Laminar Airflow Equipment: Applications and Operation

Gregory F. Peters
Lab Safety Corporation, Des Plaines, Illinois, U.S.A.

INTRODUCTION

The number and complexity of pharmaceutical manufacturing and compounding processes requiring protection from airborne contaminants has increased substantially in recent years. Because pathogenic viable and non-viable contamination may be readily introduced into a patient along with a therapeutic parenteral drug, the sterility and purity of parenterals must be controlled in the manufacture and assured in the compounding of these products. Laminar airflow (LAF) equipment is widely used as an engineering control in aseptic processing to provide a production environment free of airborne and resulting surface contamination by microorganisms, pyrogenic and drug residues, and other materials that present a risk of intravascular infection, pyrogenic response, or occlusion of the peripheral vasculature. With the growth of the small- and intermediate-size generic drug manufacturing, drug repackaging, and diverse hospital pharmacy and home health care IV admixtures, compounding industries, clean space design and management has become the direct responsibility of an increasing number of middle- and line-management personnel. As such, a working knowledge of LAF theory, aseptic processing, and clean space management is integral to the conceptualization, construction, and operation of a safe and effective clean space, and an important consideration in the selection or retention of the clean space manager and operative personnel.

CONTAMINATION CONTROL

All manufactured products are vulnerable to contamination by a myriad of aerosolized contaminants, including microorganisms, pyrogenic dust, ash, pollen, smoke, hydrocarbons, and other chemicals that are omnipresent in the environment (Fig. 1). Because of the potential dangers to the patient resulting from a parenteral product containing even minute quantities of these contaminants, exceptional measures are required to exclude them fromthe finished product. Careful planning is essential in preventing contamination of the environment leading to occupational exposure of personnel to hazardous substances, which are routinely manipulated in pharmacy operations. The primary objective of the aseptic process is control and elimination of viable contaminants. These contaminants are numerous and varied, normally consisting of bacteria, fungi, and viruses. Viruses are usually short-lived upon exposure to air, and require host systems to remain viable and reproduce; they are generally not of direct concern, except in excluding their vector, or transport mechanism. Aseptic processes are designed to exclude bacteria and fungi as well as their spore forms and breakdown products. Many of these contaminants are naturally airborne and occur commonly in the atmosphere. However, the contamination of greatest concern in aseptic processing is the endogenous microbiologic material generated by the operative personnel and others involved in the manipulation of parenteral products. This type of contamination is easily aerosolized and introduced into air currents by normal ''shedding'' of endogenous microbiota, and by mechanical means as microscopic droplets of sputum, produced by talking, laughing, or sneezing. Endogenous contamination is generated in enormous quantities on the skin[a][1] and may be deposited on the surfaces of containers, equipment, gowns, and materials introduced into the aseptic work field during the course of manipulations.

Waterborne contaminants may also be introduced by contaminated cleaning agents or poor cleaning and sanitizing techniques. All types of gross microbiologic contamination are found on work surfaces, gloves, and compounding materials following contact with contaminated objects. Pyrogenic and non-pyrogenic dust must also be excluded from parenteral products. Even minute quantities of this material

[a]The average adult human sheds 25,000–50,000 *Staphylococcus epidermidis* particles per minute; one person in five is a carrier and active producer of *Staphylococcus aureus*, the organism responsible for toxic shock syndrome, a bacteremia fatal in 50–90% of reported cases.

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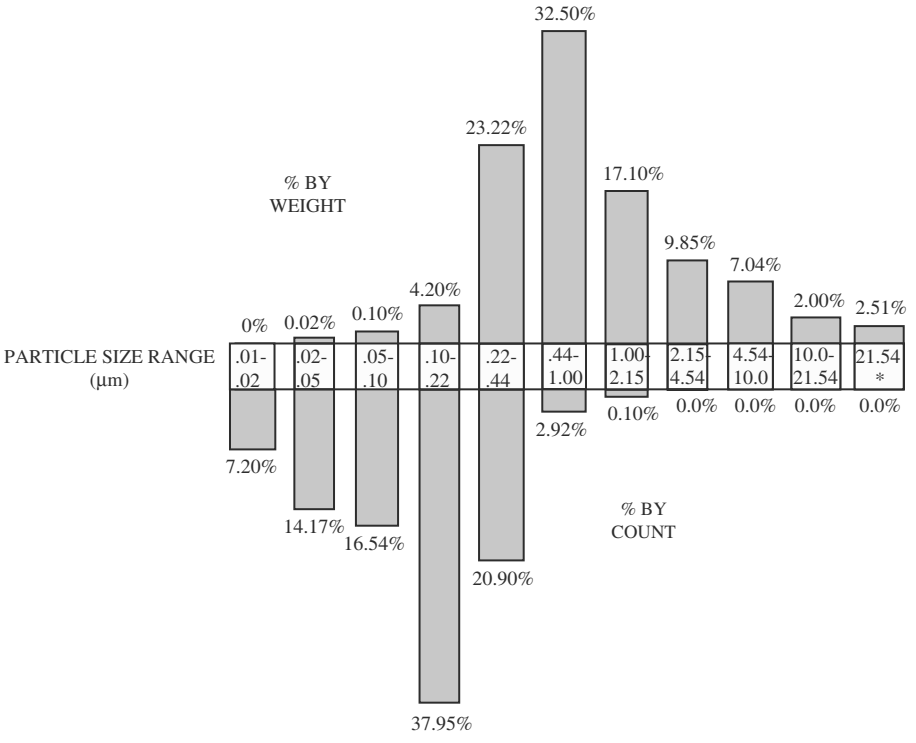

Fig. 1 Distribution by size and weight percent of particulates in normal atmospheric air. (Courtesy of American Air Filter Research, Louisville, Kentucky.)

may cause acute inflammation or abscess at the injection site, and induce a life-threatening pyrogenic response. In addition, evidence of long term dangers of fiber emboli in producing pulmonary and cerebral granulomas, stenosis, and occlusion of microcirculation, as well as clouded vision, and neurological sequelae in patients receiving particulate-contaminated intravenous admixtures has emerged.[2,3] Additionally, drug product residues remaining in the aseptic processing field as a result of improper line-clearance are a threat to the patient for whom they are not intended.

