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## Abstract

Manufacturing of oral solid dosage (OSD) forms, such as 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.

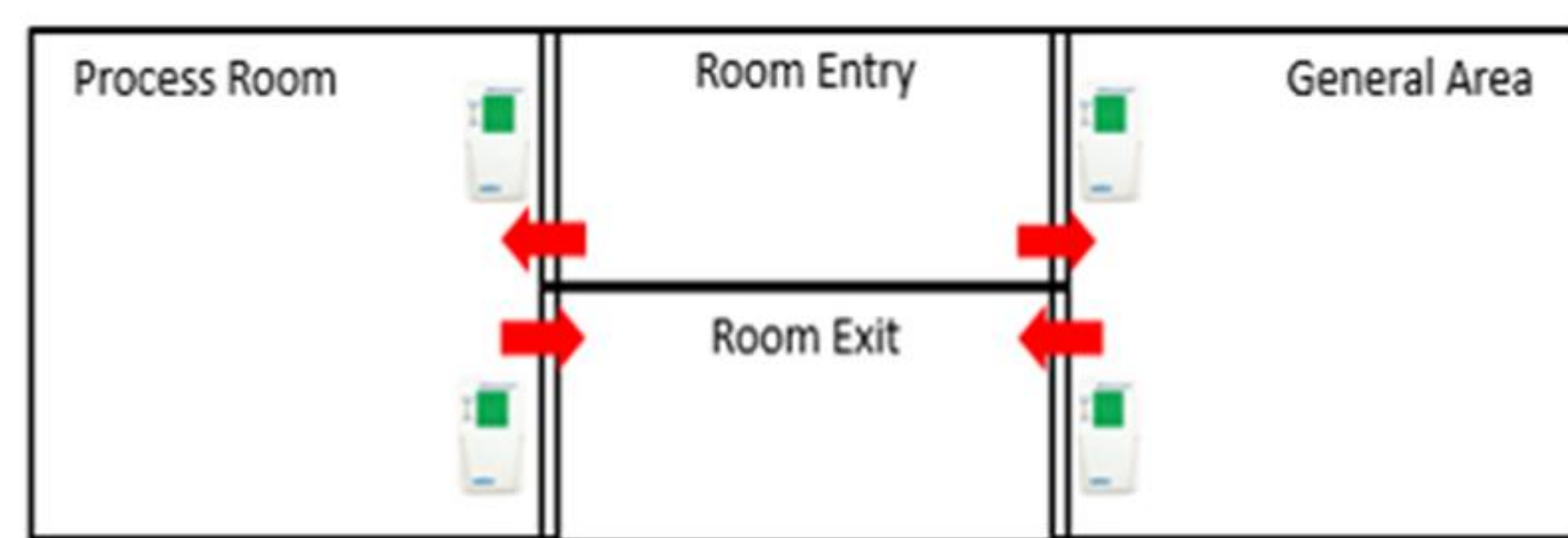
A case study will be developed from an European Regulatory Agency recommendation to a Pharmaceutical Company to improve clean rooms differential pressure monitoring strategy, in order to meet the agency standard. Aspects and tools from Process, Automation, and Quality Engineering were used in order to comply with the standard. Additionally, a potential time saving project was identified.

## 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. Some important designations during this article are:

- Cleanrooms
- Differential Pressure Monitor (DPM)
- Building Management System (BMS)
- Data Historian

DPM is an electronic device used to monitor the difference in pressure between two areas. 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



