HVAC Improvement for a Granulation Room of a Solid Dosage Manufacturer

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Abstract *— A pharmaceutical facility located in Vega Baja, Puerto Rico is dedicated to the manufacturing and packaging of prescription and consumer products that include tablets, caplets, capsules and powder for oral suspensions. A study was performed by a multidisciplinary team with the main objective of enhance the current Good Manufacturing Practice (cGMP) conditions of the existing Heating, Ventilating, Air Conditioning (HVAC) system for a manufacturing building of this facility. As a part of this study was determined to install a dedicate Dehumidifier Air Handling Unit to one of the manufacturing room dedicated to the Granulation process. The main purpose of this project is the validation of the new HVAC system and the facility of the Granulation room to demonstrate that the new design comply with the cGMP, 21 CFR Part 210 and 211, International Cleanroom Standard (ISO) 14644, World Health Organization (WHO) Guidelines on Good Manufacturing Practice for heating, ventilation and air-conditioning system for non-sterile pharmaceutical dosage form and International Society for Pharmaceutical Engineering (ISPE) HVAC Good Practice.*

Key terms*: CFR, cGMP, Facilities Qualification, HVAC, ISO.*

INTRODUCTION

Pharmaceuticals industries are regulated by local or international regulatory agency. Regulatory agencies and organizations play a vital role to meet the requirements of legal procedures related to drug development process in a country. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate drug development process, licensing, registration, manufacturing, marketing and labeling of pharmaceutical products.

The design of pharmaceutical manufacturing facility must comply with local and international regulatory standards to ensure the identity, safety, purity, quality and efficacy of the manufactured product and provide comfortable conditions to workers and do not compromised the health. The Heating, Ventilating and Air Conditioning HVAC system and how the area is conditioned is the primary importance to prevent the contamination or cross contamination and current Good Manufacturing Practice (cGMP) assure the adequate design, monitoring and control of the facilities.

In the United States (US), pharmaceuticals industries are supervise by the Food and Drug Administration (FDA) which require companies to conform the cGMP regulation and is address by the US. Code of Federal Regulations - title 21 CFR 210 & 21, also must comply with the international cleanroom standard International Standard Organization (ISO) 14644. Global distributors must incorporate international regulation for example European Community that has a "Guide to Good Manufacturing Practice for Medicinal Products" and in the United Kingdom that is British Standard (BS) 5295. The World Health Organization (WHO) version of GMP is used by pharmaceutical regulators and the pharmaceutical industry. The consequence of a pharmaceutical manufacturer to avoid the regulatory requirements means that a facility is non-compliant and will not be approved for operation. If a company is not complying with cGMP regulations, any drug it makes is considered "adulterated" under the law, unsafe or ineffective and could stop the manufacturing or distribution of product. Validation of the equipment and facilities are a

requirement of the regulatory agencies that establish a documented evidence to demonstrate the equipment or facility is appropriate for the intended use and comply with determined specification.

PROBLEM STATEMENT

A pharmaceutical facility located in Vega Baja, Puerto Rico is dedicated to the manufacturing and packaging of prescription and consumer products that include tablets, caplets, capsules and powder for oral suspensions. A study was developed to enhance the cGMP conditions of a HVAC system for a Manufacturing building. This study was performed by a multidisciplinary team comprised with Quality, Manufacturing, Environmental Health & Safety and Engineering representatives with the purpose to increase the cGMP robustness of the site. As a result of this study recommendation and corrective action were taken in consideration. This project will be focus on a manufacturing room dedicated to the Granulation process. Initially, this room and other manufacturing rooms/areas are served by a common primary system consisting in a central system concept returning and supplying air which consists of a multiple Air Handing Units, Dehumidifier units, supply and return fans, supply and return plenum and intermediate filters plenums. This manufacturing facility considers the modification of the air distribution system in several rooms and the installation of a new air distribution system to improve the performance of this facility.

RESEARCH DESCRIPTION

The purpose of this project is to improve the overall cGMP state for a Granulation Room while maintaining in compliance with local and international regulation by changing the actual design and demonstrate by qualification of the new Air Handling Unit and Facility Qualification that is adequate as specified, comply with the intended use and is in compliance with cGMP regulations. The room to be impacted consists of a Ganulator and Bowl Inverter, an area which handle open product and required a high degree of cleanliness. A possible cause that could affect the GMP condition, could be the use of a common system that serve different manufacturing area.

RESEARCH OBJECTIVES

The objectives of this project are the following:

- Improve the cGMP condition for a manufacturing room with high probability of dust generation.
- Qualify the new recirculating Air Handling Unit dedicated to the granulation room and the Facility Qualification to verify that the modification to the air distribution system in the manufacturing room is in compliance with cGMP requirement, according to its room classification.
- The impacted room must maintain the environmental condition in compliance with the classification of the area (Table 1).

