where special conditions are required (e.g., temperature, humidity, differential pressure), they must be recorded, monitored, and alarmed". The agency states that the actual manual process does not necessarily meet the expectation of being "recorded and monitored".

ACTUAL PROCESS

The manufacturing site has five buildings that are interconnected. For the purpose of this project, we will name the buildings as follows: A, B, C, D, and E. Refer to Figure 2.

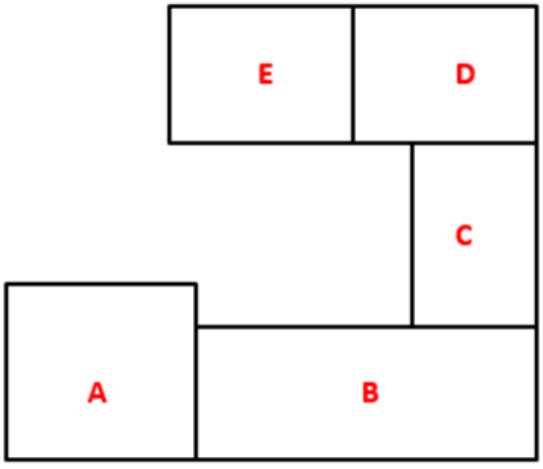
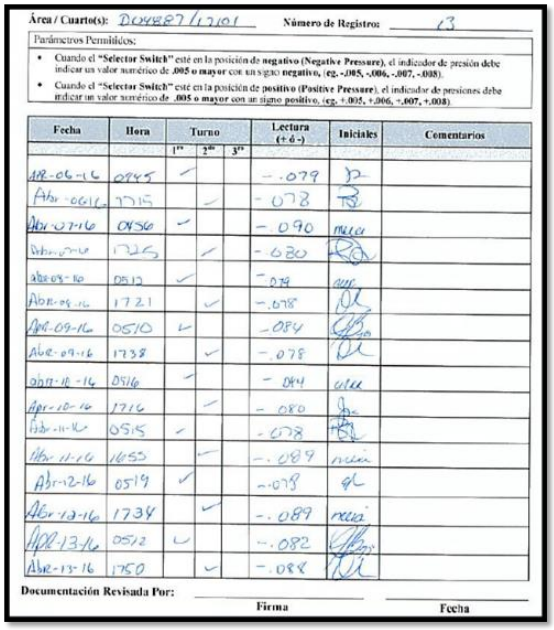


Figure 2
Building Top View Sketch

According to the actual procedure, next to each DPM there is an annex sheet of the procedure in order to log the DPM condition once per shift. During this process the operator logs the DPM actual reading, actual condition (whether or not the unit is in an alarm state), and signs the sheet in order to confirm the process. If an alarm is active, a corrective work order is generated in order to correct the situation with the maintenance department. This process is documented in the comments section of the sheet. Refer to Figure 3 for an example of the data collection form. At the end of the week, the sheet needs to be evaluated and signed by the area supervisor.


Área / Cuarto(s): D04827/17101 Número de Registros: 13

Parámetros Permitidos:

- Cuando el "Selector Switch" esté en la posición de negativo (Negative Pressure), el indicador de presión debe indicar un valor numérico de .005 o mayor con un signo negativo, (eg. -.005, -.006, -.007, -.008).
- Cuando el "Selector Switch" esté en la posición de positivo (Positive Pressure), el indicador de presiones debe indicar un valor numérico de .005 o mayor con un signo positivo, (eg. +.005, +.006, +.007, +.008).

Fecha	Hora	Turno 1er	Turno 2do	Turno 3er	Lectura (+ ó -)	Iniciales	Comentarios

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Figure 3
Manual Data Collection Form Example

All the buildings at the site are interconnected, yet they share a common general area, according to Figure 4. The manufacturing operator needs to go to each process room in order to collect the data. In addition, in order to get the data of the DPM located inside a process room, the operator needs to perform the Gowning/Degowning operation, a process that can take approximately eight minutes.