## 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

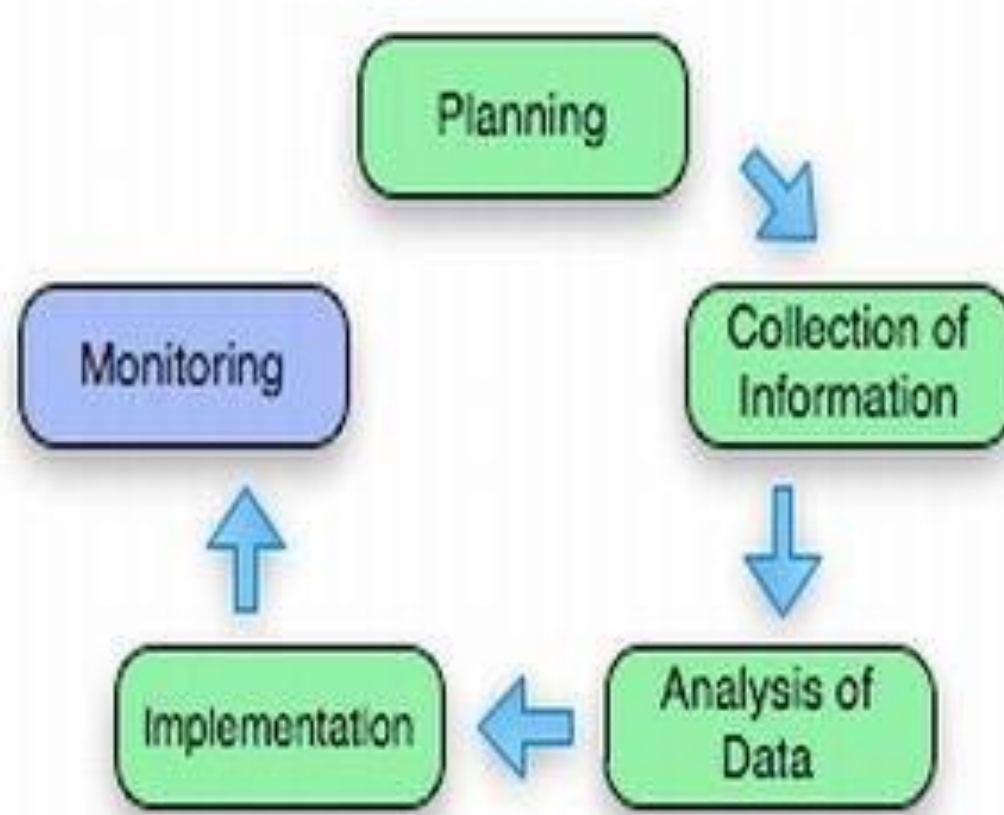
The manufacturing site has five buildings that are interconnected. For the purpose of this project, we will name the buildings as follows: A, B, C, D, and E.

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.

| Building     | Total DPMs | Data Collection Time |
|--------------|------------|----------------------|
| A            | 27         | 1 hr. 15 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         |
| <b>Total</b> | <b>250</b> | <b>9 hr. 30 min</b>  |

## Methodology

To 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.



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.



## 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 of the same company. One site is located in the United States and the other in China. The questions were the followings:

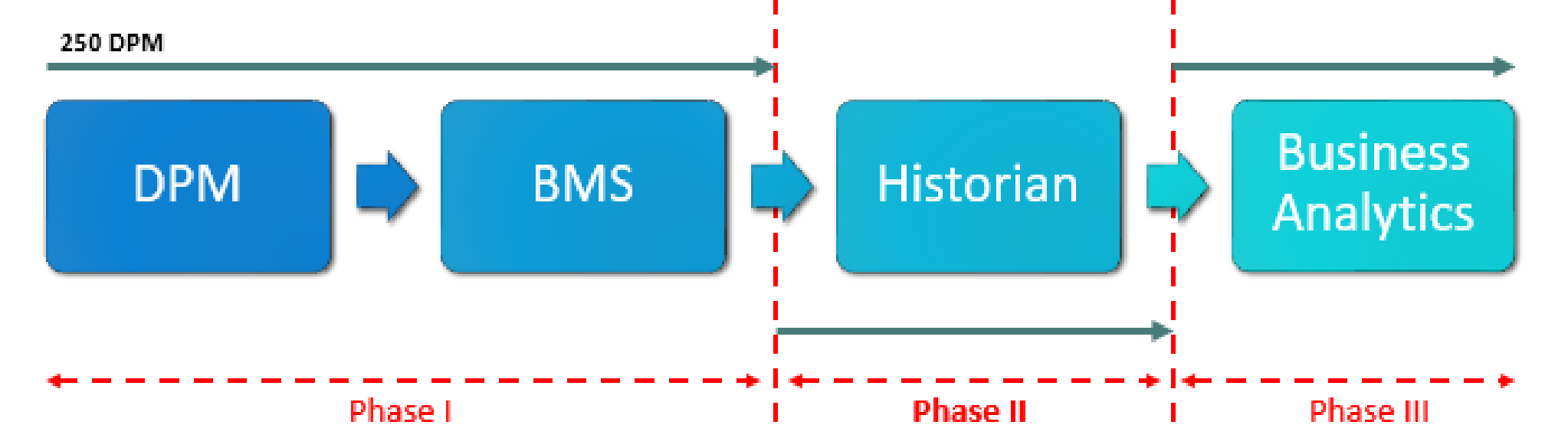
- How is the daily process for DPM readings?
- How the data is stored?
- Is there a classification system for alarms?
- Are the alarms monitored?

