

**State of Kuwait
Ministry of Health
Infection Control Directorate**

**Task Force Group for Designs and
Constructions of Health Care Facilities**

**Guidelines for Design of
Compounded Sterile Products (CSPs) Facility**

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CONTENTS

	page
Introduction.....	3
Definitions.....	5
CSP Microbial Contamination Risk Levels.....	8
International Classification of Particulate Matter in Room Air.....	9
Layout of CSPs unit.....	10
Location.....	10
Reception area.....	10
Storage area.....	11
Unpackaging (uncartoning) area.....	11
House keeping area.....	11
Waste disposal area.....	11
Changing room.....	12
Ante room.....	12
Cleanroom.....	12
Buffer zone.....	12
Finishing.....	13
The surfaces.....	13
Work surfaces.....	13
Ceiling.....	13
Walls.....	14
Floors.....	14
Pass through.....	14
Doors.....	14
Light switches& illuminations.....	15
Communication system (intercom).....	15
Hand wash basin.....	15
Carts.....	15
Storage shelving, counters, and cabinets.....	15
Additional considerations for cytotoxic preparations.....	16
Environmental / Engineering Control.....	17

A. Primary Engineering Control (PEC).....	18
Types of primary engineering control.....	19
1. laminar airflow workbenches (LAFWs).....	19
2. Biological Safety Cabinet (BSCs).....	19
3. Compounding Aseptic Isolator (CAIs).....	20
Factors to determine the number and size of primary engineering control.....	20
B. Secondary engineering controls	22
Buffer zones or clean rooms.....	23
Anteroom.....	23
International Classification of Particulate Matter in Room Air.....	23
Room air exchanges	23
HEPA filters	23
Temperature	24
Pressure.....	24
Visual observation	24
Tasks.....	24
Additional Personnel Requirements.....	25
Figure1.....	26
Environment Validation.....	27
References.....	29

INTRODUCTION

In the past few years there has been an effort to renovate and build new specialty centers throughout Kuwait. Many of them involving the renovation and expansion of many places with the addition of new specialties such as compounded sterile products (CSPs) units e.g. total parenteral nutrition (TPN) units.

This has created the necessity for national guidelines to build and renovate such facilities.

There are different types of compounded sterile products such as biologic , diagnostic, drug, nutrient and radiopharmaceutical products .

Many organizations including US Pharmacopeia (USP), has long been concerned with the quality and integrity of compounded sterile products (CSPs). In the early 1970s, thousands of cases of sepsis and hundreds of deaths occurred as a result of bacterial contamination of parenteral products, exposing an immediate need for hospitals to implement a higher standard of compounding quality. During the 1970s and early 1980s, the National Coordinating Committee on Large Volume Parenterals (NCCLVP) of the US Pharmacopeial Convention emerged as a driving force behind the call for the profession of pharmacy to ensure high quality of CSPs.

The Food and Drug Administration (FDA) also had a long-standing mission to address problems with contamination in sterile preparations in the United States.

Organizations such as the American Society of Health-System Pharmacists (ASHP) and USP issued practice recommendations centered on the pharmacist's responsibility for ensuring proper preparation, labeling, storage, dispensing, and delivery of CSPs. All of the various quality assurance measures culminated when enforceable sterile preparation compounding standard was published as USP Chapter 797 then a revised standard was developed and released in December 2007.

Clean room environments are known to reduce airborne particles and contamination rates. However, studies have shown that contamination cannot be eliminated by having a clean room environment or proper garbing alone, emphasizing the need for a multi-factorial approach to sterile compounding. Trissel et al. evaluated microbial contamination rates for compounding procedures; they determined the importance of the human element as a factor in safe compounding practices (e.g., cleansing, garbing, or aseptic technique) and that employee adherence to, and acceptance of sterile compounding standards are imperative.

The prevention or elimination of physical contact contamination and airborne particles must be given high priority. Airborne contaminants, especially those generated by sterile compounding personnel, are much more likely to reach critical sites than contaminants that are adhering to the floor or other surfaces below the work level. Further, particles that are relatively large or of high density settle from the airspace more quickly, and thus can be removed from the vicinity of critical sites. They must be precluded from ISO Class 5 environments in which critical sites are exposed.

The hospital shall have a pharmacy-based intravenous infusion admixture program, which includes services related to preparation of total parenteral nutrition, anti-neoplastic agents, large and small, continuous or intermittent volume products for infusion.

