Enhancements to Cardinal Health NPS Lab to USP-787 Standards

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Abstract—*As the world develops and populations expand, new diseases arise at an exponential rate. This research is based on employing new modifications to NPS (Nuclear Pharmacy Services) Laboratory at Cardinal Health, Inc. (Guaynabo, Puerto Rico) in order to provide facilities with the necessary enhancements to comply and provide quality products to clients and patients in the island. The primary purpose of this project is to increase the facilities capabilities in management of radioactive materials used for patient's medical solutions, increasing the cleanroom compliance under federal regulations, reducing costs in the process and provide a high-quality product without compromising safety. Current federal regulations require pharmaceutical and biopharmaceutical manufacturers to follow a specific quantity of particles in their cleanroom process stated as ISO 7 or 8 cleanroom standards. The actual project development plan is to bring this facility into these standards no later than December, 1st 2019.*

KeyTerms—*Nuclear pharmacy services, federal regulations, radioactive materials.*

BACKGROUND

A Nuclear Pharmacy is involved in the preparation and handling of medical products based on radioactive materials a principal component to treat specific diseases (i.e. Alzheimer's disease, etc.). There are two types of nuclear pharmacy environments: Institutional which works directly with hospital/medical center elaboration in site. The second is a centralized commercial pharmacy which prepares products and delivers them to distinct medical institutions (i.e Cardinal Health, Inc.). This institution which intends to bring new products for fabrication and distribution around the world will be a center for new technology and innovation in Puerto Rico.

PROBLEM STATEMENT

The pharmaceutical industry is evolving every day with new advancements and technology development. The current process requires rigorous supervision to control cleanliness and standards procedures in order to comply with federal regulations. In Figure 1, Cardinal Health 120, Inc. is a manufacturer & distributor of medical devices industry located in Guaynabo, Puerto Rico. The purpose of this research is to include all information required to integrate necessary modifications to facilities in order to comply with new USP-787 requirements. Total budget allocated for this project is $150,936.77 which is expected to return investment in 12 months period time.

Figure 1
Cardinal Health, Inc. Facilities Location

LITERATURE REVIEW

A Nuclear lab, also called in the core as a radiopharmacy, consists in the management and creation of radioactive medical solutions for treating diseases or conditions that require a specific treatment: hyperthyroidism, thyroid cancer, lymphomas and some types of targeted cancer. The majority of these products are in the form of capsules, injections, aerosols, etc. At this time in Puerto Rico, there are only two nuclear pharmacies that support patients around the island: Cardinal Health PR 120, Inc. (Guaynabo, P.R.) and Lantheus Mi Radiopharmaceuticals, Inc. (San Juan, P.R.). Cardinal Health PR 120, Inc. was established at Guaynabo, Puerto Rico in 1951. Currently from

that date, it has consistently served over 1,500 customers including hospitals, pharmacies, physicians, and other healthcare providers with over 20,000 products from over 1,000 supply sources. [1]

The Food and Drug Administration (FDA) and the United States Nuclear Regulatory Commission (U.S.NRC) regulates the nuclear pharmacy industry in order to satisfy regulations and ensure proper handling of hazardous materials such as radioactive materials. To fulfill supply demands and new product compliance, physical modifications had been designed under CAR (Capital Acquisition Request) to facilities in order to comply with ISO 7 or 8 and USP-787 Standards.

The USP-787 standard is a regulatory process established by the United States Pharmacopeial Convention (USP) for Subvisible Matter in Therapeutic Protein Injections, which became official on August 1, 2014 [2] and is based fundamentally in the number of particles present in the final manufactured product. The USP-787 chapter allows principally for two scenarios: the presence of insoluble protein particles as intrinsic parts of therapies, which are called inherent particles (no hazard) and particle populations below 10µm has to be monitored to reflect the reliability of the final drug product. [3]