Table 1
Granulation Room Specifications

Temperature	65 ^{0}F to 75 ^{0}F	
Relative humidity	No more than 35%,	
Differential Pressure	Equal or greater than 0.03 in H2O/ negative vs. corridor	
Air Change Rate	Equal or greater than 10/hour	
Non-viable Airborne Particle	At Rest	
	0.5 µm	No more than 100,000 particles per ft. ^{3}
	5.0 µm	No more than 829 particles per ft. ^{3}
	At Operation	
	0.5 µm	No more than 100,000 particles per ft. ^{3}
Microbiological Load	Bacteria	Max 9 cfu/ft.^{3}
	Mold/Yeast	Max 3 cfu/ft.^{3}
	Pathogens	None

RESEARCH CONTRIBUTIONS

The major contribution of this project is to improve the cGMP condition to maintain the complying of local and global regulation, prevent the contamination or cross contamination and

demonstrate that the systems which could have a direct impact on the product quality is capable to meet the specified ranges and environmental condition.

LITERATURE REVIEW

HVAC system design and compliance with local and international regulations, is one of the most important aspects of the manufacturing industry.

HVAC System

The heating, ventilating, and air conditioning (HVAC) is the system used to provide an adequate indoor air quality and thermal comfort for residential, commercial or industrial buildings. HVAC system is responsible of providing control of temperature, oxygen replenishment, and removal of moisture, odors, smoke, heat, dust, airborne bacteria, and carbon dioxide. HVAC systems can provide ventilation that is by "exchanging" or replacing air in any space as a result it provide a high indoor air quality. As a part of HVAC system an Air handling units (AHU) is an equipment used to supply, regulate and circulate air through a building by the distribution of ductwork system. This system consist of different equipment and devices depending on the complexity application and requirement of the served area for the proper function such as: blower or supply fan, heating or cooling coils (indirect coil) used with Steam or Chilled water according to the required application, filters, dehumidifier units, dampers, local and control instrumentation (Figure 1).

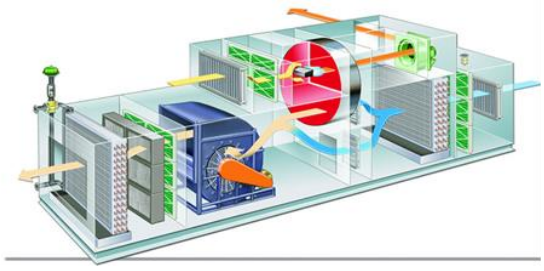

Figure 1
Dehumidifier HVAC

Air handlers usually connect to a ductwork ventilation system that distributes the conditioned air through the building and returns it to the AHU. There are several configuration types of Air Handling Units. The most common configurations are listed in table 2 [1] [2].

Table 2
Most Common Configuration Types of Air Handling Units

Inline - Supply 100% Outdoor Air	Side by Side - 100% Outdoor Air
Inline - Supply Mixed Air	Side by Side - Mixed Air
Double Flux (with Mixing Air)	U Shape - Supply 100% Outdoor Air
Double-Deck - 100% Outdoor Air	L Shape - Supply 100% Outdoor Air
Double-Deck - Mixed Air	

For the improvement of the Granulation room, an independent dedicated recirculation Dehumidifier Air Handling Unit system (Figure2) was installed. The air is provided by an air handling unit (AHU) which receives air from the outside and air recirculated from the building. The outside and return air are mixed in the mixing chamber, filtered, cooled, and delivered to occupied areas through sheet metal ducts and usually supply by air diffusers located on the ceiling.

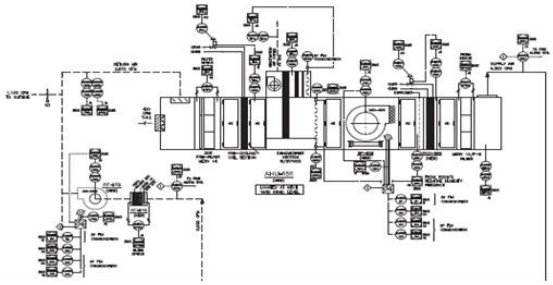

Figure 2
Recirculating Air Handling Unit

In this system the air is passed through water-filled coils which are called a cooling coil. The water flowing through the coil is around 40ºF. The ventilation air does not contact the water, only the cold metal surface of the coil resulting as an effective way to cold the air that will be vent to the area. The desiccant dehumidifier and reheat coil are required to remove moisture and humidity

control [1]. Filters in the AHU system are required because the outside and return air has dust and other contaminant which must be removed before the air goes through the coils. If not, dust will accumulate in the coils and decrease its performance or can cause cross- contamination. This causes a decrease in air flow and decreases the ability of the coil to cool the air. There are different types of filters with different efficiency rate. Is recommended for HVAC systems the use of medium or higher efficiency filters. A filter return bank with an HEPA filter and pre-filters are installed to this system in addition of the AHU filter to increase the filtration and minimize the particle load on the HEPA terminal.

HVAC System Design

Design of HVAC system for Pharmaceutical industries is one of the most important aspects because it impacts directly the parameters of an area for the manufacture of a product. The manufacture facilities are regulated by the FDA and other regulatory agency to ensure that their products are safe, pure, and effective and the GMP regulations require minimizing or eliminating contaminants, cross-contamination, mix ups and errors [1]. The design considers the following parameter shown in the Table 3 [1].