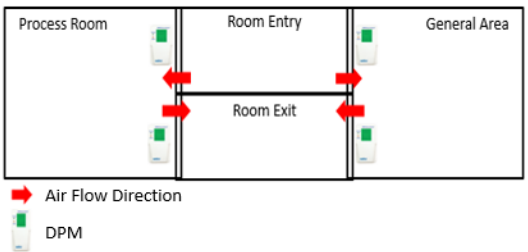

Figure 4
Simple Process Room Top View Sketch

This process is performed between five manufacturing operators, one per building. A time study data collection was performed in order to determine how many hours the operators spend in the completion of this task. The results of the study are summarized in Table 1.

Table 1
Time Study Results

Building	Total DPMs	Data Collection Time
A	27	1 hr. 20 min
B	45	2 hr. 15 min
C	123	3 hr. 30 min
D	30	1 hr. 15 min
E	25	1 hr. 15 min
Total	**250**	**9 hr. 30 min**

METHODOLOGY

To find the best strategy and find a solution for this situation, a combination of quality and project management tools will be used. Additionally, it will be necessary to build a multidisciplinary team. Some of the identified tools for quality management are research, benchmarking and brainstorming. In research, a thorough investigation of the industry's best practices will be performed using guidelines such as the International Society of Pharmaceuticals Engineers (ISPE) and the American Society of Heating, Refrigerating and Air-Conditioning Engineer (ASHRAE) will be studied. Figure 5 shows a typical Benchmarking process.

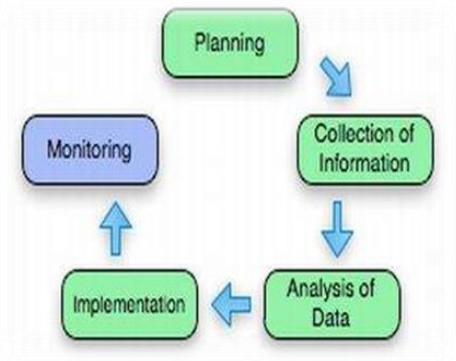

Figure 5
Benchmarking Process

According to the Project Management Institute (PMI), the five phases of project management include conception and initiation, planning, execution, performance/monitoring, and project closing. Dividing project management efforts into these five phases can help give efforts structure and simplify them into a series of logical and manageable steps. Figure 6 shows the five phases roadmap.

Figure 6
Project Lifecycle Process

QUALITY TOOLS RESULTS

For the Planning and Collection of Information of the benchmarking process, a few questions were developed in order to share information with other two sites of oral solid dosage (OSD) of the same company. One site is located in the United States and the other in China. The questions were the followings:

- How is the daily process for DPM readings?
- How the data is stored?
- Is there a classification system for alarms?
- Are the alarms monitored?

The benchmarking process of Analysis of Data will be discussed in the next section. The benchmarking process of Implementation will be substituted with the Executing phase of the Project Management Lifecycle Process. Likewise, the benchmarking process of Monitoring will be substituted with the Monitoring phase of the Project Management Lifecycle Process.

Table 2, 3 and 4 contains the answers for the questions defined as part of the Planning and Collection phase.

An investigation of the industry's best practices was performed. Some of the key points are:

- Instruments that monitor critical room parameters should be a part of a qualification program. Qualification plans should address sensors, alarms, and recording systems for critical parameters [3].
- A Quality Risk Management Process for OSD Facilities should be initiated where the potential GMP and non-GMP risks/hazards for the different design, and qualification considerations are identified. Also, a failure mode analysis should be initiated where potential GMP and non-GMP failure scenarios based on risks are identified [1].

Table 2
Puerto Rico Site Benchmarking Answers

Puerto Rico
Data is recorded manually at each shift in a controlled form.
No Data Historian. Form stored in the GMP library.
Has the capability of data historian using Apogee system, but is not connected.
Alarms don't have classification properties.
Doesn't have monthly alarm trending.

