Pharmaceutical Modular Cleanroom Guide

Introduction

This guide will describe the benefits of CLEAN^3 modular cleanrooms as used in the pharmaceutical and related industries. Construction of the various parts of the cleanroom will be detailed in this guide which will also discuss various modular cleanroom applications as related to non-potent, high-potent and hazardous drugs. Specifically, this guide will talk about conventional pharmaceutical manufacturing, 503B compounding pharmacies and aseptic pharmaceutical manufacturing. Furthermore, CLEAN^3 cleanrooms can be designed to accommodate high potency and other hazardous drug manufacture by filling and compounding using negative pressure rooms.

Chapter One-Modular Cleanrooms by CLEAN^3 Technologies, LLC

A modular cleanroom is a prefabricated, purpose-built, permanent structure that is a critical piece of processing equipment rather than a facility addition due to its unique nature. Cleanrooms in general limit and control the presence of any particles inside them. This is accomplished through the use of ceiling mounted HEPA filter units in conjunction with a tailor-made air handling unit and HVAC system. In general, the pressure differential between rooms ensures that air from the cleaner room will typically bleed cleaner air into dirtier spaces when doors are opened. This guarantees that rooms of cleaner classification stay uncontaminated by less clean air from adjacent rooms.

CLEAN^3 pharmaceutical modular cleanrooms offer superior durability, future flexibility for expansion, uniform construction, lowest installed cost per square foot, fast track assembly and cleaner result. All these qualities are present in any size CLEAN^3 cleanroom offered, from the smallest 503B modular cleanroom to those needed by a large scale aseptic pharmaceutical manufacturer.

CLEAN^3 premium modular cleanrooms are amongst the most durable of all cleanrooms. The walls can be made of a variety of wall materials such as pre-painted aluminum, 304 stainless steel, glazed walls with clear, double-pane tempered glass, or high-pressure laminate (HPL) sandwich panels. The HPL panel skin, which CLEAN^3 recommends highly, can easily withstand the occasional

bump by a cart, tank or other metal object which eliminates the need for wall bumpers or extensive repairs typically required with other wall systems.

CLEAN^3 modular cleanroom walls permit future expansion. CLEAN^3 modular walls are only 1.88" thick while standard wall systems start at 4.5" (5.5" with double drywall). Five to ten percent of valuable floor space can be saved using this thinner wall system. In addition, it is simple to add more rooms to the system later if more cleanroom space is required.

CLEAN^3 modular cleanroom components are of uniform construction and built to very tight tolerances. Walls panels, ceiling systems and doors are pre-fabricated in an ISO certified shop environment by skilled crews that are 100% dedicated to building pharmaceutical grade cleanroom components under closely monitored conditions.

CLEAN^3 cleanrooms offer the lowest installed cost per square foot compared to any other pharmaceutical grade modular cleanroom system. Shop-fabricated wall and ceiling units that are built by dedicated factory technicians have significantly lower labor rates than typical construction crews. A specialized cleanroom component factory can exploit economy of scale as they specialize in building only our pharmaceutical grade wall and ceiling panels. This particular setting utilizes dedicated tooling, fixtures, unique industrial engineering methods and techniques that both saves labor cost and increases productivity, keeping component costs down, which ultimately saves CLEAN^3 clients' money. On-site technicians assemble these prefabricated components, which fit together effortlessly using precisely extruded aluminum sections that go together easily. There is no need for expensive on-site customization or special joinery methods.

CLEAN^3 modular cleanrooms tout fast track construction. Factory prefabrication of walls and ceiling can begin immediately upon drawing approval, leveraging pre-made factory part production. Shop fabrication can be completed in weeks instead of months as compared to conventional cleanroom construction methods. Furthermore, the CLEAN^3 system is assembled from precision components resulting in a sleek final product.