Table 3
Parameters required for HVAC Design

Temperature and Humidity	Filtration	Control of particles
Classification of the room	Air flow	Pressure

This is the step where are considered regulations, codes and where is describe major equipment to be used and the level of quality of components and construction material. The following factors are considered [1]:

- Building construction and layout design: flow of personnel, material and equipment is essential for achieving and maintaining the design levels of cleanliness and pressure gradients. Particulate generation is the focus of any cleanroom design, for that reasons the selection of building elements material is very important.
- Defining the HVAC requirements system:
  1) Room temperature: for comfortable condition;
  2) Relative humidity: control humidity is necessary for personal comfort, to prevent corrosion, to control microbial growth, and to reduce the possibility of static electricity;
  3) Cleanliness level or Control Airborne Particles: the design goal is the quality of the air cleanliness of the space and prevention of contamination. The use of proper air filtration prevents the inlets of external particulates.
  4) Room pressure: to prevent infiltration of air from adjacent areas.
- Cooling load: must be calculated considering personnel, equipment, lighting, outside air entering to the AHU system to minimize uncontrolled load.
- Airflow: is determined to establish the minimum air required to satisfy the space cooling load requirements and air cleanliness classification. A drawing is develop to show the air flow quantities of supplied, returned and exhausted for an area or transferred into and out from each space.
- Selection of air flow pattern: it is made according the class of cleanroom. Flow pattern are unidirectional laminar flow (horizontal or vertical flow) and non-unidirectional flow (turbulent flow); that are influenced by the grille type and location. Return air system is also important in the cleanroom air distribution, for dust particles collection.
- Pressurization of rooms: to prevent the infiltration from adjacent room, that could cause contamination by particulate or to protect the personnel of physical damage by inhalation

of harmful substance. Air always flow from high pressure to low pressure region.

- Air handling system: there is several arrangement of AHU system as listed in Table2. Basic HVAC systems are Once-thru Air and Recirculated Air.
- Duct system design and construction.
- Selection, location and mounting of filtration system.
- Testing, commissioning, performance qualification and validation.
- Documentation: Good manufacturing practices govern the level of control of various parameters for quality assurance, regulating the acceptance criteria, validation of the facility, and documentation for operation and maintenance.

Regulations and Standards

The pharmaceutical facilities must conform the current Good Manufacturing Practice. In the United State territory are directly supervised by the U.S. food and drug administration (FDA). Also there are other regulating agencies in various countries that have formulated their own GMPs. A few of them are the European Community, United Kingdom, the Japanese Ministry and others. In the United States, it is regulated by several documents such as the International Standards Organization (ISO 14644), code of Federal regulations CFR 210 & 211. The European Community has a "Guide to Good Manufacturing Practice for Medicinal Products" and in the United Kingdom it is BS 5295 [3]. Also pharmaceutical regulators and the pharmaceutical industry use a version of GMP that is the World Health Organization (WHO). The WHO has the supplementary guidelines on GMP for Heating, Ventilation and Air-Conditioning (HVAC) system for non-sterile pharmaceutical dosage form. The International Organization for Standardization is an independent, non-governmental organization that is the world's largest developer of voluntary international standards and facilitates world trade by providing common standards between nations. ISO 14644-1 and 14644-2 Standards replaced the US Federal Standard 209E Airborne Particulate Cleanliness Classes in Cleanrooms and Clean Zones. ISO 14644-1 is divided in 12 sub part.

a) FDA and Current Good Manufacturing Practice.

This section briefly shows some aspect related to cGMP that are relevant for the scope of my project. The next information is from FDA 21 CFR part 211 [4]: Current Good Manufacturing Practice for Finished Pharmaceutical Subpart C – Building and Facilities.

Sec. 211.46 Ventilation, air filtration, air heating and cooling.

(a) Adequate ventilation shall be provided.

(b) Equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.

(c) Air filtration systems, including pre-filters and particulate matter air filters, shall be used when appropriate on air supplies to production areas. If air is recirculated to production areas, measures shall be taken to control recirculation of dust from production. In areas where air contamination occurs during production, there shall be adequate exhaust systems or other systems adequate to control contaminants.

(d) Air-handling systems for the manufacture, processing, and packing of penicillin shall be completely separate from those for other drug products for human use.

Sec. 211.42 Design and construction features.

(ii) Temperature and humidity controls;

(iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or non-laminar;

(iv) A system for monitoring environmental conditions.

b) WHO Guideline for HVAC system for Non-Sterile dosage form

The WHO guidelines are focus primarily on the design and good manufacturing practices (GMP) requirements for HVAC systems for facilities that manufacture solid dosage forms. The three primary aspects are the roles that the HVAC system plays in product protection, personnel protection and environmental protection as illustrated in Figure 3 [5] [6] [7].