DEFINITIONS

Anteroom

An anteroom is an ISO Class 8 or better area where personnel perform hand hygiene and garbing procedures, staging of components, order entry, CSP labeling, and other high-particulate generating activities. It is also a transition area that 1) provides assurance that pressure relationships are constantly maintained so that air flows from clean to dirty areas 2) that reduces the need for the heating, ventilating and air conditioning (HVAC) control system to respond to large disturbances.

Aseptic Processing

Aseptic processing is a mode of processing pharmaceutical and medical products that involves the separate sterilization of the product and of the package (containers—closures or packaging material for medical devices) and the transfer of the product into the container and its closure under microbiologic critically controlled conditions.

Beyond-Use Date

Is the date or time after which the CSPs shall not be stored or transported. The beyond-use date is determined from the date or time the preparation is compounded.

Biological Safety Cabinet, Class II (BSC)

The BSC is a ventilated cabinet for personnel, product, and environmental protection having an open front with inward airflow for personnel protection, downward HEPA filtered laminar airflow for product protection, and HEPA filtered exhausted air for environmental protection.

Buffer Area, Buffer or Core Room, Buffer or Clean room Areas, Buffer Room Area, Buffer or Clean Area

This is an ISO Class 7 area where the primary engineering control area (see below) is physically located. Activities that occur in this area include the preparation and staging of components and supplies used when compounding CSPs.

Clean room

A clean room is a room in which the concentration of airborne particles is controlled to meet a specified airborne particulate cleanliness class. Microorganisms in the environment are monitored so that a microbial level for air, surface, and personnel gear are not exceeded for a specified cleanliness class.

Compounding Aseptic Isolator (CAI)

The CAI is a form of barrier isolator specifically designed for compounding pharmaceutical ingredients or preparations. It is designed to maintain an aseptic compounding environment within the isolator throughout the compounding and material transfer processes. Air exchange into the isolator from the surrounding environment should not occur unless it has first passed through a microbially retentive filter (HEPA minimum).

Critical Area

A critical area is an ISO Class 5 environment.

Critical Sites—Critical sites include sterile ingredients of CSPs and locations on devices and components used to prepare, package, and transfer CSPs that provide opportunity for exposure to contamination.

Negative Pressure Room

A room that is at a lower pressure compared to adjacent spaces and, therefore, the net flow of air is into the room.¹

Primary Engineering Control

It is a device or room that provides an ISO Class 5 environment for the exposure of critical sites when compounding CSPs. Such devices include, but may not be limited to, laminar airflow workbenches (LAFWs), biological safety cabinets (BSCs), and compounding aseptic isolators (CAIs).

Positive Pressure Room

A positive pressure room is one that is at a higher pressure compared to adjacent spaces and, therefore, the net airflow is out of the room.

Terminal Sterilization

Terminal sterilization is the application of a lethal process, e.g., steam under pressure or autoclaving, to sealed containers for the purpose of achieving a predetermined sterility assurance level (SAL) of usually less than 10^{-6} , i.e., or a probability of less than one in one million of a non sterile unit.

Unidirectional Flow

An airflow moving in a single direction, in a robust and uniform manner, and at sufficient speed to reproducibly sweep particles away.

CSP Microbial Contamination Risk Levels

Compounding personnel are responsible for determining the appropriate compounding risk levels for CSPs. The five risk levels determine the requirements of the facility.

Table 1- Pharmacy Compounding Risk Level requirements

<p>Immediate-Use Category</p>	<ul style="list-style-type: none"> - For emergent use, or situations where low-risk compounding would add risk due to delays - No storage or batch compounding - Continuous compounding process lasting less than one hour - Aseptic technique utilized - Administer less than 1 hour after preparation begins, or discard - Simple transfer of sterile non hazardous drugs or diagnostic radio-pharmaceuticals
<p>Low-Risk Level</p>	<ul style="list-style-type: none"> - Simple admixtures compounded using closed system transfer methods - Prepared in ISO Class 5 LAFW (laminar airflow workbenches) - Located in ISO Class 7 buffer area with ISO Class 8 ante area - Examples include reconstitution of single-dose vials of antibiotics or other small-volume parenterals, preparation of hydration solutions
<p>Low-Risk Level with <12Hour Beyond Use Date</p>	<ul style="list-style-type: none"> - Simple admixtures compounded using closed system transfer methods - Prepared in ISO Class 5 PEC (Primary Engineering Control) - Compounding area is segregated from non-compounding areas - Administration must start no later than 12 hours after preparation
<p>Medium-Risk Level</p>	<ul style="list-style-type: none"> - Admixtures compounded using multiple additives and/or small volumes - Batch preparations (e.g., syringes) - Complex manipulations (e.g., TPN) - Preparation for use over several days - Prepared in ISO Class 5 - Located in ISO Class 7 buffer area with ISO Class 8 ante area - Examples include pooled admixtures, parenteral nutrition solutions using automated compounders, batch-compounded preparations that do not contain bacteriostatic components
<p>High-Risk Level</p>	<ul style="list-style-type: none"> - Non-sterile (bulk powders) ingredients - Open system transfers - Prepared in ISO Class 5 - Located in ISO Class 7 buffer area with separate ISO Class 8 ante area - Examples include CSPs prepared from bulk, non sterile components or final containers that are non sterile and must be terminally sterilized