CLEAN^3 modular cleanrooms offer a cleaner alternative. During construction there is very little waste, debris or dust due to cutting wall or ceiling panels. This saves the client money and time because both the construction crew and the CLEAN^3

client avoid unnecessary cleanup that can take several weeks or months Additionally, as a built-in feature the interior surface of a CLEAN^3 at floor air return is the same durable, smooth easy-to-clean wall surface as the exterior of the air return. There are no hidden voids inside walls for construction debris, standing water or other foreign matter to remain and cause biological contamination. Connections between floors, walls and ceilings are connected by easy to clean 3-inch radius covings. All windows and doors are the same thickness as the wall panels which makes for a smooth, continuous and easily cleanable surface.

Chapter Two: Applications for Pharmaceutical Grade Modular Cleanrooms by CLEAN^3 Technologies, LLC

CLEAN^3 pharmaceutical cleanrooms can be used for a variety of pharmaceutical related application. CLEAN^3 provides systems from smaller 503B compounding pharmacies to large scale aseptic pharmaceutical vial filling line applications and everything in between such as medical device manufacture. Classifications of pharmaceutical cleanrooms usually range from ISO 8 to ISO 5 with other classifications available upon request.

Turnkey Design Services

The CLEAN^3 design team has a design philosophy based upon two pillars: “design from the inside out” and “begin with the end in mind”. These two intermarried concepts result in an efficient cleanroom design that works well both from day one, as well as for years down the road.

“Designing from the inside out” means we look at the specific products and product configurations to be produced and shipped out the back door. In addition, the CLEAN^3 design team looks at the quantity of product to be produced, number of SKUs, and manufacturing rate to identify the production and support equipment required and then to ensure that the space fits a customer’s present and future needs. By beginning with the end in mind, we are by definition planning for the future since the CLEAN^3 design team looks at both present and future needs. The CLEAN^3 design team considers the size and shape of the rooms compared to the staging needs, size of equipment, flow of material, flow of personnel, flow of

product which all affects location of doors, pass throughs and other design considerations needed to support those specific end products.

The CLEAN^3 team will design a durable, easy to maintain cleanroom that is sized properly and with the correct HVAC configuration to ensure that it will work very well for the client's current and future needs. The complete design will work right the from day one onward and for years to come. As an added bonus, we size and supply all required manufacturing, equipment, support systems, storage, and anything else needed to furnish each room in the cleanroom. Furthermore, CLEAN^3 can help design the workspace immediately adjacent to the cleanroom such as warehouse space, inspection, packaging, case and tape, QC and QA space, and anything else needed to equip these areas thus providing the end user with a complete turnkey solution if desired.

CLEAN^3 is a private branded cleanroom product of AWS Bio-Pharma Technologies, who is also a distributor of capital support system such as water for injection (WFI) stills, high purity steam generators and fill finish equipment used for pharmaceutical processing and production, along with cleanroom furnishings such as sinks, tables, storage rack and cart, etc.

503B Compounding Pharmacies

503B compounding pharmacies will find CLEAN^3 modular cleanrooms an indispensable part of their operation. The 1.88" thick walls allow maximal usage of allotted space as compared to thicker walls used in stick-built construction and competitors' modular cleanrooms. Rooms can be classified for more ordinary compounding, buffer and filling operations at positive pressure or negative pressure if needed for potent drugs. CLEAN^3 expert in-house technical staff will design your cleanroom and then build it on your site. CLEAN^3 can offer just the cleanroom alone or an entire turn key operation complete with all pharmaceutical equipment sized and specified correctly for a client's present and future operation.

Aseptic Pharmaceutical Manufacturing

Aseptic and parenteral pharmaceutical manufacturing is another process which AWS/CLEAN^3 is very familiar with in regards to cleanroom requirements. The

CLEAN^3 team designs cleanrooms that will meet any suite of classifications needed to meet specific needs for aseptic manufacturing, parenteral drug vial filling, IV bag filling, etc.