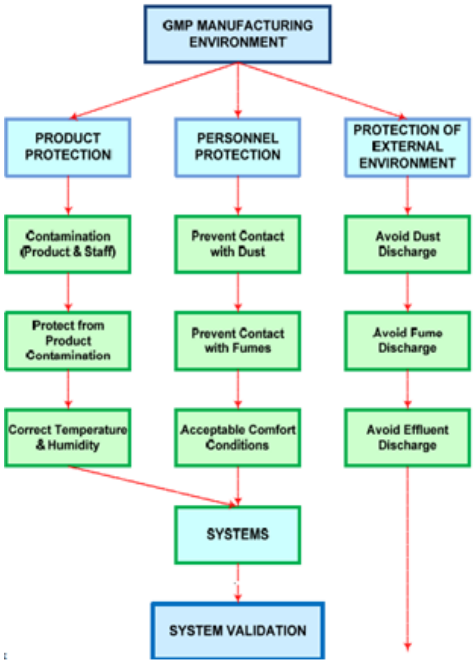

Figure 3
Aspects Addressed in the WHO Guidelines

Some of the WHO guidelines that are related to the Improvement of this manufacturing room will be presented briefly. This guideline tells us that architectural design and the HVAC design are related each other, and both has an effect in the room differential pressure and the cross-contamination control. The design of recirculation systems should consider the following criteria [5]:

- Sufficient fresh air to compensate for leakage from the facility and loss through exhaust air systems;
- Sufficient fresh air to comply with national building regulations;
- Sufficient fresh air to provide the required building pressurization;

There should be no risk of contamination or cross-contamination due to recirculation of air, but depending on the product, is required the installation of HEPA filter in the return duct. Depending on the airborne contaminants we could use recirculated air, but with an HEPA filter installed in the supply air stream or return air stream to remove contaminants and thus prevent cross-contamination. The HEPA filters efficiency should have an EN 1822 classification of H13. This granulation room is used for different product it is required to installed HEPA filters to avoid cross contamination located in the Air Handling Unit or placed terminally mounted, preferably connected in a rigid duct connection due to the high pressure. Automated monitoring for critical parameters such room temperature, humidity, differential pressure are required and be capable of send an alarm if any is out of specification. The alarm system should be located in areas where it alerts the personnel and utility technician. Common platform used to monitor the facility are Building Management System (BMS) and system control and data acquisition [5] [6]. Other component that is required for low humidity level (as is the case of the Granulation room), is the installation of a desiccant wheel as illustrated in Figure 4 [5].

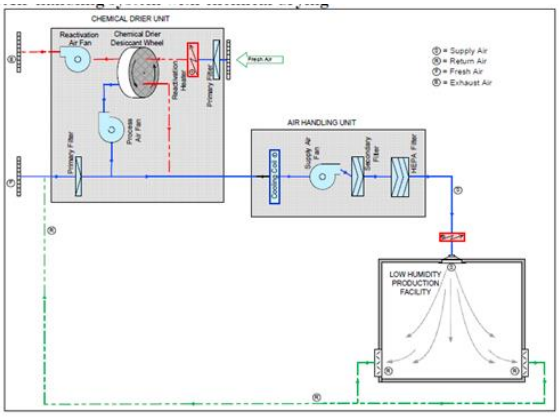

Figure 4
Air Handling Unit with Desiccant Wheel

Areas for the manufacture of pharmaceuticals, where products and equipment are exposed to the environment are defined as "clean areas" or "cleanrooms". Some of the basic criteria to be considered which affects room cleanliness are building finishes and structure, dust control and containment, air filtration, air change rate or flushing rate, room pressure, location of air terminals and directional airflow, temperature, relative humidity, material and personnel flow and gowning procedures. Air filtration and air change should be adequate to ensure the achievement of a clean area. Air change rates are normally determined by room cleanliness classification, the product characteristics, the quality and filtration of the supply air; particulates generated by the manufacturing process or operators; locations of air supply and returns grilles; sufficient air to clean up the area; sufficient air to balance extract rates and sufficient air to maintain the required room pressure. Airborne particulates and the efficiency of filtration should be considered critical parameters.

A) Cross contamination:

Where different products are manufactured at the same time, in a multiproduct Oral Solid Dosage (OSD) manufacturing site, there must be controls to ensure that dust cannot move from one area to another, such as the correct directional air movement or differential pressure between areas.

B) Differential Pressure:

The pressure differential should be of sufficient magnitude to ensure containment and prevention of flow reversal, but should not be so high as to create turbulence problems.

C) Temperature and Relative Humidity:

Temperature and relative humidity should be controlled, monitored and recorded, to ensure compliance with requirements pertinent to the materials and products and provide a comfortable environment for the operator where necessary.

c) International Standard Organization ISO 14644.

The ISO 14644 consists of various parts. Some concept related to this standard will be introduced. The ISO 14644 – 1 (Part1) is the international designation that cover the classification of air cleanliness in cleanrooms and associated controlled environments. Classification is in terms of airborne particulates [8]. The ISO standard replaces the FED-STD-209 that was a federal standard related to the classification of air cleanliness, intended for use in clean rom environment. There is different room classification is according to the particulate size as illustrated in Figure 5 [9].