In order to fulfill federal regulations and requirements, nuclear pharmacies must have a controlled environment, free of contaminants and pollutants, which is called a cleanroom. The aim of the clean room is to remove pollution by particulate matter, some of which may possibly include microorganisms and biotoxins in order to provide a controlled physical environment with a close monitoring of temperature, pressure and humidity. Temperature is measured by a digital sensor with multiple ranges, high-accuracy static pressure differential gage (Magnahelic sensors) and relative humidity sensor [4]. Cleanrooms are divided with several rooms, which are suited with different purposes before entering the clean area, these are divided by: WBC, Ante & Buffer Room. The anteroom is an area close next to the cleanroom which are engineered as an ISO 7 or ISO 8 room standards conditional on the product created in the cleanroom. The buffer zone or clean room which is positive pressurized room must be in an effective pressure cascade to assure a clean environment.

Figure 2, shows timeline execution following implementations at CAH-PR NPHS laboratory facilities:

- Maintain the CFM/ACH Values As ISO 7 ($30 < x < 60$)
- 4 Clean Air Pass Thru
- Fixed Window Vision Panel
- Double Vestibule Door (Ante Room) *
- Air Diffusor Unit, Filter fan Units (2”X4”)
- Air Diffuser Relocation
- New Return Air Duct at 1’-0” to the Finish Floor
- New BMS connection to site temperature Humidity Relative monitoring and alarms.
- New Interlock for ante to Buffer Room and Weight room.

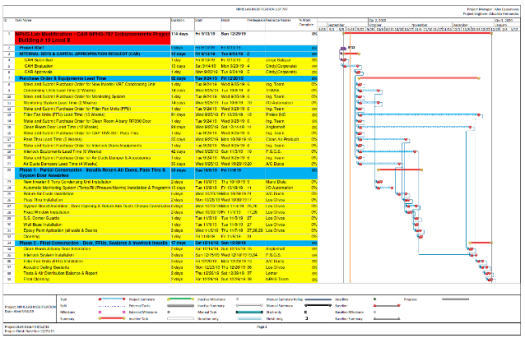

Figure 2
Project Timeline(Gantt Chart)

These modifications to current infrastructure will allow the facilities to achieve ISO 7 and USP-787 industry standard regulations.

METHODOLOGY

Controlled environments consist in a specific group of variables to be monitored in order to ensure product quality and federal regulations compliance. However, in order to establish a process that is well documented and simple to

follow, Figure 3 shows a DMAIC diagram performed to illustrate the data gathering, analysis and process implementation.

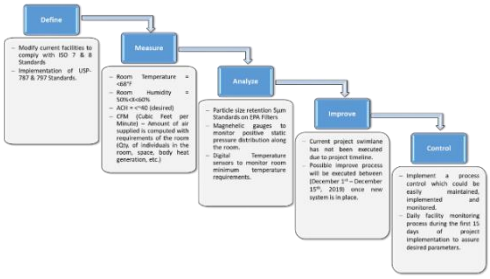

Figure 3
DMAIC Project Chart

On December 1st, 2019 project execution will be developed with current regulations and process agreed under project CAR: CAH-PR NPHS. In order to satisfy these requirements, parameters will be monitored such as (i.e. room temperature, static pressure differential across rooms, humidity, particle size, etc.

Current system arrangement does not comply with laboratory criteria. Therefore, agreed by project CAR, all existent ductwork must be removed and existent machinery applicable will be re-routed to comply with agreed scope of work.

RESULTS AND DISCUSSION

In order to successfully create a HVAC system that satisfies an ISO7 or ISO8 nuclear lab federal regulation requirement, the following criteria or methodology was implemented. For the purpose of this project, some of the equipment and structure was re-utilized according to CAR and requirements permitted.