Table 3
United States Site Benchmarking Answers

United States
Data is retrieved using BMS (Building Management System).
Stored on a Validated Data Historian.
Alarms are sent to a common database from which the reports are created.
Alarms are classified by levels as Critical, Warning and Normal. DPMs alarms are considered Critical.
Monthly alarm trending is performed.

Table 4
China Site Benchmarking Answers

China
Data is retrieved using BMS (Building Management System).
Stored on a Validated Data Historian.
Alarms are sent to a common database from which the reports are created.
Alarms are classified by levels as Critical, Warning and Normal. DPMs alarms are considered Critical. They are also classified by color (Red, Yellow, Black, Green) and by priority number.
Doesn't have monthly alarm trending.

ANALYSIS OF DATA

A multidisciplinary team composed of HVAC Process Engineer, Automation Engineer, and Quality Engineer analyzed the results, and using the brainstorming process, created a new process for the Puerto Rico site, which is outlined in Table 5.

Table 5
Benchmarking Results

Puerto Rico new process
Retrieve data using BMS (Building Management System).
Store on a Validated Data Historian.
Send alarms to a common database from which the reports are created.
Classify alarms by levels as Critical, Warning and Normal. DPMs alarms are considered Critical. Also classify by color (Red, Yellow, Black, Green) and by priority number.
Perform monthly alarm trending.

Using the planning process of project management tools, this project will be developed using three phases. Refer to Figure 7.

- Phase I consists of connecting the 250 DPM units to the current BMS (which in the Puerto Rico site is Siemens Apogee). This connection will be Daisy-Chain FLN P1 Siemens Protocol. With this connection, it will be possible to perform real time remote monitoring and have remote access to the DPMs configurations.
- Phase II consists of transferring the data from the BMS to the current validated Data-Historian OSIsoft. This connection will be via OLE for Process Control Unified Architecture (OPC-UA) servers. With this connection in place, historical data will be retrievable from the server. The amount of data able to be retrieved will depend on how long the client is willing to store that data. This project is focused on this phase.
- Phase III involves transferring the data from the Data-Historian to the Business Analytics also via OCP-UA. With this integration, the custom Data-Reports for alarms evaluation will be available. Additional details will be discussed in the next section.

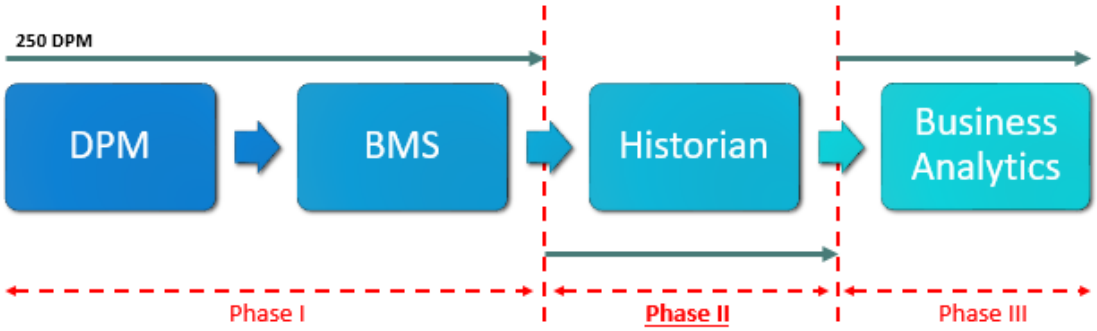

Figure 7
Project Phases

Project Management Tools: Initiating

To initiate the project, the multidisciplinary team collected information to develop the project charter. Project Charter refers to a statement of objectives in a project. This statement also sets out detailed project goals, roles and responsibilities, and identifies the main stakeholders. Table 6 presents a Project Charter example of this project to be presented to the stakeholders.