|   | Puerto Rico   | United States   | China  |
|---|---|---|--|
| <b>Recorded manually at each shift in a controlled form</b> | Use BMS (Building Management System)                                    | Use BMS (Building Management System)                                    | Use BMS (Building Management System)   |
| <b>No Data Historian. Form stored in the GMP library</b>    | Stored on a Validated Data Historian                                    | Stored on a Validated Data Historian                                    | Stored on a Validated Data Historian   |
| <b>Have the capability of data historian using Apogee</b>   | Alarms are sent to a common database from which the reports are created | Alarms are sent to a common database from which the reports are created | DP alarms are called by classification, (Critical, Warning and Normal) by color (Red, Yellow, Black, Green) and by priority number |
| <b>Alarms don't have classifications properties</b>         | Alarms is classified by levels (DP is Level 3)                          |   |  |
| <b>Doesn't have monthly alarm trending</b>                  | Monthly alarm trending  | Monthly alarm trending  | Doesn't have monthly alarm trending  |

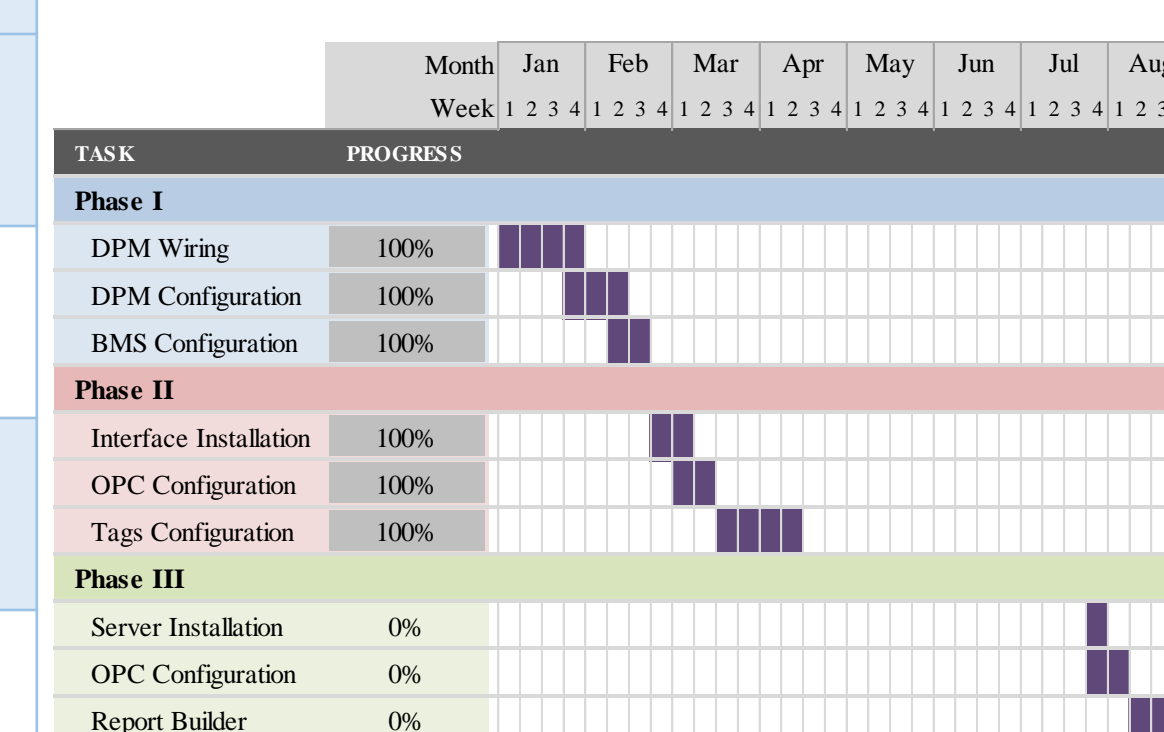
A multidisciplinary team composed of: HVAC Process Engineer, Automation Engineer, and Quality Engineer analyzed the results, and using the brainstorming process, created a new process for the Puerto Rico site.