International Classification of Particulate Matter in Room Air

Limits are measured by :

1- particles 0.5 μm and larger **per cubic meter** (current ISO 4644-1:1999, Clean rooms and associated controlled environments - Part 1: Classification of air cleanliness.)

2- particles 0.5 μm and larger **per cubic feet** Adapted from Federal Standard No. 209E, General Services Administration, Washington, DC, 20407 (September 11, 1992)

For example, 3520 particles of 0.5 μm per m^3 or larger (ISO Class 5) is equivalent to 100 particles per ft^3 (FS Class 100)

Table 2:

Class Name	Particles	
ISO Class	ISO / m^3	U.S. FS 209E / ft^3
3	35.2	Class 1
4	352	Class 10
5	3520	Class 100
6	35,200	Class 1000
7	352,000	Class 10,000
8	3,520,000	Class 100,000

LAYOUT OF CSPs UNIT

Location

Preferably at the end of the wing and if this is not possible within the wing, it should be far from the elevators and stairways and corridors main hospital.

Reception area

Minimum of 20 sq meter for receiving CSPs request from wards and for delivering prepared items. It may contain a place for holding & storing transport means e.g. carts, trolleys.

Storage area

- 1- Drug store: for raw compounding materials and all other items needed for compounding
- 2- Storage area for prepared CSPs: containing refrigerators for storing prepared compounds until it is delivered.

For cytotoxic drugs, **Cytotoxic drug storage** It is recommended to have a dedicated, clearly-marked and identifiable by all workers storage area. It should have refrigeration available for cytotoxic drugs. Use of a dedicated facility offers quick and efficient containment and management of a spill. A dedicated facility should also be designed to limit the chance of breakage and limit the extent of contamination if breakage occurs. Generally, the quantity of cytotoxic drugs stored in pharmacy departments, wards, clinics and satellite pharmacies should generally be restricted to those required for short-term use. Areas where cytotoxic drugs are stored must have a current material safety data sheet for each drug. Storage areas should be secured and access limited to authorized personnel.

Unpackaging (uncartoning) area:

Area for uncartoning & disinfection of items before introducing to the work area.

For cytotoxic drugs a separate dedicated area should be provided for the unpacking of cytotoxic drugs.

House keeping area:

Area for storage of supplies and house keeping equipment and items. It should have hand washing facility.

Waste disposal area:

For holding waste disposal containers

For cytotoxic drug unit, Employers should consider the following factors when storing cytotoxic waste:

- store in a dedicated, identified and secure storage area with adequate lighting and ventilation
- locate away from drains and other sensitive areas
- storage areas should facilitate cleaning and decontamination
- seal cytotoxic waste bins prior to collection, and do not open or reprocess on site
- place sealed bins or bagged material in specially designed, large receptacles whilst awaiting collection for off-site transport
- where waste is stored for more than 72 hours prior to disposal, the waste should be refrigerated, particularly where waste is mostly organic and can decompose

Changing room

Appropriate areas shall be provided for male and female personnel (pharmacist, technician, nurses and cleaners) working within the unit. The area shall contain lockers & cabinets for holding personal belongings and personal protective equipments e.g. gowns, head covers, masks. It also contain the hand washing facility for scrubbing. These areas shall be arranged to encourage a one-way traffic pattern so personnel entering from anteroom can change and move directly into clean room.

Ante room

An anteroom is an area where personnel perform hand hygiene and garbing procedures, staging of components, order entry, CSP labeling, and other high-particulate generating activities. It is also a transition area that provides assurance that pressure relationships are constantly maintained so that air flows from clean to dirty areas.

Clean room:

The room in which compounding is taken place. It should be of appropriate size to accommodate all expected functions with enough space to install the workbenches or isolators.

Buffer zone

The buffer zone is the area in clean room where the workbenches or isolators are installed, compounding taking place and the operator is moving during the activities of compounding.