High Potency Drug/ Hazardous Drug Manufacturing

High Potency Drug manufacturing presents its own unique challenges for a successful cleanroom design, and every client will find that CLEAN^3 is up to the task. Negative pressure rooms ensure that the high potency drug will not escape; neither into the area immediately surrounding the cleanroom, the airlocks, gowning nor de-gowning areas. Once-through air is used to ensure that no air is recirculated, further guaranteeing that drug-contaminated air cannot be reintroduced into the room. In other words, with once-through airflow incoming air only touches the product and personnel once, and is then promptly exhausted out of the cleanroom.

Chapter 3-Types of Modular Cleanrooms

Standard Cleanroom Offering

In general, the CLEAN^3 standard cleanroom offering is available with classifications ranging from ISO 8 to ISO 5. As described earlier in chapter 1, the reasons for choosing a CLEAN^3 pharmaceutical Grade cleanroom are superior durability, future flexibility for expansion, uniform construction, lowest installed cost per square foot, fast track construction and cleaner construction. These qualities are some of the reasons that make CLEAN^3 a good choice for any client. Perfectly flush, easy to clean windows are always available, in walls, doors or both. Windows are always preinstalled at the factory, not in the field saving time, effort and cost. Electrical and plumbing cut-out provisions are made at the factory, ensuring wall panels are ready to be wired and pipes hooked up on site with no cutting required in the field.

Aesthetics do come into play when selecting a cleanroom. Three standard colors of the highly recommended HPL panels are available, spring white, sand or silver blue. If desired, a variety of custom colors are available. CLEAN^3 has one client that chose their Alma Mater’s school colors for their cleanroom doors’ color

choice. Functionally, different rooms can be color themed depending upon their purpose and usage in processing pharmaceutical products.

Several flooring options are available in a variety of colors. Flooring colors can be used to denote various subdivided areas such as the dirtier vs cleaner area in a gowning room or the area designated for specific equipment or tables. Flooring materials adhere to the three-inch radius rigid aluminum coving in the wall/floor corner. A variety of flooring options exist, with epoxy resin being the most durable. Vinyl flooring is a good choice for some applications.

As discussed earlier, the three-inch coving and other graceful aluminum corner termination extrusions serve a practical purpose. While the covings do please the eye in giving CLEAN^3 the visual appearance of a very modern, clean space to work in they serve a very practical purpose; by having such curved transitions, this makes the space very easy to clean and keep clean.

Furthermore, other engineering considerations can be detailed as well. Airflow can be recirculated in order to reduce the size of specified air handlers and the HVAC system. Conversely, once through air that is needed for high potency or hazardous drugs can be selected. CLEAN^3 double ceiling construction, in some cases referred to as a negative pressure plenum, is highly recommended for a variety of good reasons, including less complexity, lower HVAC installation cost and simpler pressure balancing.

Environmental monitoring measures and, in many cases, documents room pressure differentials, humidity and temperature. All these parameters affect GMP compliance for pharmaceuticals. With this data all GMP criteria can be measured and effectively controlled.

Another item to address is energy efficiency. CLEAN^3 HEPA fan filter units consume 67% less electrical energy than other units commonly in use. This results in a net savings on energy as well as up to 50% of HVAC capital costs and operating expenses. Recirculated air, when appropriate, can result in energy savings. Furthermore, energy efficient air handling units, simple HVAC system design and LED light systems can be specified, thus further serving the need to save on energy costs.

Access to the CLEAN^3 cleanroom can be controlled through the use of badges, code input or fobs. This ensures only authorized personnel may enter the

cleanroom, or various zones of the cleanroom. In this way security and protocol needs are met.

CLEAN^3 pass throughs permit product flow between rooms without the need for personnel to go through a door. Each pass through consists of two GMP quality doors and a box contained within a wall opening. The doors are electronically interlocked so that only one door is permitted to be open at any time, thus ensuring the higher classification room retains it clean air and is not contaminated. Pass throughs can be of a variety of sizes ranging from a one cubic foot pass through to large enough to pass a cart and even those large enough to pass a tank. There are two main types of pass throughs, active (those with built-in HEPA filtration) and passive (those with no built-in HEPA filtration).