History

LAF is an ''offshoot technology'' stemming from development of the high efficiency particulate air (HEPA) filter, spearheaded by the U.S. Army Chemical Corps, Naval Research Laboratories, and the Atomic Energy Commission in the 1940s and 1950s. Known as an absolute filter, the HEPA filter was further developed by the nuclear industry to provide fail-safe removal of extremely hazardous microscopic airborne particulates[b] at nuclear facilities. In the late 1950s, a proliferation of laminar flow clean benches (LFCBs), incorporating a HEPA filter, made it possible for the hospital pharmacy to achieve a small, but exclusive compounding environment of sterile air and sanitized, bacteriostatic worksurfaces in which to prepare small numbers of individual, patient-specific sterile products.

On a broader scale, pharmaceutical manufacturers were beginning to utilize absolute filtration as a primary engineering control in the maintenance of large, carefully controlled clean spaces in the batch production of quality-controlled parenteral products. In this application, LAF was supplied directly to production lines and extended critical worksurfaces within defined, non-turbulent entrance and exit planes as parallel or ''columnated'' airflow (misnamed''laminar flow'').[c] This highly controlled laminar airstream was supplied to the critical worksurface, in addition to conventionally supplied turbulent airflow to the general space, provided through terminal diffusers for filtration of the balance of room air. In this manner, the ''stepped'' control of all critical, as well as support areas was achieved.

In the mid-1970s, increased control of manufacturing process air quality became possible with the refinement of LAF clean space design, the growing body of historical process quality data, the refinement of

[b]99.97% of particulates smaller and larger than 0.3 microns.

[c]Laminar flow is defined as a fluid stream having discernible differentiations (laminations or layers) of velocity, pressure, temperature, or other characteristic, whereas parallel flow is uniform throughout its vertical, horizontal and longitudinal extent.

statistical process controls (SPCs), and the emergence of industry operating standards.[4] In 1979, concern for the safety of pharmacy personnel compounding antineoplastic drugs in LFCBs was expressed, following studies that clearly identified the potential health risks to these personnel.[5] The introduction and widespread use of the Class II laminar flow biological safety cabinet (BSC) by oncology/hematology pharmacy occurred in the late 1970s, and was almost universal by the end of the 1980s. Additional studies conducted in the late 1990s clearly indicated that, in spite of pharmacy-wide implementation of Class II BSC containment technology, the same potential health risks identified in 1979 continued to exist in the workplace.[6] The swift, anecdotal response in some segments of the pharmacy industry was to strongly recommend immediate retrofit of the Class II design with the Class III BSC, or Barrier Isolator (sometimes referred to as a ''barrier hood'') in the glovebox or half-suit configuration, as an alternative to ''open'' Class II units used by pharmacy in a manner that had ostensibly failed to protect workers and the environment. This recommendation, however, was not based upon adequate and careful engineering failure analysis (FA) of the Class II design as implemented in pharmacy operations, by which the Practice might rationally evaluate and address the reasons for such failure. Neither, as of this writing, have any systematic, scientifically based feasibility studies, validation and monitoring protocols, or operating specifications leading to proper, corrective retrofit with the Class III or barrier isolator designs been developed as a corollary to such FA. (It should be noted that not all ''barrier isolators'' or ''gloveboxes'' are Class III BSCs.) These steps are absolutely essential in preventing a repeat failure of any type of BSC in the engineering control of hazardous substances manipulated by pharmacy personnel, and the resulting characterization of the IV pharmacy as a serious occupational risk environment.

THE HEPA FILTER

The essential element common to all LAF equipment is the HEPA filter.

Construction

The HEPA filter is normally constructed of borosilicate microfibers, formed into a flat sheet by a process similar to papermaking (Fig. 2). This sheet is pleated to increase the overall filtration surface area, in order to minimize the static pressure drop across the filter

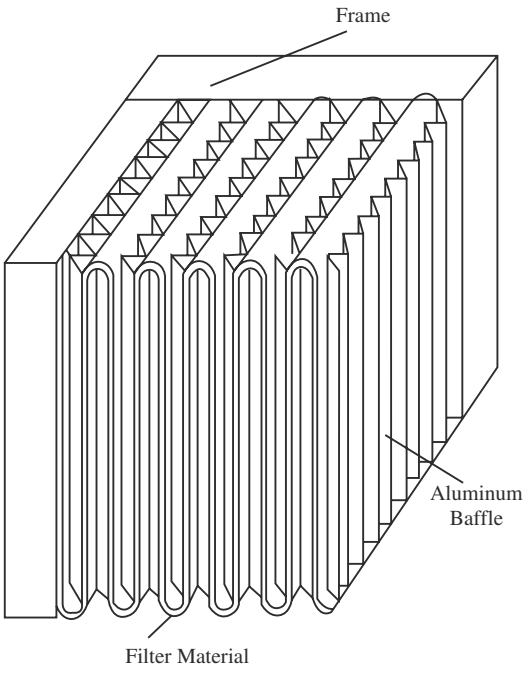

Fig. 2 HEPA filter cross-section showing pleated construction. (Courtesy of the Baker Company, Sanford, Maine.)