Table 6
Project Charter Example

Problem	• Production personnel spend approximately 10 hours daily recording DPMs readings for the entire site. • Reading history is hard to track. • Manual data recording does not comply with new regulatory agency expectations and standards of data integrity.
Scope:	• Include DPMs reading in the Apogee System (hardware and software), and configure the alarms. • Visualization plots in OSIsoft (per room). • Include a report per room in SAP Business Object.

Typically, the Project Charter is presented to the upper management in a one-page power point summary. This information must include the total project cost (refer to Table 7) and the project benefits (refer to Figure 8).

Table 7
Capital Request for Project Charter

Capital Request	Amount
Field to Apogee Installation	$80,000
Field to Apogee Qualifications	$10,000
New Historian Server	$20,000
Apogee-Historian Installation	$30,000
Apogee-Historian Qualification	$10,000
Internal/External Engineering	$30,000
Contingency (10%)	$18,000
Total Request	**$198,000**

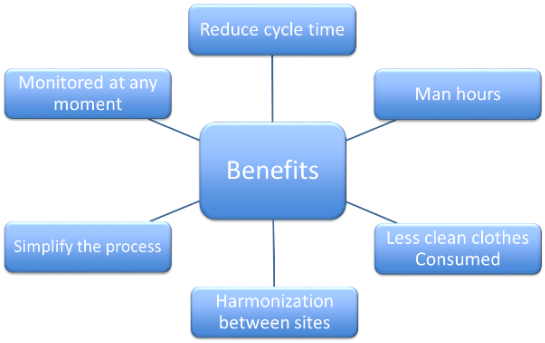

Figure 8
Benefits Grid

Project Management Tools: Planning

Figure 9 shows project phase specification as a continuation of Figure 7. In the next section the project phases will be explained.