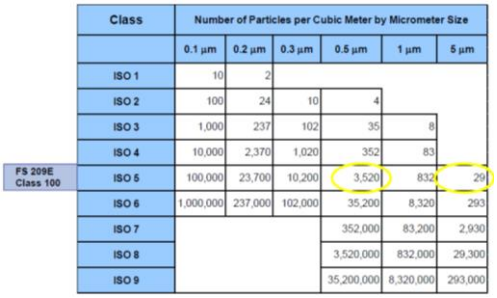

Figure 5
Number of Particles per Cubic Meter (m3) according to Size

The following table shows the particle concentration of different regulatory standards for room classification based on a particle size of 0.5 µm.

Table 4
Room Classification as per Regulatory Standards

ISPE	US-STD 209		ISO 14644-1		EU GMP		
Class	Class	Part./m^3(ft^3)	Class	Part./m^3 (ft^3)	Class	In -operation Part./m^3 (ft^3)	At- rest Part./m^3 (ft^3)
5	100	3530 (100)	5	3520 (100)	A	3520 (100)	3520 (100)
7	10 000	353 00 (10 000)	7	352 00 (10 000)	B	352 00 (10 000)	3520 (100)
8	100 000	3 530 000 (100 000)	8	3 520 000 (100 000)	C	3 520 000 (100 000)	352 00 (10 000)
Controlled- Not-classified CNC (with local monitoring)	--	--	--	--	D	Not defined	3 520 000 (100 000)

The ISO 14644 – 2 (Part2) cover the requirement for the monitoring of a cleanroom or clean zone, to demonstrate that is in compliance with the ISO 14644-1 for the designated classification [10]. The continued compliance is verified by performing the corresponding test and the frequency depends on the classification. Testing for particle concentration limit for ISO Class equal to Class 5 and lower; the maximum interval should be 6 months. For ISO class higher than Class 5 the maximum interval for testing should be 12 months. The monitoring activity for air borne microbial and non-viable particle should not compromise the product quality.

d) Validation

In 1970, Ted Byers and Bud Loftus, officials of the FDA proposed the concept of validation in order to improve the quality of pharmaceuticals. The first validation activities were focused on the processes involved in making parenteral products. Validation is a process of establishing documentary evidence to demonstrate that a procedure, process, or activity carried out in production or testing maintains the desired level of compliance at all stages and consistently produce the expected results. According to WHO guidelines, validation is an essential part of good manufacturing practices (GMP) [11]. Validation should be performed for new premises, equipment, utilities and systems, and processes and procedures; at periodic intervals; and when major changes have been made. There are different validation activities such as Process Validation, Equipment and Facilities validation, Cleaning validation, Computer system validation and Packaging validation, etc. Validation of HVAC system and Facility is very important not only for the quality of the product, also for the protection of personnel and the environment by determination of critical and non-critical parameters. The validation activity of qualifying systems, equipment and facility are divided in the following: Validation Master Plan, Design qualification (DQ), Installation qualification (IQ), Operational qualification (OQ).

The Facilities Qualification qualifies the overall manufacturing production environment. The requirement is as usual driven from the product processes, considering specific room condition, as defined in ISO 14644. The engineers must design the respective process area or the improvement of the area to enable these conditions to be achieved and maintained. Good engineering principles and practice must be used to protect these conditions as required, using the appropriate quality of air filtration, temperature control, humidity control, air flows control, and differential air pressures controls [11]. Some of the typical HVAC system parameters that should be qualified for a pharmaceutical facility may include: temperature, relative humidity, supply air quantities for all diffusers, return air or exhaust air quantities, room air-change rates, room pressures, HEPA filter integrity tests, room particle counts, microbiological air and surface counts, warning/alarm systems where applicable.

Commissioning of the HVAC system should involve the setting up, balancing, adjustment and testing of the entire HVAC system, to ensure that the system meets all the requirements, as specified in the user requirement specification, and capacities as specified by the designer.

PROJECT METHODOLOGY

The HVAC system improvement of the Granulation room will be tested by the development of a Facility Qualification Protocol to verify the condition on the room due to the modifications of the existing air distribution system. Prior to the Qualification activities a Room User Requirement (UR) and a Design Basis (DB) document will be develop to establish the requirement for this manufacturing room. The Installation Qualification (IQ) part is to verify and document the modifications to the existing air distribution system has been performed operationally safe, and meet established design requirements and the Manufacturer specifications. The Operational Qualification (OQ) part consist in to verify and

document via appropriate testing the environmental conditions of this room are capable of operating within established limits and tolerances after modifications. The modification of this Granulation room consist in the installation of a dedicate recirculation Air Handling Unit with dehumidifier, installation of new HEPA filters and volume damper and the installation of new supply air diffusers and wall returns grilles. This Room is classifying Area M1 (Blue) that involves the immediate production area and open product is handled in this area and required a high degree of cleanliness according to the manufacturer Standard Operating Procedure (SOP).