to a predetermined value[d] at a given airflow specification. The pleats are separated by serrated aluminum baffles or stitched fabric ribbons, which direct airflow through the filter. This combination of pleated sheets and baffles facilitates maximum exposure of the upstream filtration area to the airstream and is referred to as the filtration medium. It is constructed in a predetermined size, and installed into an outer frame made of fire-rated particle board, aluminum, or stainless steel. The frame-media junctions are permanently glued or ''pot-sealed'' to ensure a leakproof bond. The frame is fitted with a continuous, closed-cell neoprene gasket or other suitable occlusive seal to provide a gas-tight installation of the filter into the air handling system.

Filtration Efficiency

Refinement of HEPA filter manufacturing and testing technology and development of the ultra low particulate air (ULPA) filter, have led to an increase of absolute filtration retention efficiency of greater than two orders of magnitude above 99.97%. HEPA filtration efficiencies range from a minimum of 99.97 to 99.99%, with ULPA efficiencies above 99.9999% for particulates larger and smaller than 0.3 μm in diameter

[d]Normally 0.50–1.2 in. water column (WC) or water gauge (WG).

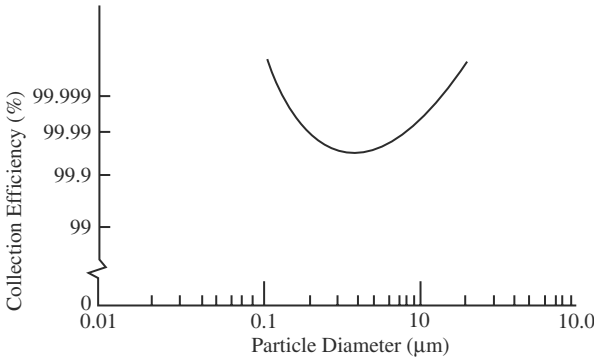

Fig. 3 Theoretical HEPA filter-collection efficiency. (Courtesy of the Baker Company, Sanford, Maine.)

(Fig. 3). (HEPA filters used in pharmaceutical and pharmacy-compounding applications rarely exceed 99.99%.) Expressed another way, the HEPA filter is capable of trapping and retaining 999,700–999,900 of every 1,000,000 particles smaller and larger than 0.3 μm in diameter.

Filtration Mechanisms

The three principal filtration mechanisms (Fig. 4) by which aerosols are collected on the HEPA filtration medium are:

- Inertial impaction, where particle inertia causes it to leave the flow streamlines and impact on the fiber;
- Interception, a screening effect dependent upon particle fiber-size relationships; and
- Diffusion, a Brownian motion diffusion of very small particles due to molecular bombardment.[7]

Other filtration mechanisms, such as sedimentation and electrostatic attraction, provide some degree of aerosol collection, however most particulates are removed from the airstream by the above methods.

Shipment, Storage, and Handling

The HEPA filter is extremely fragile and should be shipped, stored, and handled in the same manner as delicate instrumentation. Personnel responsible for receiving and handling HEPA filters should receive training in proper handling technique. All incoming HEPA filters should be visually inspected for apparent damage due to mishandling, and all damage described in detail on the shipping documentation prior to acceptance.

Filtration Performance Certification

Individual HEPA filter efficiencies are established by an exacting challenge of the filter frame and medium, usually incorporating a ''cold-boil,'' polydisperse aerosol of dioctylpthalate (DOP) or equivalent,[8] which is introduced into the upstream plenum-side of the filter in a manner that ensures even distribution of the test aerosol behind the filter, at its rated airflow.

Following verification of acceptable airflow velocities, expressed by the manufacturer in linear feet per minute (LFPM) or meters per second (m/s), leakage is determined by measuring the penetration of the test aerosol through the filter as a percentage of the upstream plenum aerosol concentration, using an aerosol photometer[4] or optical particle counter[9] to carefully scan the entire filter media face and frame. Penetration of the test aerosol at or above 0.01% of the upstream concentration is considered a leak requiring repair. Leakage should be repaired only with room temperature-vulcanizing (RTV) silicone caulk, which is easily applied, and exhibits long term stability and resistance to deformation. Repairs to the filtration medium should be made in the manner specified in the literature.[10] Individual repair ''patches'' should not exceed 1.5 in. in length or width, nor should the sum total of all repairs exceed 3% of the total area of the filter face. During operation and at all times no

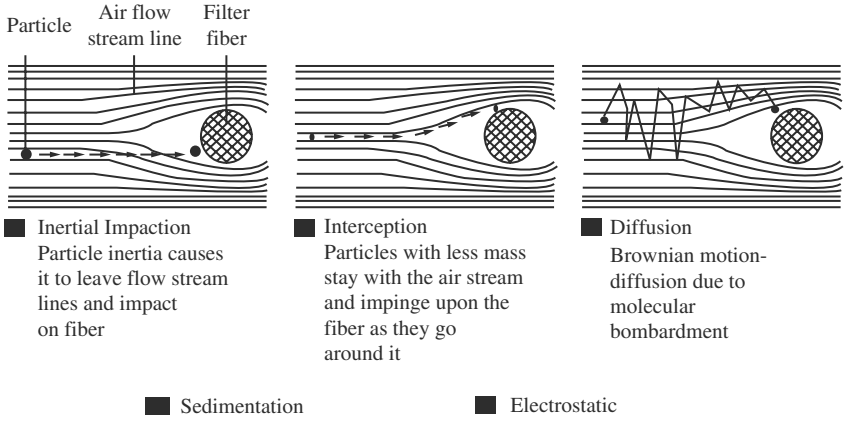

Fig. 4 Air filtration theory particle-collection mechanisms. (Courtesy of the Baker Company, Sanford, Maine.)

object, drug residue, or debris should be permitted to come into contact with the HEPA filter.