FINISHING

The surfaces

The surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets – particularly in the buffer area- should be smooth, impervious, free from cracks and crevices, and non-shedding, thereby promoting cleanability and minimizing spaces in which microorganisms and other contaminants may accumulate. The surfaces should be resistant to damage by disinfectant agents.

Work surfaces

It should be constructed of smooth, impervious materials, such as stainless steel or molded plastic, so that they are easily cleaned and disinfected.

Placement of devices (e.g., computers and printers) and objects (e.g., carts and cabinets) that are not essential to compounding in buffer zones and clean rooms is dictated by their effect on the required environmental quality of air atmospheres and surfaces, which must be verified by monitoring.

Ceiling

Ceilings are either gypsum board or hard polymer inlaid panels. If the ceiling is gypsum board, it is painted with epoxy paint that is smooth, non porous and non absorbent. If ceilings consist of inlaid panels, the panels should be impregnated with a polymer to render them impervious and hydrophobic, and they should be caulked both around each panel and around the perimeter to seal them to the support frame.

Junctures of ceilings to walls should be coved or caulked to avoid cracks and crevices where dirt can accumulate.

Dust-collecting overhangs, such as ceiling utility pipes, or ledges, such as windowsills, should be avoided.

The exterior surface of ceiling lighting fixtures should be smooth, mounted flush, and sealed. Any other penetrations through the ceiling or walls should be sealed.

Walls

Walls may be constructed of flexible material (e.g., heavy gauge polymer), panels locked together and sealed without commas or sharp corners, or of epoxy-coated gypsum board. All extensions (water, electricity and ventilation lines) are hidden inside walls. The keys for lighting within the outer region or changing room The walls must be without any windows connecting to the outside

Supply pipes

Should be hidden inside the walls

Floors

Preferably, floors are overlaid with wide vinyl Mono sheet flooring with heat-welded seams and coving to the sidewall. It should be rolled up onto the walls without commas or angles (Curved) at height of at least 15 cm from the ground, preferably light-colored and without any inscriptions.

Pass throughs

Are placed in the wall going into the buffer area to allow movement of product into and out of the room. Ensuring the pass-through hatch has no direct access to the external environment

Doors

Be sealed (Air Lock) and without handles, and works automatically and preferred to be Sliding doors.

Light switches & illuminations

Must be in changing room & with closed system not permitting any external air leak
Room lighting is supplied by ceiling modules, often incorporated into ceiling HEPA filter modules. Work area lighting may be supplied by illuminations (concentrated light sources that are placed next to the work area which can be adjusted to focus light on a desired area. Fixtures are sealed to prevent contamination.

Communication system (intercom)

Should connect the internally all rooms of the unit and external with all hospital departments

Hand wash basin

In the anteroom, should be deep, installed in the wall, without stands and the tap is Hand-free operated. The buffer area shall not contain sources of water (sinks) or floor drains.

Carts

Should be of stainless steel wire, nonporous plastic, or sheet metal construction with good quality, cleanable casters to promote mobility.

Storage shelving, counters, and cabinets

Should be smooth, impervious, free from cracks and crevices, non shedding, cleanable and disinfectable. Their number, design, and manner of installation e.g. (hanged) should promote effective cleaning and disinfection. limitation of the number of surfaces and shelves, to minimize particle shedding or the accumulation of particulate matter, provision of access for cleaning

ADDITIONAL CONSIDERATIONS FOR CYTOTOXIC DRUG UNIT

Additional considerations in designing and setting up a clean room and anteroom for cytotoxic preparations include:

- Installation of recessed lights
- Installation of an accessible emergency shower outside the anteroom
- Maintenance of an effective airlock between the cytotoxic suite and external environment
- Ensuring all equipment used is dedicated to the cytotoxic clean room
- Ensuring the anteroom provides access to only one clean room
- Installation of a manometer to monitor the pressure differential within the cytotoxic suite and record daily differential pressure readings
- Installation of a spill switch that reverses the airflow, minimizing contamination to the external environment.

ENVIRONMENTAL / ENGINEERING CONTROL

Engineering controls reduce the potential for airborne contamination in workspaces by limiting the amount and size of contaminants in the CSP processing environment.

Primary engineering controls used must provide quality of air to which sterile ingredients and components of CSPs are directly exposed.

Secondary engineering controls generally provide a buffer zone or buffer room as a core for the location of the workbenches or isolators.

A. PRIMARY ENGINEERING CONTROL (PEC)

Primary engineering controls typically include, but are not limited to, laminar airflow workbenches (LAFWs), Biological Safety Cabinet (BSCs), and Compounding Aseptic Isolator (CAIs), which provide an ISO Class 5 environment for the exposure of critical sites(see Table 1). Primary engineering controls must maintain ISO Class 5 or better conditions for 0.5- μm particles (dynamic operating conditions) while compounding CSPs.