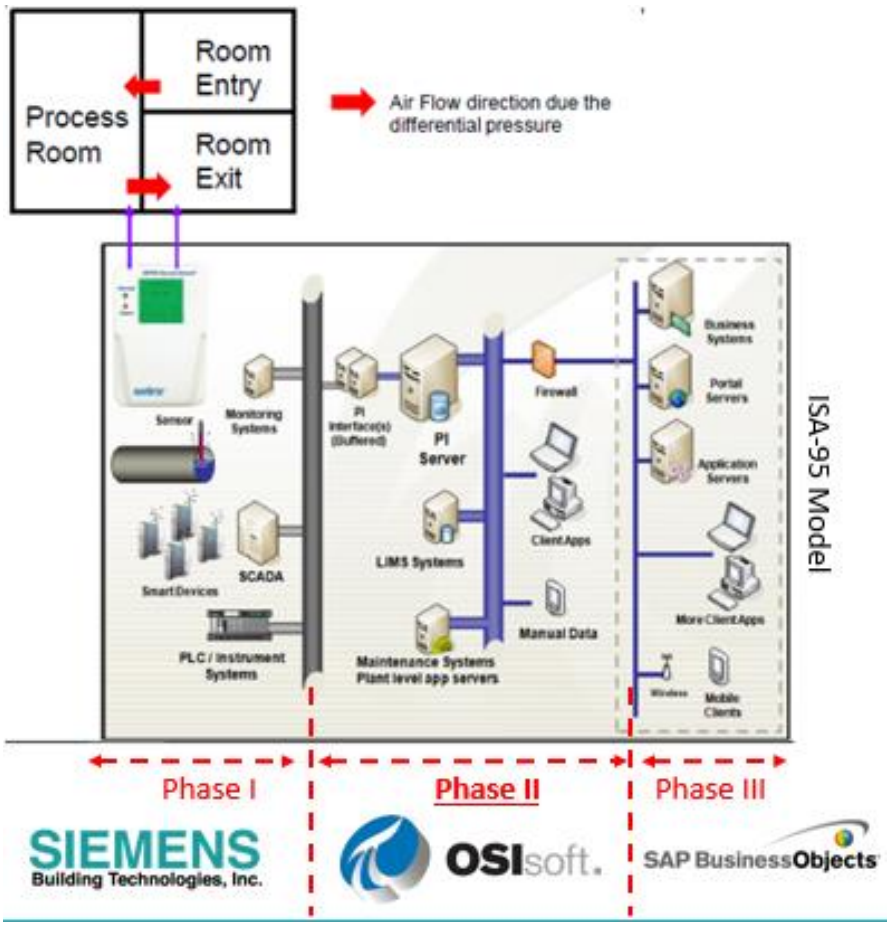

Figure 9
Project Phase Specifications

- Phase I: The existing DPMs read the differential pressure between the clean rooms and the adjacent rooms. The new FLN connection will be installed between the sensor and the existing Programmable Logic Controller (PLC). With this connection in place, continuous monitoring will be possible directly from the current Monitoring System workstation. This phase was part of another project that was completed last February.
- Phase II: Install a new OPC Connection that will serve as the PI interphase between the existing PLC and PI server. This phase is the main focus of this article.
- Phase III: Once the data are in the OSIsoft system, it can be connected to the SAP Business Objects Applications Server. With the data in SAP, any custom report can be built. This phase is scheduled to be completed in August 2019 due to server delivery.

Table 8 shows a high-level schedule of the entire project.

Table 8
High Level Schedule

TASK	PROGRESS
Phase I	
DPM Wiring	100%
DPM Configuration	100%
BMS Configuration	100%
Phase II	
Interface Installation	100%
OPC Configuration	100%
Tags Configuration	100%
Phase III	
Server Installation	0%
OPC Configuration	0%
Report Builder	0%

Project Management Tools: Executing

As mentioned in the planning section, Phase I of the project was already implemented. Figure 10 shows an example of the results in the BMS configuration. The blue small rectangles in the middle of the picture represent the room temperature and relative humidity readings, which was the main purpose of the BMS. The green rectangle represents a manufacturing room, and the yellow and light pink are manufacturing general areas. The black numbers next to the room doors, are the DPMs real time readings that were implemented as part of the Phase I.

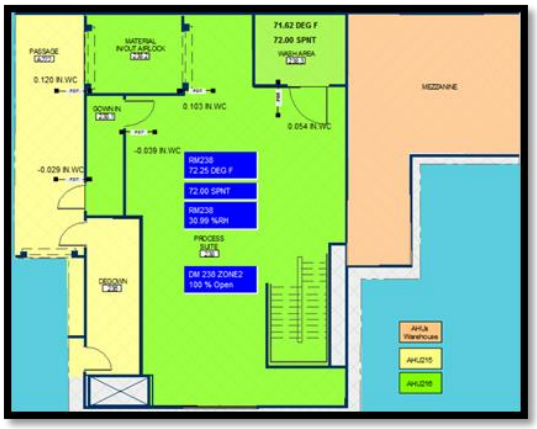

Figure 10
BMS Example

As part of Phase II of this project, a new OPC Connection was installed that serves as the PI interphase between the existing PLC and PI server. This enables real time data gathering from the DPMs. Figure 11 shows a screenshot of the PI Vision Data-Historian DPMs readings in table form. At the bottom of the picture is the timeframe configuration. The table shows the following:

- Tag name
- Tag description
- DPM actual value
- Trend Chart
- Minimum reading during timeframe
- Maximum value during timeframe

A historian can provide full historical trending capabilities. The trending on a local controller has a limited memory capacity, whereas a historian is designed to retain the process data to meet compliance requirements. The data can either remain on the server or be archived for long term storage [3]. As a company best practice, the data should remain on the server and a backup should be performed on a weekly basis to a cloud service. Additionally, per regulation this data should be stored up to twelve years in case the data is required for an investigation.