LAF AS A BARRIER TECHNIQUE

LAF has long been the primary method of controlling airborne contamination in the aseptic processing of pharmaceutical and pharmacy products. Also known as non-turbulent, or unidirectional airflow, LAF is generally defined as ''HEPA-filtered air having parallel streamlines, flowing in a single pass and direction through a clean zone.''[4] LAF is technically defined as fluid flow without macroscopic fluctuations, which generally occur when the Reynolds number[e] is less than 2000. Industry standards require that 80% or more of the total airflow exhibit this characteristic, in order to meet the definition of LAF.[11] LAF is necessary to maintain the most stringent air cleanliness classes[f][4] in the production of ''first air''[g] at the critical worksurface of the LFCB and BSC, and in operational cleanrooms.[4,11] It is important to note that the terms ''laminar airflow'' and ''Class 100'' are not interchangeable; LAFfirst air incorporating properly validated HEPA filtration produces air cleanliness of approximately Class 1, nearly two orders of magnitude cleaner than Class 100. Class 100 non-laminar airflow does not constitute first air within a critical work zone, and should not be substituted in applications requiring or designating LAF.

Conventional Airflow

Conventional airflow (also known as turbulent, or non-unidirectional airflow) incorporates HEPA filters, located in-duct, or as room terminal filtration modules (TFMs; Fig. 5). Often confused with LAF, conventional airflow does not meet that definition because it allows multiple-pass circulating characteristics or a non-parallel airflow direction, or both. This type of airflow is incapable of producing first air, and is normally used as secondary or ''buffer'' filtration in treating a processing or compounding space that contains laminar airflow devices (LAFDs) to maintain primary critical work surface conditions, or in treating other processing or support areas about which a definitive air cleanliness statement must be made. Properly designed, a conventional airflow system is effective in maintaining the less-stringent air cleanliness classes[f] in operational cleanrooms.[4,11]

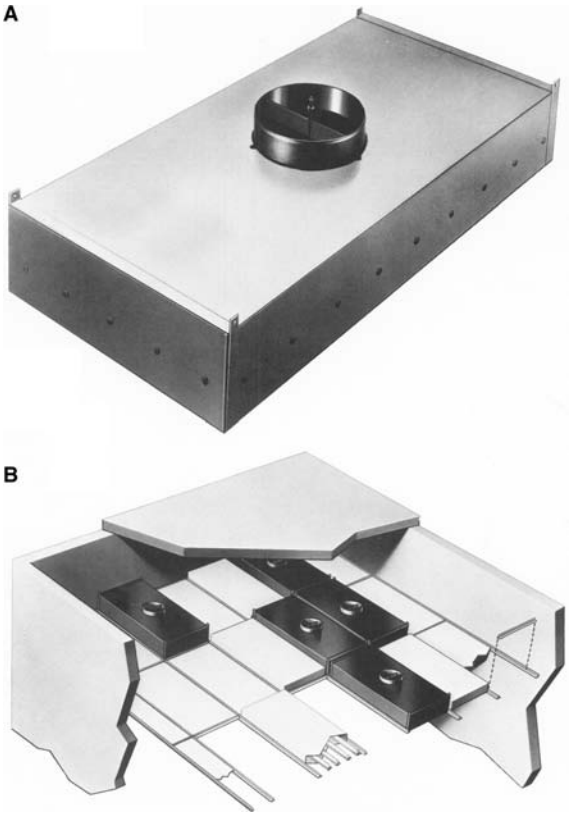

Fig. 5 (A) The self-contained terminal HEPA filtration module (TFM). (B) Arrangement of TFMs in the T-Bar ceiling in a conventional-flow application. (Courtesy of American Air Filter, Inc., Louisville, Kentucky.)

Advantages

When used properly by trained personnel, employing adequate process controls, the LAF environment provides a reliable barrier to measurable airborne viable and non-viable, solid particulate contamination, which may defeat the aseptic process. LFCBs, BSCs, and heating, ventilation, and air conditioning (HVAC) installations are easily validated. These systems normally continue in operation with little or no variation in output quality for long periods of time, and are easily maintained and tested.

Limitations

Any discussion of LAF equipment must include consideration of aseptic technique and the aseptic process as a whole. Often relied upon as an infallible process

[e]The ''Reynolds number'' is the ratio of inertial to viscous forces in a pipe or duct.

[f]''...Most stringent air cleanliness classes '' are defined as class 10–100, (F.S. 209e); Classes C, D, and E (British Standard 5295); Classes 4–5 (EN ISO); Grades A-B (EC). ''...less stringent air cleanliness classes...'' are defined as Class 1,000–100,000 (F.S. 209e); Classes F through K (B.S. 5295); Classes 6–8 (EN ISO); Grades C-D (EC).