The new air Handling Unit will be validated by a Commissioning Protocol. This activity will be performed to ensure that the system is installed and operates according to design and the Manufacturer requirements. The purpose of the protocol is to verify the installation of of the new equipment and associated parts, local and control instruments, new utilities. Also, the protocol will have Functional Test, Alarm and Interlock test and HVAC system air balance and Hydronic Test. The HVAC Control system modification will be qualified in a separate protocol. The Automation Qualification will include verification that the system has been properly installed or modified and performs as expected. This project will be focus on the Facilities Qualification activity.

1. User Requirement

This document will be develop to provide a comprehensive direction and user requirement specifications for the new design associated with the changes in the HVAC air handling and facility in order to improve the system and maintain in compliance with the GMP regulation. This document is considered a living document and shall be kept updated in order to reflect the system current state throughout its lifecycle.

2. Design Basis

This section will be performed to provide comprehensive direction for the new design associated with the changes in the HVAC system to establish that the system is designed as established and confirming that the design is suitable for its intended use and conforms to Regulatory requirements.

3. Installation Qualification

The Installation Qualification (IQ) consists of Construction Verification, As Built Verification, Air Flow Balance Verification, HEPA Filter Integrity Verification, Air Changes per Hour Verification, and Safety Evaluation Verification. The following section shows the test and a description that will be performed in the IQ.

3.1 Construction Verification: to document all changes performed in the facilities of the Granulation room in terms of construction materials and room finishes specifications. This is a field verification against drawings.

3.2 Drawing Verification: to confirm accuracy of all drawings associated with room. This is performed by obtaining a copy of the latest revision of the applicable drawing and comparing it with the installed system.

3.3 Air Flow Balance Verification: to verify that the room was balanced. An external contractor will performed and provide the Test and Adjusting Balance Report.

3.4 HEPA Filter Integrity Verification: to verify that all HEPA filter installed at the supply ductwork was certified. An external contractor will performed and provide the HEPA Filter Integrity Report.

3.5 Air Changes per Hour Verification: to verify that the room is within the Air change per hour parameter, that is no less than 10 ACH for the classification of this room. An external contractor will provide the Air Change per Hour Report.

3.6 Safety Evaluation Verification: will be perform to ensure that the room is in safe condition and ready for its intended use. The room will be evaluated by the Environmental, Health and Safety (EHS) department personnel to ensure that is safe after construction activities.

4. Operational Qualification

The Operational Qualification (OQ) consists of Air Flow Pattern and Smoke Test, Environmental Conditions Temperature Test, Environmental Conditions Relative Humidity Test, Environmental Monitoring Differential Pressure Test, Environmental Conditions Non-Viable Airborne Particles Test, Microbiological Evaluation and Cleaning Verification. The following section shows the test and a description that will be performed in the OQ.

4.1 Air Flow Pattern and Smoke Test: will be perform to ensure that the air flow pattern is in accordance with design specifications. This test is performed by the generation of a smoke and evaluating the direction. The airflow direction (Negative) was performed from inside the room near to the door and compared to near room (reference room).

4.2 Environmental Conditions Temperature Test: this test is to ensure that the Granulation room is within the temperature parameters. The temperature test monitoring will be performed for one (1) day in Static Mode and for twenty-four (24) consecutive hours. The temperature monitoring will be performed using the SCADA HVAC System Apogee and appropriate calibrated instrument.

4.3 Environmental Conditions Relative Humidity: this test is to ensure that the Granulation room is within the Relative Humidity parameters. The Relative Humidity monitoring will be performed for one (1) day in Static Mode and for twenty-four (24) consecutive hours. The Relative Humidity monitoring will be performed using the SCADA HVAC System Apogee and appropriate calibrated instrument.

4.4 Environmental Conditions Differential Pressure: this test is to ensure that the Granulation room is capable of maintaining differential pressure requirement over a pre-defined period of time. The differential pressure monitoring will be performed for one (1) day in Static Mode and for twenty-four (24) consecutive hours. The Relative Humidity monitoring will be performed using the SCADA HVAC System Apogee and appropriate calibrated instrument.

4.5 Environmental Conditions Non-Viable Airborne Particles: this test is to ensure that room is in accordance with Manufacturer requirements of Non-Viable Airborne Particle air filtration. The Environmental Conditions Non-Viable Airborne Particles test monitoring will be performed one (1) day in static mode (at rest) and one (1) day in dynamic mode (in operation). The sample will be taken according the Standard operating Condition.

4.6 Microbiological Evaluation: this test is to ensure that room is capable of maintaining Microbial Load counts within parameters following the established method of the manufacturer. QC Lab performed studies of microbial load to the Granulation room. The sample will be taken during one (1) day in in dynamic mode.

4.7 Cleaning Verification: this verification is to ensure that room has been properly cleaned following the SOP of the pharmaceutical manufacturer.

RESULTS AND DISCUSSION

This chapter presents the results and analysis performs during the Qualification activities for the improvement of this manufacturing room.

1. User Requirement

The requirements for this manufacturing room are presented in Table 5.

Table 5
Room User Requirement

Room		Granulation Room
Area (ft^2)		980
Ceiling (ft)		22
Volume (ft^3)		21,560
Supply CFM	Proposed Design	4,300
Air Changes	Proposed Design	11.0

	Operate	10.0
Remarks		Room will have a recirculation unit. Room with dedicate Dehumidifier Unit

2. Design Basis

After a multidisciplinary team perform the assessment over the all solid dosage manufacturing site, the following recommendation was performed for this manufacturing room and are presented in Table 6.