ISO 7 Particle Size Requirements:

- ≥ 0.5µm = 352,000
- ≥ 1 µm = 83,200
- ≥ 5µm = 2,930

To calculate load requirements, the volume of area to be supplied has to be calculated in Figure 4, which is as follows:

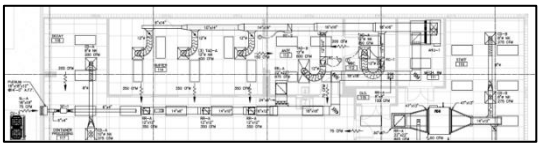

Figure 4
Actual HVAC Layout (NHPS) Area

HVAC Design is based on basic thermodynamics and heat transfer principles which are been develop for the past century and are still been used on modern engineering innovations. In a closed loop system (HVAC system) a basic equation is used to state the amount of energy needed or dissipated on a system, called: Sensible Heat Equation [5]:

$$\frac{BTU}{hr} = (1.08 * CFM\ X\ \Delta T) + (0.68\ x\ CFM\ X\ \Delta W_{gr}) \textbf{(1)}$$

$CFM = cubic\ feet\ per\ minute\ (air)$

$\Delta W_{Gr} = change\ in\ humidity\ ratio\ (psychrometric\ chart)$

$\Delta t = temperature\ change$

Room Dimension Calculations:

$$Room_{Area} = Room_{Width}\ x\ Room_{Length} \textbf{(2)}$$

$$Room_1 = 8.83\ ft. * 11.33\ ft. = 100\ ft^2$$

$$Room_2 = 13.5\ ft * 12.63\ ft. = 170.5\ ft^2$$

$$Room_3 = 26.92\ ft. 12.58\ ft. = 338.\ ft^2$$

$$Room_{Volume} = Room_{Area}(ft^2) * Height\ (ft^2) \textbf{(3)}$$

$$Room_1 = 100\ ft^2 * 9.5ft = 950ft^3$$

$$Room_2 = 170.5ft^2 * 9.5\ ft = 1620ft^3$$

$$Room_3 = 338.7ft^2 * 9.5ft = 3217ft^3$$

Codes for ISO7 or ISO8 quality standards required a quantity of ACH (Changes in Air Per Hour) in a clean room [3]. Calculations is as follow:

Assumptions:

Per project requirements,

- BUFFER & ANTE Room = 45 > ACH
- WBC = 40 > ACH

$$\text{Required CFM} = \frac{\text{Volume of Room} * \text{ACH}}{60\ \text{minutes}} \textbf{(4)}$$

$$Required\ CFM_{Room1} = \frac{(950) * (40.00)}{60} = 634\ CFM$$

$$Required\ CFM_{Room2} = \frac{(1620) * (45.00)}{60} = 1215\ CFM$$

$$Required\ CFM_{Room3} = \frac{(3217) * (45.00)}{60} = 2413\ CFM$$

*Required CFM = **4320 CFM***

An additional Outside Fresh Air Supply is provided to the system = 75 CFM in order to maintain a proper air/moisture ratio percentage.

As a rule of thumb, 1 ton equals 460 CFM, therefore the requirement load for complying to the system is 10 ton.

In Table 1, to provide consistent supply across all rooms, the following formula was used for pipe sizing requirements:

Table 1

Piping Size, Length and CFM Balance

Duct	CFM Balance	**Width (in.)**	Height (in.)
A	2500	18	16
B	2100	16	16
C	1750	14	14
C	1400	14	14
D	1050	10	14
E	700	6	14
E	350	6	14
F	260	14	11
G	260	14	14
H	260	16	12
I	260	18	14
J	260	18	18
K	260	18	18
Total Supply	4320	-	-
Total Return	4275 + 75 (Outside Air	-	-
Σ	0 (Balanced System)		

Air supply into the rooms will be controlled with a HEPA (High Efficiency Particle Air) FFU (Fan Filter Unit) which traps high level of particles

For a properly contained system, a (BDD) Back Draft Damper would be installed on ducts return air to Room#2 and Room#3 (i.e. similar to Ruskin CBD2). A back draft damper acts as a one-way flow valve allowing contaminated air to come out of the system but not allowing to return into the closed room system. Below is the proposed concept HVAC System ISO7 compliant.