[g]''First air'' is uninterrupted air issuing directly from a HEPA filter in a laminar-airflow environment.

support, LAF is in fact a fragile, protective envelope of slow-moving, aerosol-free air[h][4] the effect of which is easily disrupted and defeated by improper placement of processing materials, poor manufacturing and personnel practices, inadequate aseptic technique, or failure to maintain the HVAC components. Although the laminar slip stream itself is free of particulates, it does not eliminate particulates or other surface contaminants present in the aseptic field, or contamination introduced into the aseptic field on the surfaces of improperly prepared processing materials, and their manipulation and storage within the aseptic environment. Neither is LAF a substitute for proper manipulative and aseptic technique. Excessive confidence in any LAF system should not lead to the neglect of proper precleaning and staging of processing materials, personnel selection, training, and validation;[i][12] effective routine housekeeping and maintenance procedures;[13] and aseptic process monitoring and auditing methods.[j] This may result in a breakdown of the process and a compromise of product integrity. In addition, the use of improper manipulative technique in BSCs and containment systems may result in a compromise of the waste-stream, resulting in cumulative contamination of operative personnel and the environment.

Operating procedures

Although the design of each type of LAFD dictates certain specific operating procedures, several general principles apply to all LAFDs.[9]

Cleaning and Preparation. *LFCB*: The LFCB should be allowed to run for at least 30 min before the commencement of aseptic operations. All work-zone accessible surfaces, with the exception of the filter-protective screen, should be cleaned and sanitized by application and recovery of a low-residuing, water-base disinfectant cleanser (household bleach or other hypochlorite solutions should not be used at any time on stainless steel surfaces), followed by application of 70% ethyl or isopropyl alcohol sprayed evenly lengthwise across the work surface from the back of the cabinet to the front, and allowed to dry.[14] (The combination of a water-base disinfectant cleanser with alcohol provides both the broadest antimicrobial action and the widest range of surfactant and solubility factors for the recovery of surface residues during the cleaning process.)

BSC: The BSC should operate continuously to ensure containment of hazardous substances. All work-zone interior surfaces with the exception of the HEPA filter-protective screen should be cleaned and sanitized carefully in the manner of the LFCB in the proper order to ensure protection of operator's garb from contaminants and cleaning residues during the cleaning process. This sequence will also prevent the transfer of drug residues to the general environment.[14]

Staging

Following complete drying of the work surface, operations in the LAFD should begin with the staging of all working materials for introduction into the aseptic work area.[14] This should include:

- assembly of all required working materials, such as drug components, syringes and sterile fluid pathways, diluents, dispensing and venting devices, wipes, final containers, etc.
- preparation, in a Class 100,000 environment,[4] of all working materials that are to be placed into the aseptic field by sanitizing with 70% ethyl or isopropyl alcohol spray and wiping all containers, including careful removal of gross contamination and filth from any container that does not have an outer wrapper, removal of inner containers from their outer wrappers, and placement of all materials on a sanitized, stainless steel surface. This is preferably a cart or tray at a close proximity to the LAFD for direct loading of materials into the aseptic work zone.

Materials such as paper, labels, writing implements, etc., should not be placed into the work zone.

Aseptic manipulation

Prior to introduction of the working materials into the LAFD, the gloved hands of the operator should be thoroughly washed and rinsed to remove dry lubricants, sanitized by spraying with 70% alcohol, and allowed to dry in the laminar airstream. The working materials may then be transferred to the work zone, and aseptic manipulations begun. The operator's

[h]Airflow velocity exiting an unobstructed workstation should be maintained at *90 LFPM average with a uniformity within* ±20% across the entire area of the exit.

[i]1) Personnel selection and screening criteria; 2) a formalized training program to include a period of supervised manufacturing or clinical experience culminating in a recommendation for validation by the supervisor; 3) a personnel validation method, including a written exam with a required passing grade, and a practical assessment of aseptic technique, utilizing sterile microbiologic growth media in a process simulation incorporating all processing steps encountered by the candidate during the actual processing operation.

[j]Quality assurance (QA) testing and recertification of LAF systems and other engineering controls, which support the aseptic process (process auditing), irrespective of quality control, or procedures to demonstrate conformance with product specifications of identity, purity, sterility, and apyrogenicity (product auditing).

hands should be slowly inserted into, and removed from the laminar airstream, in order to minimize backwash and cross-stream contamination of the work zone. Working materials should be arranged in such a way that work progresses laterally, from right to left or left to right, so that non-interrupted first air is continuously supplied to the critical surfaces of all working materials at all times. If the operator must leave the work zone area, his or her gloved hands should be resanitized with 70% ethyl or isopropyl alcohol prior to reentering the work zone. This practice takes little time and minimizes contamination of the work zone by endogenous and residual environmental flora. An alcohol-spray bottle or other suitable dispenser should be provided close to the work zone entrance for this purpose, with the alcohol filtered and the dispenser sanitized each time the dispenser is refilled. Good aseptic technique is essential to retain the sterility of compounded products, and properly fitting surgeon's gloves, mask, laboratory coat (or arm barrier), and hair cover are recommended for all pharmacy operators working in the LAFD.[a][1,14]

LFCB

The oldest and most basic LAFD is the LFCB, universally referred to as a "hood." It is an enclosed work area with its own HEPA-filtered air supply (Fig. 6). The LFCB provides only product protection by capturing room air, passing it through a HEPA filter, and directing the filtered air horizontally or vertically uniformly across the work surface toward the operator at a constant speed.

Limitations

The LFCB should not be used in operations requiring the manipulation of cytotoxic, radioactive, microbiologic, or other hazardous materials, which may become aerosolized and aspirated directly by the operator. Reconstitution and manipulation of antineoplastics and vesicants, mass reconstitution of antibiotics, antivirals, vaccine formulation, and similar manipulations should be carried out in a laminar flow BSC.