The airflow in the primary engineering control is typically unidirectional (laminar flow) and because of the particle collection efficiency of the filter, the “first air” at the face of the filter is, for the purposes of aseptic compounding, free from airborne particulate contamination. Barrier isolators provide a suitable environment by restricting any ambient air from the work chamber. These systems are not as sensitive to external environments as the HEPA-filtered unidirectional airflow units.

In general, sterile product preparation facilities utilize laminar airflow workbenches (LAFWs) to provide an adequate critical site environment. A well-designed positive pressure barrier isolator, supported by adequate procedures for its maintenance, monitoring, and control, may offer an acceptable alternative to the use of conventional LAFWs in clean rooms for aseptic processing.????

Airborne contamination control is achieved in the primary engineering control through the use of HEPA filters. HEPA-filtered air should be supplied in critical areas (ISO Class 5) at a velocity sufficient to sweep particles away from the compounding area and maintain unidirectional airflow during operations. Proper design and control prevents turbulence and stagnant air in the critical area. In situ air pattern analysis via smoke studies should be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions.

The primary engineering control should be placed within a buffer room in such a manner as to avoid conditions that could adversely affect its operation. For example, strong air currents from opened doors, personnel traffic, or air streams from the HVAC systems can disrupt the unidirectional airflow in open-faced workbenches. The operators may also create disruptions in airflow by their own movements and by the placement of objects onto the work surface. The primary engineering control should be placed out of the traffic flow and in a manner to avoid disruption from the HVAC system and room cross-drafts.

Primary engineering controls (LAFWs, BSCs, and CAIs) are located within a restricted access ISO Class 7 buffer area within a cleanroom.

CAI can be located in worse than ISO Class 7 environments if meet the following conditions: The isolator must provide isolation from the room and maintain ISO Class 5 during dynamic operating conditions including transferring ingredients, components, and devices into and out of the isolator and during preparation of CSPs. Particle counts sampled approximately 6 to 12 inches upstream of the critical exposure site must maintain ISO Class 5 (see Table 1) levels during compounding operations. It is incumbent on the compounding personnel to obtain documentation from the manufacturer that the CAI will meet this standard when located in worse than ISO Class 7 environments.

Types of primary engineering control

1. laminar airflow workbenches (LAFWs)

Laminar flow hoods do not sterilize, it will maintain an area free of microorganism contaminants and particulate matter when it is properly maintained, prepared, and used by operators with good aseptic technique.

The Laminar Flow Workstations operate by drawing ambient air, under negative pressure, into the top of the unit. This air first passes through a prefilter which traps the larger dust and dirt particles. The blower then directs this prefiltered air, now under positive pressure, through the 99.99% efficient HEPA filter engulfing the entire work area with sterile, unidirectional ultra-clean air. This air travels at a velocity calculated to prevent the intrusion of unfiltered room air into the work area. It also washes away particles that may be generated by manipulations within the Workstations.

2. Biological Safety Cabinet (BSCs)

The Class II cabinet is defined as a ventilated cabinet for personnel, product and environmental protection, having an open front with inward airflow for personnel protection, downward HEPA-filtered laminar airflow for product protection, and HEPA-filtered exhaust air for environmental protection. The cabinets are differentiated into various types based on their construction, airflow velocities and patterns, and by their exhaust system

Preference should be given to Class II Type B-BSC, which does not exhaust any cabinet air into the workroom. Class II Type A BSC exhaust HEPA-filtered cabinet air into the work room. They are also **approved** if:

A. They are used with a canopy or thimble hood that captures air released from the BSC and exhausts the air out of the building; or

B. There are means to ensure that the HEPA filter is functioning effectively before each use (e.g., by reading a properly installed pressure differential gauge) and the exterior surface of the HEPA filter is protected from damage. (Option A is recommended instead of this approach.)

The BSC must be inspected and certified by a competent person at least annually and when the cabinet is moved. The BSC must be cleaned, maintained, and used according to the manufacturer's recommendations. The exhaust blower on the BSC should be operated continuously even when not in use.

3. Compounding Aseptic Isolator (CAIs)

The use of a barrier isolator protects the sterility assurance level of the TPN solutions by eliminating direct personnel contact in the critical zone and minimizing the number of particulates and microorganisms in the environment.