## Implementation Overview

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



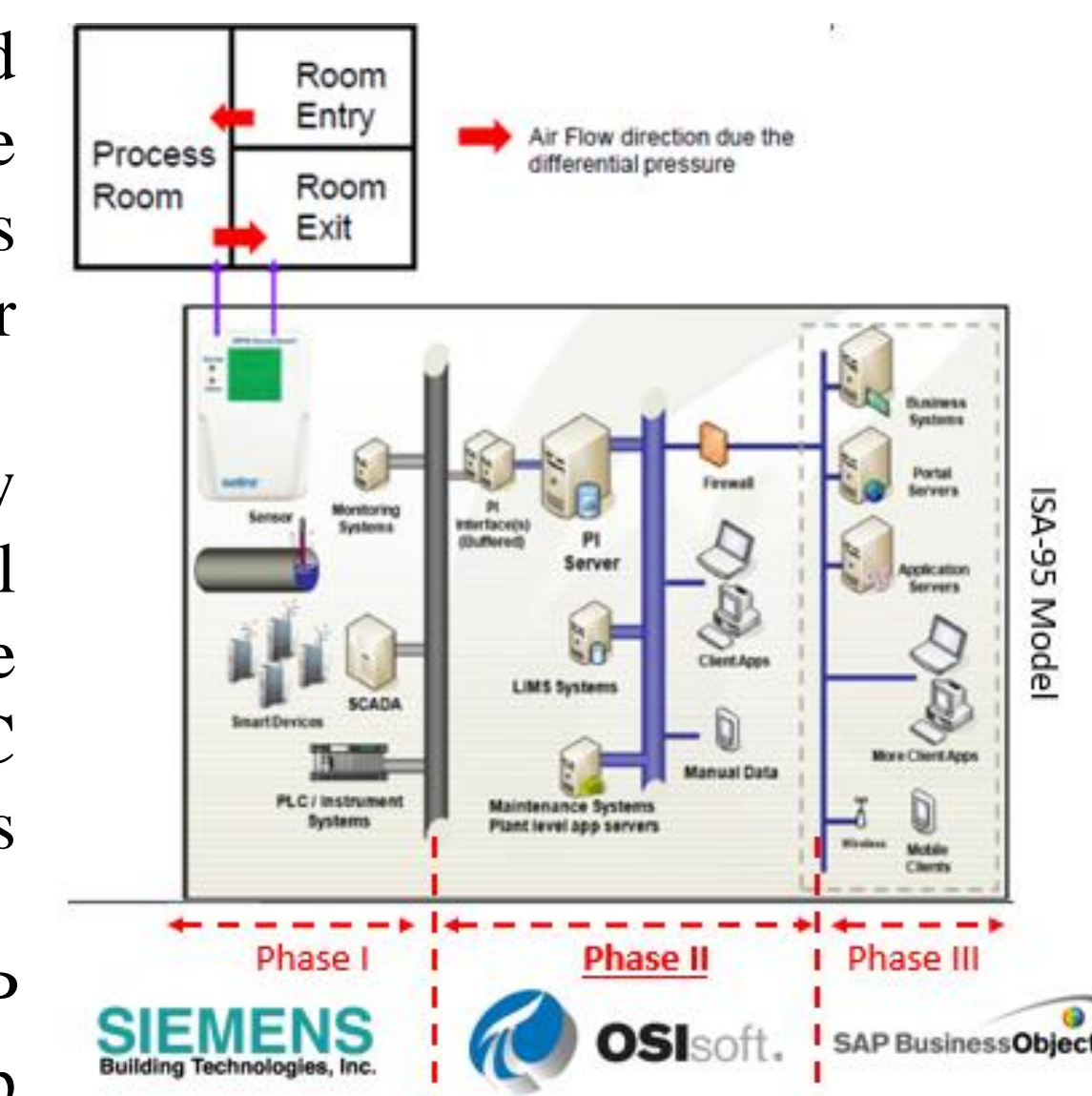
| Capital Request                | Amount           |
|--------------------------------|------------------|
| Field to Apogee Installation   | \$80,000         |
| New Historian Server           | \$20,000         |
| Apogee-Historian Installation  | \$30,000         |
| Apogee-Historian Qualification | \$10,000         |
| Internal/External Engineering  | \$30,000         |
| <b>Total Request</b>           | <b>\$170,000</b> |