Project Management Tools: Monitoring

In the Monitoring phase the project progression and performance are measured to ensure that everything aligns with the project management plan. For this project, the key performance indicators (KPIs) for measuring project performance and progression are the Quality Deliverables and the schedule.

- Quality Deliverables: As previously mentioned in the justification section, the European standard states: “Where special conditions are required (e.g., temperature, humidity, differential pressure), they must be recorded, monitored, and alarmed”. Moreover, the main purpose of this project is the Recorded section of the standard. As explained in the Executing section, the real time monitoring of DPMs readings have successfully been implemented using the Data-Historian. Thus, it can be determined that the Quality Deliverables were accomplished.
- Schedule: Table 8 shows a high-level project plan schedule. Currently, the first two phases of the project have been completed. The third and final phase of the project is on track and scheduled for August 2019. The purchase orders have already been placed to the server manufacturer and is scheduled to arrive to the site at the end of July 2019.

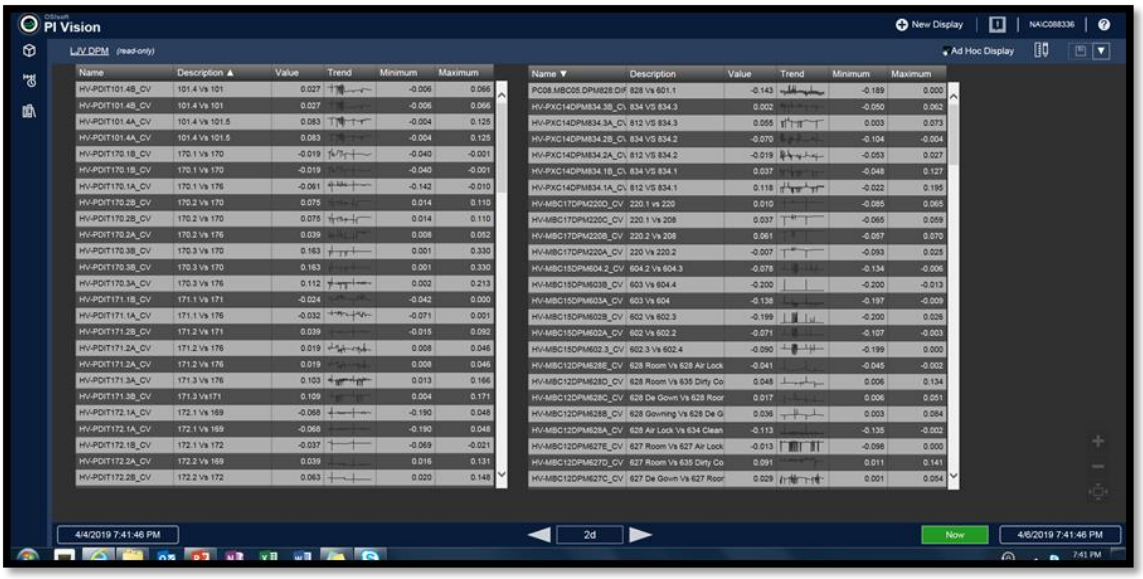

Figure 11
Data-Historian Example

Project Management Tools: Closing

This phase represents the completion of the project. Given the scope of this article, the project can be declared as successfully completed. However, the area management is engaged to continue the project until Phase III to be able to generate automated reports and modify the actual procedure to discontinue the practice of manual data collection. Additionally, one of the key decisions to successfully implement the project on time was to choose a contractor with experience in handling similar projects, despite the fact that it was more expensive.

Recommendation

The principal recommendation for this project is to continue the completion until Phase III. With the completion of Phase II, the site is completely in compliance with the regulation. As part of Phase III implementation, the procedure should be modified to remove the manual collection instruction and replace it with the automated report in order to be in compliance in the Monitored section of the standard. With the implementation of Phase III, the procedure can be modified to use automated report and replace the manual collection form. Is important to mention that this Phase III can save up to 10 hours daily of a manufacturing operator.

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