Balancing dampers also will be incorporated as essential pieces of the system which actuates as a regulator of air passing by the duct which reduces pressures imbalances (ie. Random drafts or air, randomly slams of doors, etc.)

An Airflow Diagram (Figure 5) represent a basic visual layout on overall air supply distribution.

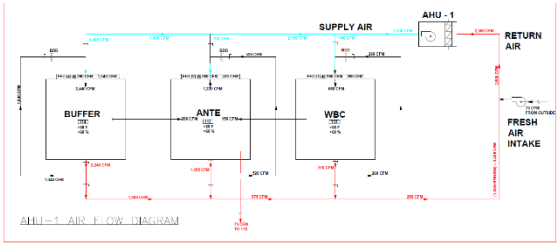

Figure 5

Airflow Diagram

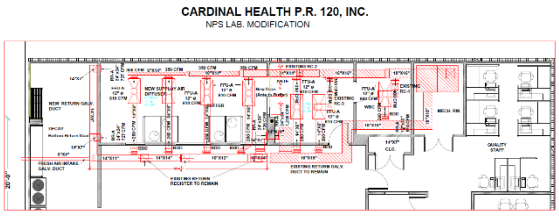

Figure 6

Final Proposed Concept

Figure 6 shows final layout of the nuclear pharmacy and current setup. At this time, nuclear pharmacy lab acoustic ceiling, as it is, does not comply with ISO 7 standards established by the Food & Drug Administration (FDA). Therefore, to completely seal the system NPS Dow Caulking 732 Non-flowable white silicone caulking will be used in all grids in direct contact with the panels, light fixtures, edges, etc.

To successfully assure project execution, NPS Cardinal Health Nuclear Pharmacy must record and test the following items to be in agreement with design intent:

- Test and adjust each blower RPM to design requirements.
  - Test and record each motor full load ducts and obtain design cfm at fans.
  - Measure coil face velocities.
  - Test and record system static pressure; i.e. filter "clean and dirty", cooling and heating coils, fan suction and discharge, air flow measuring stations, etc.
  - Test and adjust system for design recirculated air, cfm.

- Test and adjust system for design outside air, cfm.
- Test and record entering air temperatures. (D.B. cooling).
- Test and record entering air temperatures. (W.B. cooling).
- Test and record leaving air temperatures. (D.B. cooling).
- Test and record leaving air temperatures. (W.B. cooling).
- Adjust all main supply and return air ducts to proper design cfm.
- Adjust all zones to proper design cfm, supply and return.
- Test and adjust each diffuser, grille, and register to within percent of design requirements for system.
- Identify each grille, diffuser, and register as to location and area.
- Identify and list size, type, and manufacturer of diffusers, grilles, registers, and all tested equipment. Use manufacturer's ratings on all equipment to make required.
- In rooms requiring pressure or flow differentials between rooms, test and record the values obtained.
- Include required velocity and test velocity, and required volume and test volume after adjustments of diffusers, grilles and registers.
- In cooperation with the control manufacturer's representative set adjustments of automatically operated dampers to operate as specified, indicated and/or noted.
- Adjust all diffusers, grilles and registers to minimize drafts in all areas.
- Test duct systems for "dirty" filter condition by providing temporary resistance in ductwork, and then for "clean" filter condition.

Recommendations or Future Next Steps

In the process of developing the project, new potential improvements emerged to increase efficiency and ensure consistent and continuously 100% clean environment.

- All light switches and receptacles when possible, be oriented vertically instead of horizontally to reduce the accumulation of foreign or contaminants materials on the surfaces exposed.
- Monthly (potentially bi-weekly) recurrence pressure gauges constant pressure validation.
- Constant compliance of 6S criteria in nuclear pharmacy laboratory requirements to assure top efficiency and cero waste processes.

Conclusions

Cardinal Health, Inc. as one of two facilities in the island that provides services for radioactive materials in the pharmaceutical controlled environment, which this project has expanded its capacity and provided a new market that could reach new products to elevate company market cap and support local economy. As a process verification, HVAC system reached desired specifications required.

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