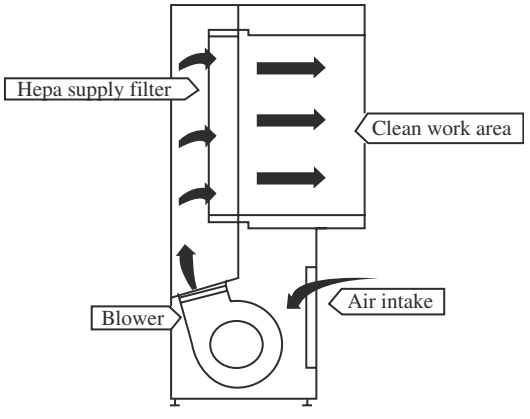

Fig. 6 The LFCB airflow profile. (Courtesy of the Baker Company, Sanford, Maine.)

Placement of materials in the work zone

Working materials placed into the LFCB should be positioned a minimum of three object-diameters in from the open end of the unit when the object is exposed to the laminar airstream on all sides, and a minimum of six diameters in from the open end when working at either end of the unit or when the object is exposed to the laminar airstream on only one side.[14] This general method counteracts backwash contamination, which may compromise the aseptic field. The introduction of any large object (automated, high speed compounding devices, water baths, carboys, etc.), obstruction, or complicated process into the laminar airstream may likewise induce backwash contamination, and should be validated to maintain cohesion of the airstream and exclude both backwash and cross-stream contamination during the process. This may be accomplished by the use of visual tracers, such as smoke sticks or other smoke-producing devices, to introduce quantities of smoke both upstream of the critical worksurface and at the open end of the unit during a process validation or qualification run for visual observation of airstream behavior. Work should take place not less than 6 in. in from the open end of the work surface. Although engineering improvements in the laminar airstream recovery have been made, the laminar airstream is slow-moving,[k] and care should be exercised in the location, operation, and maintenance of this unit.

Location and performance testing

The LFCB should be located in an area free of ventilation or other air currents, steady or intermittent, which might hamper the laminar airstream by backwash effect.[l] Performance testing of the LFCB by a qualified inspector is recommended at least every 6 months, and servicing or replacement of the unit prefilters every 60 days or less.

Applications

The LFCB is used in hospital, clinical, and home health care pharmacies to provide a sterile field in

[k]Normally *90 LFPM* ±20% or as specified by the user.
[l]"Backwash contamination" is the general term given to the reflux entry of unfiltered room air into the LAFD work zone.

which to conduct aseptic manipulations in the compounding of large-volume parenterals (LVPs) in the form of IV admixtures, hyperalimentation, and small-volume parenterals (SVPs) in the form of piggybacks, syringes, or other parenteral products of less than 250 ml, and for general sterile manipulation of non-hazardous materials.

In industry, the LFCB is used to conduct small batch sterile filling operations, in the general manipulation and isolation of non-hazardous materials, and in quality assurance/quality control (QA/QC) sterility testing.

Laminar Flow BSC

Pharmaceutical and clinical research in the past four decades has led to the development of drug products and other hazardous substances, the manufacture, handling, and compounding of which are considered hazardous to operative personnel in both the short and the long term.[15] In addition to protection of the purity and sterility of the product, it is necessary to consider protection of personnel and the environment. The need to protect both the product and personnel has resulted in the adaptation and use of a variety of laminar flow BSCs in the manufacture and compounding of numerous biological, radioactive, cytotoxic, allergenic, and antibiotic drug products. It is necessary that proper containment and barrier techniques be followed in the preparation, operation, and cleanup of any BSC. Although both are considered to be LAFDs, a clear distinction between the LFCB and BSC should be made in the training of operative personnel. There should be no generalized ''grouping'' of BSCs and LFCBs as ''hoods'' requiring similar use and maintenance patterns; each type of LAFD has airflow patterns, containment characteristics, and operating requirements unique to its design (Fig. 7).

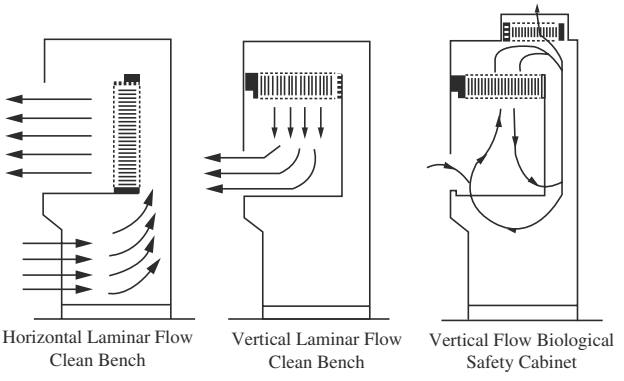

Fig. 7 Airflow patterns in horizontal- and vertical-flow LFCBs and vertical-flow laminar flow BSC. (Courtesy of the Baker Company, Sanford, Maine.)

Operative personnel must understand that the containment and barrier techniques used in the operation of the BSC are significant not only as protection against sudden, overt contamination, but more importantly, as barriers to traces of residual contamination to which constant exposure may present long term health risks.[15,16] Current pharmacy practices and contamination control manipulative techniques have been shown to be inadequate to contain hazardous substances in all phases of compounding and administration, and a pharmacy-wide study and standardized, remedial training programs must by quickly developed and carried out to protect operative personnel.[6,17]

Classification

BSCs are divided into three classes. Class I and Class II are used for low to moderate risk agents, and Class III for high risk agents. The risk level serves as a guide for pharmaceutical manufacturing and pharmacy compounding operations based on a reasonable extrapolation from the personnel risk levels, containment models, and product/personnel protection factors encountered in operations using the biological agents for which this type of equipment was originally designed.