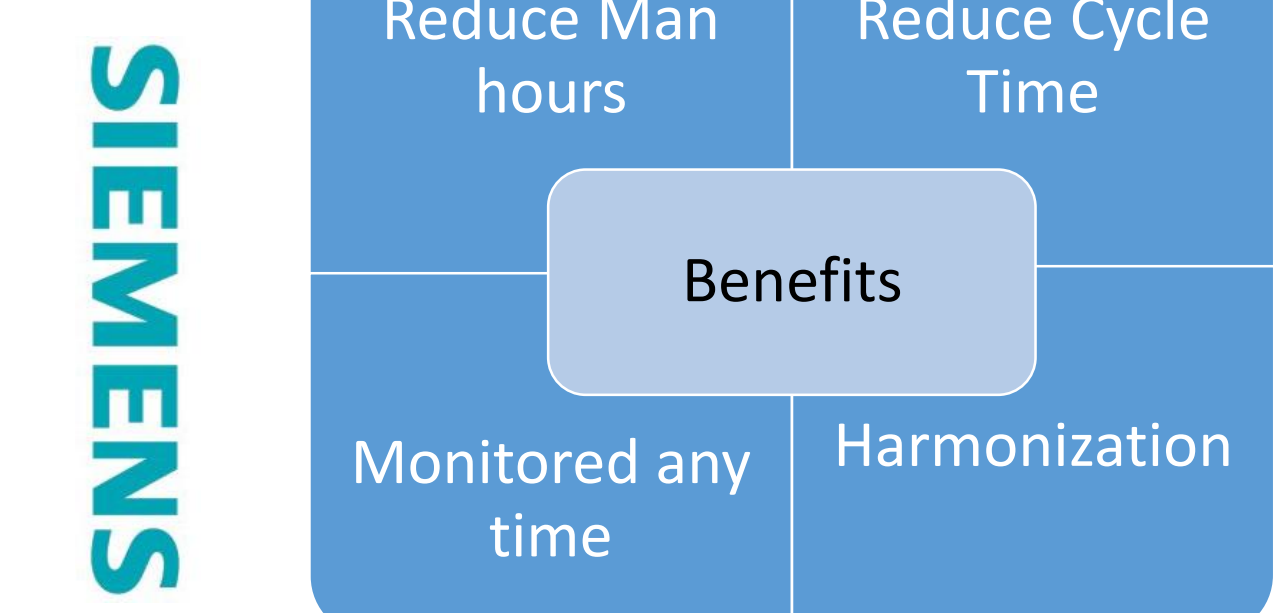
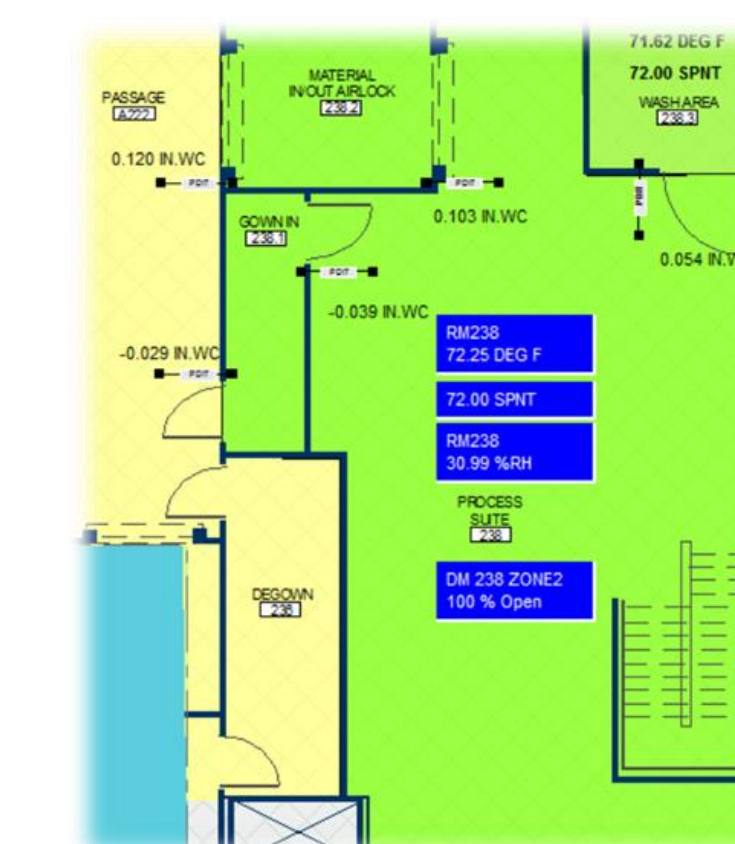
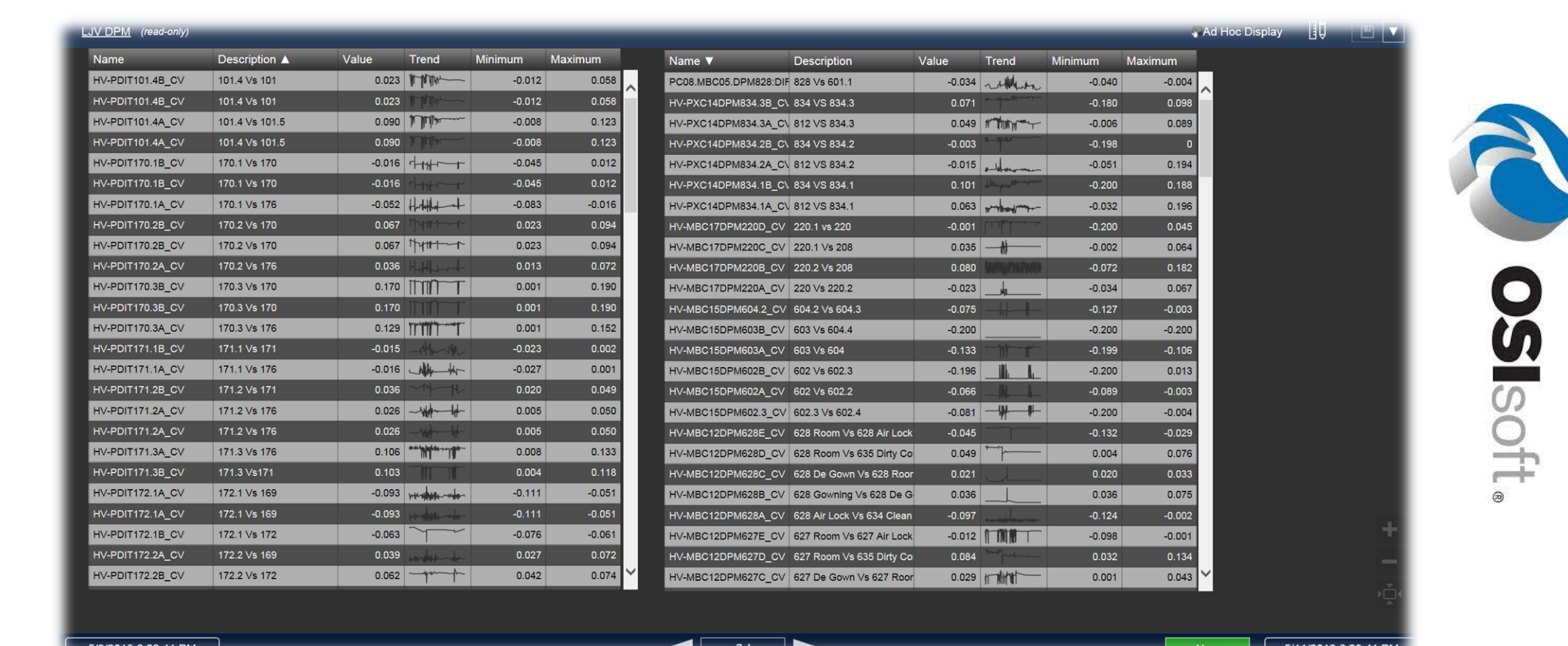
## Implementation Details

Current Automation Architecture follow ISA-95 standard.

- Phase I: The new FLN connection will be installed between the sensor and the existing Controller. This phase was part of another project.
- 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: Use SAP Business Objects to develop custom reports.



## Final Outcome



## Acknowledgements

Special thanks to my Design Project advisor Miriam Pabón, Ph.D. for providing feedback during the work. Thanks to the Polytechnic University of Puerto Rico to be part of my professional development. And very special thanks to my family for their support during the entire process.

## References

- [1] American Society of Heating, Refrigerating and Air-Conditioning Engineers, ASHRAE Design Guide for Cleanrooms: Fundamentals, Systems and Performance, Georgia, 2017.
- [2] International Society for Pharmaceutical Engineering, Heating, Ventilation and Air Conditioning (HVAC), Florida, 2009.
- [3] International Society for Pharmaceutical Engineering, Oral Solid Dosage Forms Volume 2, 3rd ed., Florida, 2016.