Barrier isolators are also used in the preparation of hazardous drugs such as anti-neoplastics agents and those required for gene therapy. Any product in the categories described above should be prepared in a properly designed barrier isolator. Studies have identified gross contamination from anti neoplastic agents in cancer centers in which traditional class II biological safety cabinets are used. Recommendations about the pressurization scheme of cytotoxic isolator, which are subject to regulations for both sterile and hazardous materials, differ according to regulatory agency. OSHA recommends negative pressure and the FDA prefers positive pressure, which protects the product. Usually, the FDA wins this argument

The physical structure of primary engineering control

- Interior surfaces must be smooth and cleanable and must have coved junctions of walls, ceilings, and floors. All welds must be ground smooth.
- It should be sealed with gasketing materials that have been approved by the international authority such as type 316 stainless steel.

- Those construction materials must be chemical resistant to protected from cleaning and sanitizing agents.
- A high-efficiency particulate air (HEPA) filter that has an efficiency rating of 99.97% or greater should be used to filter the air that enters and exits.
- It must be possible to clean the internal surface area of the HEPA filter or to cover it during cleaning and to sanitize the surface of the filter.
- Documentation of methods used in certification to meet regulations should be provided.

Factors to determine the number and size of primary engineering control

Pharmacists who plan to establish CSP unit should consider the following three factors:

1. The proper size of the primary engineering control required and the number of Work stations necessary. The determination of the number and size of work stations should be based on both current and projected pharmacy activities.

Given the number of daily doses that must be prepared, the required number of primary engineering control (by type) can be determined.

2. The most functional layout for the area in which the primary engineering control will be located. Design a plan for that layout. In the plan, the movement of pharmacist and technicians, compounding materials that will be used, and the quantity of supplies that must be stored should be considered.

3. A specification sheet describing the primary engineering control. The specifications should include the four components common to all systems; physical structure, the internal environment, transfer and interaction technologies, and monitoring systems.

B. SECONDARY ENGINEERING CONTROLS (ANTEROOMS, CLEAN ROOMS, BUFFER ZONES)

Secondary engineering controls such as clean rooms and anterooms generally provide a buffer zone or buffer room as a core for the location of the primary engineering control.

Ensure that the anteroom provides the only access to the clean room

Buffer zones or clean rooms

The CSP work environment is designed to have the cleanest work surfaces (primary engineering controls) located in a buffer area.

The room should be segregated from surrounding, unclassified spaces to reduce the risk of contaminants being blown, dragged, or otherwise introduced into the filtered unidirectional airflow environment and this segregation should be continuously monitored.

Anteroom

In general, the buffer area is preceded by an anteroom that provides ISO Class 8 conditions for 0.5- μm and larger particles under dynamic conditions. The ante room is a clean area for donning personnel barriers, such as hair covers, gloves, gowns, or full clean-room attire. It is an area near, but physically isolated from the buffer room area. The supplies, such as needles, syringes, ampuls, bags, vials of parenteral fluids, and packages of transfer tubing sets for large-volume fluids are **uncartoned ??** and **disinfected** there.

Hand sanitizing and gowning activities also occur in the anteroom area adjacent to the buffer area. Faucet handles are designed to be hands-free. Before processing CSPs, hands are resanitized after donning all appropriate garb, except for gloves. A demarcation line or barrier identifies the separation of the buffer area from the anteroom area.

Compounding personnel must be capable of accessing the buffer area without use of their hands. Anteroom areas adjacent to buffer areas are intended to minimize the introduction of contaminants into buffer areas.

International Classification of Particulate Matter in Room Air

The buffer area should maintain at least ISO Class 7 conditions for 0.5- μm and larger particles under dynamic operating conditions.

Measuring, weighing, mixing, and other manipulations of non sterile in-process CSPs are also performed in air quality of at least ISO Class 8. Appropriate air conditioning and humidity controls must be in place for the buffer area.

Room air exchanges

Room air exchanges are typically expressed as air changes per hour (ACPH). Adequate HEPA filtered airflow supplied to the clean room and anteroom is required to maintain cleanliness classification during operational activity through the number of air changes per hour. Factors that should be considered when determining air-change requirements include number of personnel working in the room, compounding processes that generate particulates, as well as temperature effects.

An ISO Class 7 clean room supplied with HEPA filtered air shall receive an ACPH of not less than 30. The primary engineering control is a good augmentation to generate air changes in the air supply of a room but cannot be the sole source of HEPA filtered air. If the room has an ISO Class 5 re-circulating device, a minimum of 15 ACPH through the room supply HEPA filters is adequate providing the combined ACPH is not less than 30. More air changes may be required based on the number of personnel and processes.