The BSC in pharmacy operations

Although the BSC was not specifically designed for pharmaceutical manufacturing or pharmacy compounding operations, reasonable analogies in the management of hazardous aerosols may be made, justifying use of the BSC in such operations. Such was the case in 1979, following a comprehensive study[5] that determined that pharmacy and nursing personnel were experiencing occupational exposures to antineoplastic agents following their compounding in LFCBs and routine administration. As a prudent response to these findings, recommendations based upon such analogies by segments of the pharmacy community facilitated pharmacy-wide use of Class II BSCs. The Class II design was quickly implemented without attendant feasibility studies, validation and monitoring protocols, or standardized operating, cleaning, and line-clearance procedures, resulting in the installation and operation of this equipment with wide variation in its effectiveness from institution to institution.

Recent studies have indicated the unabated occupational exposure of pharmacy personnel to these substances, causing an inference of the inadequacy of the Class II system in controlling environmental contamination.[6] These findings have again prompted vendors and segments of the pharmacy community to aggressively

promote use of the Class III BSC, or barrier isolator, postulating that a so-called ''closed system'' would unfailingly prevent the transfer of hazardous agents to the environment, thus preventing personnel exposures. Pharmacy-wide promotion of a containment technology is thus being repeated without the benefit of comprehensive engineering studies to both identify the reasons for any ''failure'' of the Class II system, and to provide standardized procedures to properly implement and operate the Class III system. It must be noted that Class II systems are completely effective in the management of particulate and aerosol contaminants in the microbiologic and toxicologic procedures for which they were originally designed. These contaminants include numerous dangerous agents, for which exacting, albeit decades-old manipulative and management techniques remain effective. No applications' failure of the Class II system has yet been reported by these industries, implying that it is improper use of this equipment and/or poor manipulative, product transfer, and cleaning techniques by pharmacy and nursing personnel, rather than any inherent design or applications' flaw in the Class II system, which would account for unabated occupational exposures.[17] At this writing, insufficient evidence appears to exist supporting the remedial, pharmacy-wide retrofit of the Class II system with the Class III BSC, or barrier isolator. The pharmacy community should, rather than prematurely dispose of an effective and functional containment system for a more complex and expensive design, seek to identify and correct the cause(s) of such personnel exposures. A controlled study measuring the nature and magnitude of personnel exposures prior to, and following implementation of carefully designed and executed training exercises, containment procedures, and waste-streaming techniques should be carried out prior to any measures to retrofit these engineering controls.

Following any scientific determination of the inadequacy of the Class II technology in providing the necessary levels of operator and environmental protection, the Class III and barrier isolator systems should, without presumptions, be carefully evaluated for use in this application. Such evaluation should systematically encompass the full range of performance, operational, and maintenance factors, which bear upon gloveboxes or other closed systems, such as lowered productivity because of the cumbersome nature of gloves, half-suits, and reduction of dexterity; difficulty in effective cleaning, resulting in increased residual and cross-contamination of products; inferior product protection characteristics of turbulent Class 100 supply airflow; lowered throughput; increased compounding time and errors; and the manner in which these factors may inhibit the product protection capabilities of the Class III design.

Suitability

Prior to choosing a BSC for any pharmaceutical manufacturing or pharmacy compounding operation, all risks should be assessed by a qualified process engineer, safety officer, or industrial hygienist, ensuring that the equipment meets occupational safety as well as process requirements.

Class I BSC. The Class I BSC is an open containment unit suitable for work involving agents of low to moderate risk to the user and environment, where there is a need for containment but none for product protection or isolation. The Class I BSC provides protection to personnel using the cabinet by means of constant, controlled airflow into the work area and away from the operator, preventing the escape of aerosols through the front opening. It is of limited use in manufacturing and has no reported use in the current practice of pharmacy.

Class II BSC. The Class II BSC (Fig. 9) provides product, personnel, and environmental protection, and is the most common BSC employed in pharmaceutical manufacturing and pharmacy-compounding operations. The Class II BSC has several subclassifications, based upon cabinet ventilation design (Table 1).[18] The Class II BSC (Fig. 8), the most widely used by hospital and home-care pharmacies, features a front access opening with carefully maintained inward airflow for replacement of air exhausted from the cabinet, a HEPA-filtered vertical laminar flow airstream within the entire work area, and HEPA-filtered exhaust air. The vertical laminar flow airstream and front access opening are common to all Class II cabinets, although LAF velocities and patterns, HEPA filter sizes and position, ventilation rates, and cabinet exhaust methods vary considerably in different designs (Fig. 7).

Class III BSC. The Class III BSC (Fig. 9) provides the highest level of personnel, product, and environmental protection from high-risk microbiologic and toxicologic agents. It is usually employed in pharmaceutical manufacturing operations involving weighing, diluting, and high volume aerosol generation of high-risk agents, as well as for handling contaminants that are slowly or rapidly vaporized. This type of laminar flow device affords the maximum containment and product protection barrier, and is used only in cases of extreme exposure hazard or product sensitivity.