Table 6
Design Basis Requirement

Item	Design Basin Requirement
General Improvements	Increase the design air changes per hour (ACH) to 11 and the operational air changes per hour to 10
System #1 replacement	Room will have independent dedicated recirculation DAHU systems receiving make up air from one of the new independent zone systems
Room Air Change Rates	It is expected that the installed HVAC systems for the open product rooms will be capable of delivering 11 air changes per hour (ACH) in the spaces served at the time of commissioning.
Differential Pressure Gradient	Rooms requiring a differential pressure gradient within the manufacturing areas of this site must be designed to a target delta-P of 15Pa (0.06 inches of water) with a targeted operating differential pressure of 7.5Pa (0.03 inches of water) at rest.
HVAC System Design	The base HVAC system type is Constant Volume supply. Dedicated outside air pre-conditioning units coupled with recirculation-only air handling unit. Dedicated recirculation-only air handlers used on specified rooms for final room temperature and particle count control by providing the required air changes. The use of independent terminal cooling or reheat coils for final room temperature control, as required by AHU system application serving multiple room. AHU systems serving rooms with terminal HEPA filters must provide Minimum filters rated MERV 14/F-8 (90% dust spot test efficiency) on discharge to minimize small particle load on HEPA filters. AHU system serving open product rooms shall be provided with central HEPA filters in the system returns to provide overall double HEPA filtration for the prevention of cross contamination. Central Return HEPA filters shall be provided with pre-filters rated for MERV 7-8/G4 (30%) and MERV 14/F-8 (90% dust spot test efficiency) to minimize small particle load on HEPA filters. All manufacturing areas should be designed to a room design-target cleanliness level air particle concentration of 3,500,000 particles per m3 (100,000 per cubic foot) with the room in the “at-rest” state. Room Terminal HEPA filters is the preferred approach but HEPA installed at the air-handling unit discharge is also acceptable on room dedicated AHU systems or where terminal filter is not feasible. The HVAC system will consist of the air handling unit equipped with fan(s), cooling coils, pre-filters,

Table 6
Design Basis Requirement (Continued)

HVAC System Design	HEPA filters, and desiccant dehumidifiers where required to obtain the necessary moisture removal. Supply fans should be provided with Variable Frequency (Speed) Drive for maintaining constant volume control. Return air fans should be included, where necessary, and should also be fitted with variable frequency (speed) drive.
Manufacturing Low Humidity Areas	No more than 35%
Air Recirculation Rooms	Dedicated Air Recirculation

3. Installation Qualification Results

3.1 Construction Verification Results
Construction Verification was performing to document all changes performed in the facilities for this manufacturing room. Changes were verified according to specification and as-built drawing and it comply with construction materials and room finishes specifications. The changes for this room consist of the installation of: seven (7) new supply HEPA filter housing (Manufacturer: Flanders, Flange size: 2' x 4', Grill Material: Stainless Steel and Housing Material: Aluminum), for a total of eight (8) supply HEPA Filters and the installation of two (2) new Return Grill housing (Manufacturer: Metalaire, size: 24" x 14", Material: Aluminum).

3.2 As Built Drawings Verification Results
Drawings were reviewed, verified, and updated as require reflecting the "As-Built" condition of the system. Red lined drawings were submitted in Drafting Department. The acceptance criteria were met.

3.3 Air Flow Balance Verification Results
The Room was balanced and approved TAB raw data was obtained. An engineering representative from this site approved the TAB raw data report. The TAB raw data was perform according to airflow (cfm) design. The final readings was obtained after setting the required room differential pressure at 90% of the total supply airflow in to the room.

3.4 HEPA Filter Integrity Verification Results
This test verifies the HEPA filters installed at the supply ductwork for this manufacturing room were certified. The new HEPA filter efficiency for the installed filters was verified and the information submitted specify that the efficiency is no less than 99.99% for particles of critical size of 0.3µm. HEPA filter integrity certification for the new filter was performed according to the SOP of this manufacture. The acceptance criteria were met.

3.5 Air Changes per Hour Verification Results: This test was to ensure that this manufacturing room is within the Air Change per Hour (ACH) parameters. The Air Changes per Hour were obtained from the approved balancing raw data. The acceptance criteria were met.

Table 7
Air Changes per Hour Verification Form

Room Description	Granulation Room
Room Class	M1
Expected Results (ACH)	≥ 10 ACH
Actual Results (ACH)	11

3.6 Safety Evaluation Verification Results: This manufacturing room was evaluated by the EHS Department and they found it safe for use as per safety regulatory standards, requirements and procedures. Safety Evaluation Document is included in Appendix 1 of the executed protocol. Test results were documented. No deviation was found during the completion of Safety Evaluation Verification Form. The acceptance criteria were met.