HEPA filters are a minimum of 99.97% efficient when tested using 0.3- μm thermally generated particles and a photometer or rated at their most penetrating particle size using a particle counter and should be leak tested at the factory and then leak tested again in situ after installation. HEPA filtered supply air is introduced at the ceiling with low-wall mounted returns, creating a general top-down dilution of room air with HEPA filtered make-up air. Ceiling mounted returns are not recommended.

Temperature

A Comfortable working environment is required for compounding with an area temperatures of 20 °C or cooler.

Pressure

For rooms providing a physical separation, through the use of walls, doors and pass-throughs, a minimum differential positive pressure of 0.02 to 0.05 inches water column is required. For clean rooms or buffer zones not physically separated from the anteroom, the principle of displacement airflow should be employed. This concept utilizes a low pressure differential, high airflow principle. Using displacement airflow typically requires an air velocity of 40 feet per minute (fpm) or more from the buffer room across the line of demarcation into the ante-area. The displacement concept is not applied to high risk compounding applications ???.

Visual observation

Window for Visual observation for all compounding and non compounding personnel must be present.

Tasks

Tasks carried out within the buffer area should be limited to those for which a controlled environment is necessary. Placement of devices (e.g., computers and printers) and objects (e.g., carts and cabinets) that are not essential to compounding in buffer zones and clean rooms is dictated by their effect on the required environmental quality of air atmospheres and surfaces, which must be verified by monitoring.

Only the furniture, equipment, supplies, and other goods required for the tasks to be performed may be brought into this room, and they should be non permeable, non shedding, and resistant to disinfectants. Whenever such items are brought into the room, they should

first be cleaned and sanitized. Whenever possible, equipment and other items used in the buffer area should not be taken from the room except for calibration, servicing, or other activity associated with the proper maintenance of the item.

Only authorized personnel and materials required for compounding and cleaning are permitted in the buffer area. Pre sterilization procedures for high-risk level CSPs, such as weighing and mixing, shall be completed in an ISO Class 8 (see Table 1) or better environment.

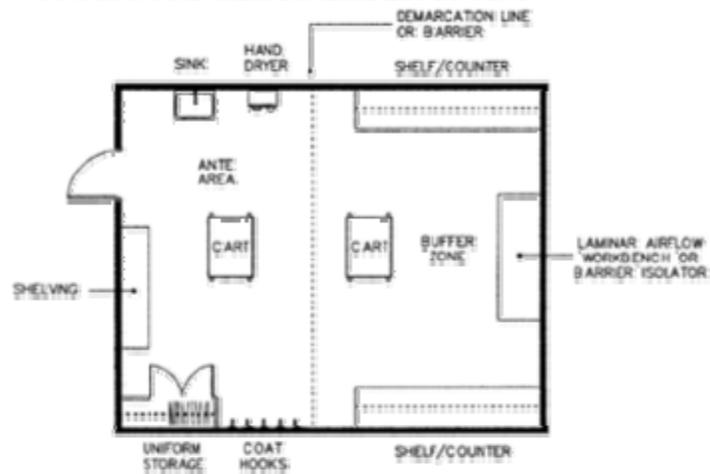
Additional Personnel Requirements

Food, drinks, and materials exposed in patient-care and treatment areas, must not enter anterooms, ante-areas, and buffer areas where components and ingredients of CSPs are present. When compounding activities require the manipulation of a patient's blood-derived or other biological material (e.g., radiolabeling a patient's or a donor's white-blood cells), the manipulations must be clearly separated from routine paths and equipment used in CSP preparation activities, and they must be controlled by specific standard operating procedures in order to avoid any cross-contamination. Packaged compounding supplies and components, such as needles, syringes, tubing sets, and small- and large-volume parenterals, should be uncartoned and wiped down with a disinfectant that does not leave a residue (e.g., 70% IPA) when possible in an anteroom-type area, of ISO Class 8 air quality, before being passed into the buffer areas. Personnel hand hygiene and garbing procedures are also performed in the anteroom or ante-area, which may contain a sink that enables hands-free use with a closed system of soap dispensing to minimize the risk of extrinsic contamination. There shall be some demarcation designation that separates the anteroom, or ante-area, from the buffer area. Adequate provision for performing antiseptic hand cleansing utilizing an alcohol-based surgical hand scrub with persistent activity followed by the donning of sterile gloves should be provided after entry into the buffer area.