The CLEAN^3 interlock concept is applied at a larger scale with personnel doors. In a room with interlocked doors, only one door is permitted to open at any time, with the others automatically locking to prevent egress. This system prevents two doors from being open at any one time, preserving room pressure balancing and room cleanliness. When a door is open a red light illuminates and an alarm tone is generated. When all doors are closed, each door has a green light is lit indicating the door is unlocked and it is permissible to entry.

A Value Engineered Cleanroom Offering

Another option separate from our premium grade CLEAN^3 offering is a This is a "C Grade" cleanroom. This "C Grade" cleanroom is used in a variety of different industries such as aerospace, manufacturing and engineering test chambers. This is a less expensive option available that has different features than our premium CLEAN^3 pharmaceutical grade modular clean room. In-wall air returns and coving-free corners and non-flush windows are standard; these panels are typical of most panels manufactured in the USA. Softwall cleanrooms are also an option.

Chapter 4-How Clean^3 Modular Clean Rooms are Made

From the Manufacturing Facility to the Client's Site

Once final drawings are approved, shop drawings are sent to the factory then ceiling, wall panels and doors are fabricated to order. Panels can include windows

when desired. All panels, interior ceiling with grid, aluminum extrusions, coving, corner pieces, doors with doorframes and any other constructed parts are shipped to the jobsite just before construction begins. Shipping parts this way is still far more affordable than paying for onsite cutting and conventional construction costs of non- CLEAN^3 cleanrooms.

Room Layout Method

The complete cleanroom is laid out with marks made on the floor corresponding to the approved drawings. The completely rigid, tight tolerance-extruded wall base support extrusions are mounted on the marks to ensure that the wall panels mounted on top of them will be assembled straight, true and plumb.

Construction of Each Wall Panel

CLEAN^3's HPL panels provide a highly impact resistant finished surface. Here is a video of it withstanding a strong impact with an aluminum section. Note how there is no damage to the panel other than deposition of the aluminum onto the panel; this discoloration will wash off easily with a little water.

<INSERT VIDEO HERE>

CLEAN^3's highly recommended 48mm thick prefabricated panels consist of two 4mm layers of High-Pressure Laminate (HPL) that are adhered to a four-sided frame that is a precision extruded aluminum frame. Inside the panel are insulation options that will be explored in depth later. The frame is recessed around the wall's perimeter in order to accept mating aluminum H-beam sections that mate them together accurately every time, with no need for field made joints. The bottom face is recessed in order to accept the wall base supports. Each panel is made to its standard width of 1280mm, but narrower panels can be made to accommodate specific room sizes with one panel on the end or middle of a wall made narrower to allow this variation in room size.

Adjacent wall panels are caulked with 100% silicone in order to maintain a flush surface that is easy to clean. The H-beam aluminum extrusion prevents wall panels

from moving in shear away from the flush plane of the wall. In addition, the H-beam provides a backer plate for the silicone caulk that is approximately 3mm deep, ensuring GMP quality finished seam that is neat, professional and permanent.

Insulation options include high density polystyrene, high density rockwool or Aluminum honeycomb. While 95% of our installations utilize the polystyrene, the other insulation options are available depending upon your needs or requirements. High density polystyrene ensures good soundproofing. Rockwool or honeycomb can be selected depending upon fire resistance criteria. All panel assemblies have been tested to ASTM E-84.

Door Construction

Doors are similar in construction to wall panels. Doors are the same thickness as wall panels rendering the wall/door combination very easy to clean. Doors are available with operators and motion sensors to enable hands-free operation. CLEAN^3 doors also come standard with specially shaped door pulls that permit "hands-free" operation where the wrist is used instead.