4. Operational Qualification Results

4.1 Air Flow Pattern and Smoke Test: This verification was to ensure that the air flow pattern for this manufacturing room is in accordance with design specifications. The Air Flow Patterns was verified by recording and analyzing a video of the smoke generated in the room. It was demonstrated that air flow occurred in the appropriate direction. The airflow direction (Negative) was performed from inside the room and compared to near room (reference room). The testing was performed near to the doors of each room.

Table 8
Air Flow Pattern and Smoke Test Results

Room Description	Granulation Room
Room Class	M1
Reference Room	Corridor
Result (Air Flow Direction)	Negative

4.2 Environmental Conditions Temperature Test: This test is to ensure that the Granulation room is within the temperature parameter.

Table 9
Environmental Conditions Temperature Test Results

Room Description		Granulation Room
Start Date / Time		03-15-16 / 0130
Stop Date / Time		03-16-16 / 0130
Expected Results Temp (°F)		65^0 F to 75^0 F
Actual Results	**Temp min (°F)**	71
	Temp Max (°F)	72

4.3 Environmental Conditions Relative Humidity: This test is to ensure that the Granulation room is within the relative humidity parameter.

Table 10
Environmental Conditions Relative Humidity Test Results

Room Description		Granulation Room
Start Date / Time		03-15-16 / 0130
Stop Date / Time		03-16-16 / 0130
Expected Results (%RH)		No more than 35%
Actual Results	**RH Min (%RH)**	29
	RH Max (%RH)	34

4.4 Environmental Conditions Differential Pressure: This test is to ensure that the Granulation room is capable of maintaining differential pressure requirement.

Table 11
Environmental Conditions Differential Pressure Test Results

Room Description		Granulation Room
Start Date / Time		03-15-16 / 0130
Stop Date / Time		03-16-16 / 0130
Expected Results (in H2O)		65^0 F to 75^0 F
Actual Results	**Differential Pressure Min (in H2O)**	-0.08
	Differential Pressure Max (in H2O)	-0.09

4.5 Environmental Conditions Non-Viable Airborne Particle Test: This test is to ensure that room is in accordance with Manufacturer requirements of Non-Viable Airborne Particle air filtration.

Table 12
Environmental Conditions Non-Viable Airborne Particle Test Results

Room Description / Class		Granulation Room/ M1
Test Mode: At Rest/Static		
Expected Results		
Point 1	**0.5 µm**	NMT 100,000 particles per ft^3
	5.0 µm	NMT 829 particles per ft3
Point 2	**0.5 µm**	NMT 100,000 particles per ft3
	5.0 µm	NMT 829 particles per ft3
Point 3	**0.5 µm**	NMT 100,000 particles per ft3
	5.0 µm	NMT 829 particles per ft3
Actual Results (particles per ft^3)		
Point 1		143

		20
Point 2		745
		101
Point 3		72
		3
Test Mode: At Operation / Dynamic		
Expected Results		
Point 1	**5.0 µm**	NMT 829 particles per ft3
Point 2	**5.0 µm**	NMT 829 particles per ft3
Point 3	**5.0 µm**	NMT 829 particles per ft3
Actual Results (particles per ft^3)		
Point 1		756
Point 2		946
Point 3		294

4.6 Microbiological Evaluation: The Microbial Load results complied with the following specifications as per SOP, current version, as follow:

Table 13
Microbiological Evaluation Test Result

Room Description / Class	Granulation Room/ M1
Test Mode: At Rest/Static	
Expected Results	
Near Bowl inverter	
Bacterial Count	Max 9 cfu/ft^3
Pathogens	None
Mold / Yeast Counts	Max 3 cfu/ft3
Near Granultor	
Bacterial Count	Max 9 cfu/ft3
Pathogens	None
Mold / Yeast Counts	Max 3 cfu/ft3
Actual Results (particles per ft^3)	
Test Mode: At Operation / Dynamic	
Near Bowl inverter	
Expected Results	
Bacterial Count	1 cfu/ft^3
Pathogens	None
Mold / Yeast Counts	0 cfu/ft^3
Near Granulator	
Bacterial Count	0 cfu/ft3
Pathogens	None
Mold / Yeast Counts	0 cfu/ft3

4.7 Cleaning Verification: This verification ensures that the manufacturing room has been properly cleaned following the SOP current version of this oral solid dosage manufacture.

CONCLUSION

An independent dedicated recirculation Air Handling Unit system which supplies 4,300 cfm with an integrated Dehumidifier Unit was installed to serve the Granulation room to satisfy space cooling load requirement and air cleanliness classification. In addition this system was installed with a new control system to integrate the necessary instrumentation and equipment. This AHU system complies with the user requirement. Based on the results obtained during the execution this system is in accordance with the Design

specification. The results of this Facility Qualification for this Granulation room were satisfactory according to the requirement of this pharmaceutical.

The Installation Qualification (IQ) tests results were verified and documented demonstrating that the modifications to this room met the specification and established design requirements. The Operational Qualification (OQ) test results were verified and documented demonstrating that the environmental conditions, microbiological evaluation and non-viable airborne particle for this room were capable of operating within established limits and tolerances after the installation of a new Air Handling Unit.

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