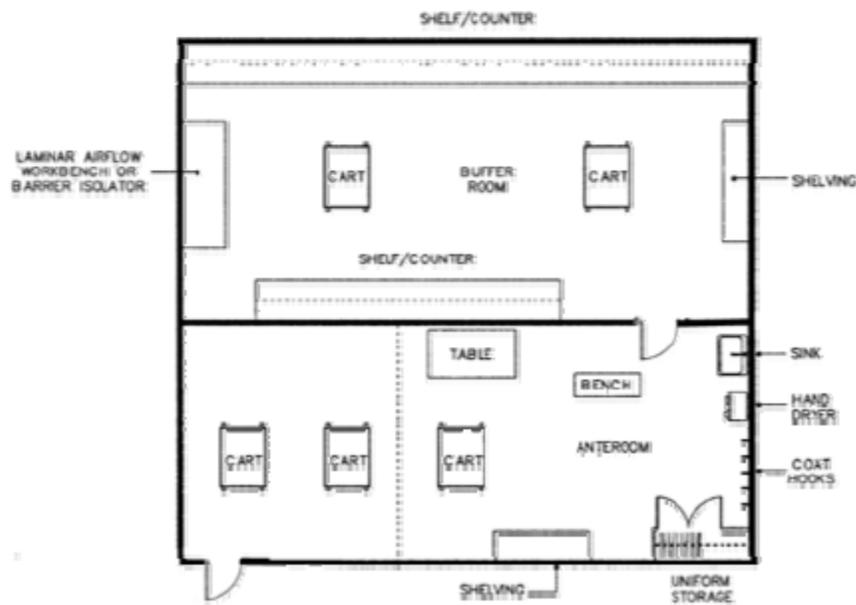
- An example of the arrangement of a clean-room floor plan for low- and medium-risk level CSPs is illustrated in the first drawing in Figure 1.
- An appropriate multi compartment clean-room floor plan for high-risk level CSPs. is illustrated in the second drawing in Figure 1.

Figure1.

EXAMPLE OF CLEAN ROOM FLOOR PLAN SUITABLE FOR LOW AND MEDIUM RISK-LEVEL CSPs



EXAMPLE OF CLEAN ROOM FLOOR PLAN SUITABLE FOR HIGH RISK-LEVEL CSPs



ENVIRONMENT VALIDATION

1. Prefilters of the Primary engineering control are changed or cleaned at least monthly. A record sheet is provided on the horizontal flow hood for documentation.

2. Particle Testing is conducted by a trained professional with air sampling equipment.

Total particle counts must be conducted at a minimum of every 6 months for Primary engineering control (PECs), buffer areas, and ante-areas. Counts must also be obtained if the PEC is relocated or if physical alterations are made to the buffer or ante-areas.

Records of the particle testing are maintained in the pharmacy for a minimum of 5 years.

3. Evaluation of Particle Test Results:

a. An increase in particle count indicates a need for evaluation of cleaning procedures.

Counts are kept below 100,000 particles per cubic foot. Counts above 100,000 particles per cubic foot result in stricter compliance with sterile product procedures and remonitoring.

b. Testing is repeated after adjustments are completed.

4. Bacterial Air Testing is conducted monthly by all areas compounding low and medium risk preparations. Record Colony Factor Units (CFU) results in log.

5. Evaluation of Bacterial Air Testing:

a. Each area compounding low and medium risk products performs bacterial testing of each Primary engineering control (left side and right side), clean room, and ante room. The first 6 months of bacterial testing is used to determine the baseline CFU's for each test area. For each area, average the CFU results from the 6 monthly tests. This gives a baseline for each tested area. A new baseline is calculated following any renovation of an IV area.

b. Following the baseline test period, monthly tests are compared to the baseline value. An increasing trend over baseline (100% for Low Risk or 75% for Medium Risk warrants a prompt re-evaluation of the adequacy of cleaning procedures, operational procedures, and air filtration efficiency.

6. HEPA filter validation is performed no less frequently than once every six months, but more frequently if the filter is splashed with solution or there is other possibility of degradation of the filter. New filters are checked immediately following installation for leakage, particularly around the periphery.

7. In the chemotherapy preparation room: Record pressure from vertical flow hood weekly on Monday. Review pressure from previous week. The pressure goes up weekly until 6 month cleaning. If the pressure goes down, there is a need for immediate action.

8. On Mondays, record from Flow Safe Safety Alert whether the air flow is in the normal range and the green light is on. This records that there is negative pressure in the room.

9. Documentation of the integrity of the refrigerator is maintained.

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- Standard practiced to ensure safe cytotoxic drug reconstitution in hospital pharmacies: An international review, W. Griffiths¹, M. Ackermann¹, J.- C. Schira², F. Sadeghipour¹, P. Bonnabry¹, Pharmacy¹ and Staff Medical Officer ², University Hospitals of Geneva, Switzerland
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