Construction of Ceiling Panels

There are two main varieties of CLEAN^3 ceiling systems, walkable and non-walkable. In both cases, the ceiling is nested inside the walls of the cleanroom which extend somewhat beyond the height of the exterior wall panels.

Walkable ceilings have panels very similar to the aforementioned 48mm thick wall panels with the addition of an extruded aluminum inter-panel connector channel which is used to support the ceiling by means of threaded rod connected. The rod and turnbuckle combination transmits loads from the channel which is bearing the weight of adjacent ceiling tiles to the underside of overhead joists in the as-built structure housing the CLEAN^3 cleanroom.

Non-walkable ceilings feature a grid similar to an office-style drop ceiling, but of a much more robust construction. Single rigid 5mm High Pressure Laminate (HPL) panels are placed inside the grid with the grid supporting the panels. The grid is in

turn supported by threaded rods and turnbuckles that are attached to the as-built roof joists or, in the case of dual ceiling construction, to the walkable ceiling.

Ceiling System Options

Our CLEAN^3 design team recommends a double ceiling system consisting of an inner and outer ceiling panel array which creates a clean interstitial space. Such an arrangement is also referred to as a negative pressure plenum. One advantage of such a configuration is that it frequently saves up to 50% of HVAC system capital cost as well as ongoing operating cost. A single duct from an air handling unit (AHU) feeds conditioned air from the HVAC system into each individual room's plenum which, in turn, feeds a multitude of HEPA Fan Filter Units (FFUs). Each room has an intake and exhaust damper which is used to control the individual pressure of each room system. The intake damper permits the correct amount of makeup air to enter the plenum whereas the exhaust damper restricts the return air that is exiting the plenum and return to the HVAC return; this method is an robust method for statically balancing the room to room air pressure differentials. The FFU takes the conditioned air from inside the plenum and blows it through a HEPA filter and then into the room below, thus cleaning it thoroughly, and increasing the Air Changes per Hour (ACPH) rate. The FFU's draw air from the backside of the fan which pulls air in from the room through the our CLEAN^3 "at floor" air returns and forces the air back into the room through the HEPA filter. This recirculation method reuses approximately 80% of the previously conditioned room air, which results in lower energy cost.

In the case of a once-through air design, there is no recirculated air, and all air is 100% makeup air going into the cleanroom. This scenario has significantly higher capital and operating costs, but is usually required for high potency or hazardous drug applications.

Aluminum Extrusions (trim and coving)

CLEAN^3 makes extensive use of easy to clean anodized aluminum extrusions which is a perfect product when exposed to the standard cleaning and sanitizing agents used in today's pharmaceutical cleanrooms. Structural aluminum extrusions are the base of the walls, alignment H-sections between wall sections and hold up

the ceiling. Streamlined anodized aluminum three-inch cove sections ensure wall to wall, wall to floor and wall to ceiling transitions are all easy to clean and they present a “state-of-the-art” GMP appearance. In CLEAN^{3}s cleanrooms, we employ “3D” corners featuring spherical three-inch radius quarter and eighth-sphere sections ensuring ease of cleaning and highly compliant with GMP requirements.

Flooring Options

A smooth, level, and clean concrete surface is required to build any cleanroom. The concrete surface will require cleanroom compatible flooring. The two main options available for flooring are trowelable epoxy resin or vinyl welded seam flooring.

Vinyl flooring is used in many cleanrooms and it offers a variety of options. Almost any color is available for both appearance and for denoting zones within a room and/or in the cleanroom itself per each room. The vinyl flooring is applied to the floor as well as the three-inch aluminum coving in order to create a very clean “bathtub” effect so that sharp transition seams are eliminated and thus the floor is very easy to keep clean. All seams are welded and flush, maintaining all the flooring as coplanar with no divots, sunken areas or crevices. Trowelable epoxy flooring offers a hard, very durable surface. This material is applied as a paste and it is 100% continuous with no welded seams. As a premium option this substance will last many years. A variety of colors are also available similar to the vinyl flooring.