The Class III BSC is a gas-tight enclosure, utilizing total air displacement ventilation that protects personnel from exposure to the products contained within the enclosure, the product from contaminants found in the ambient environment, and the environment from release of potentially hazardous substances. The Class

Table 1 BSC cabinet ventilation

(Type) Class II	Cabinet air characteristics	Air recirculated (%)
Type A	30% Vented back into room	70
Type B3	30% Ducted to outdoors	70
Type B1	70% Ducted to outdoors	30
Type B2	100% Ducted to outdoors	0

III BSC is used where absolute containment of hazardous agents is required, and is normally configured with glove ports housing gas-tight, full length latex, neoprene, PVC, urethane, or laminated polymer gloves.[19]

Operating procedure

In addition to cleaning all accessible work zone surfaces, the Class II BSC worksurface tray should be lifted up and back, and the area under the tray should be thoroughly cleaned with the same frequency as the other user-accessible worksurfaces; this is of particular importance in preventing the buildup of potentially harmful product residues. All materials used in cleaning and sanitizing should be treated as toxic waste, and disposed of in accordance with state and local ordinances. Following complete drying of the work surface, operations may begin by staging all working materials for introduction into the aseptic work area. The working materials may then be transferred to the work zone, and aseptic manipulations begun. Work should be performed only on the worksurface, taking care not to handle or store materials on or near the ventilation grilles. First air should be maintained at the critical surfaces of all working materials in the aseptic field; interference with the vertical flow of first air by passing anything over critical orifices or septa in the aseptic field must be prevented. Good aseptic technique is essential to retain the sterility of compounded products[m][14] and surgeon's gloves, mask, laboratory coat (or arm barrier), and hair cover are recommended for all pharmacy operators working in the BSC.[n]

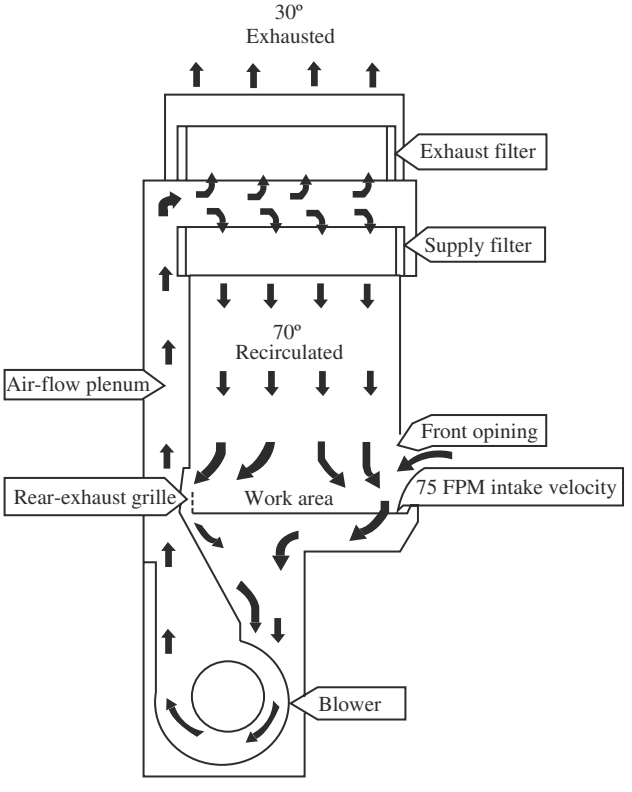

Fig. 8 Airflow patterns of the Class II(a) laminar flow BSC. (Courtesy of the Baker Company, Sanford, Maine.)

Location

The location, operation, and maintenance of the BSC should be carefully planned. Similar to LFCB, the BSC should be located in an area free of steady or intermittent air currents, which might defeat the laminar airstream by a backwash effect.[1] The BSC should be connected to an adequate power source, having the minimum possible current fluctuation. The effects of voltage variation on cabinet performance can be pronounced (Fig. 10A), causing a variation in intake and supply velocities sufficient to result in an unacceptable unit performance (Fig. 10B), thereby compromising personnel and product protection design features

[m]The importance of good aseptic technique is occasionally deemphasized by personnel compounding cytotoxic and antibiotic agents in the BSC, based on the belief that these substances are themselves toxic or germicidal to any microbiologic contaminants. It should be noted that numerous microbiologic organisms remain viable and replicate in cytotoxic compounds, and that no antibiotic has a universal antimicrobial action. Proper aseptic technique is therefore mandated in all operations carried out in the LAF environment.

[n]These are basic barriers, proven to aid in the retention of gross endogenous contamination at close working proximity to the critical field, but as importantly, these barriers protect the operator from direct contact with potentially hazardous substances, and should be used in accordance with established guidelines (see"Regulatory Issues").

(Table 2). Performance testing of the BSC by a qualified inspector is recommended at least every 6 months and always after relocation of the unit. Appropriate surface decontamination is recommended prior to moving or refiltering the unit.[o]

Applications

The BSC is used in hospital, clinical, and home health care pharmacies to provide a sterile field in which to conduct aseptic manipulations in the compounding of LVPs, SVPs, antineoplastics, antibiotics, antivirals, and vaccines, the direct exposure to which may be hazardous to the operator and the environment. Most hospital and clinical pharmacy operations are currently carried out in a Class II(B3) BSC, which is vented to the outside by a dedicated, non-recirculating HVAC exhaust, directly connected to the BSC.[p] Although direct connection to an HVAC exhaust is not required for proper Operation of the Class II(a) BSC in the containment of biological aerosols, such direct connection is recommended in all pharmaceutical manufacturing or pharmacy-compounding applications. The Class I BSC is almost never used in pharmacy compounding operations, and the Class III BSC technology is currently being evaluated for use in pharmacy compounding following comprehensive evaluation of any Class II FA, and outcomes of feasibility studies of the Class III system in such operations.

In industry, the BSC is used to conduct small batch sterile-fill operations, manipulation (weighing and pouring), isolation of hazardous materials, and in QA/QC testing applications. All classes of BSC are encountered in pharmaceutical manufacturing operations for a wide variety of processing applications.

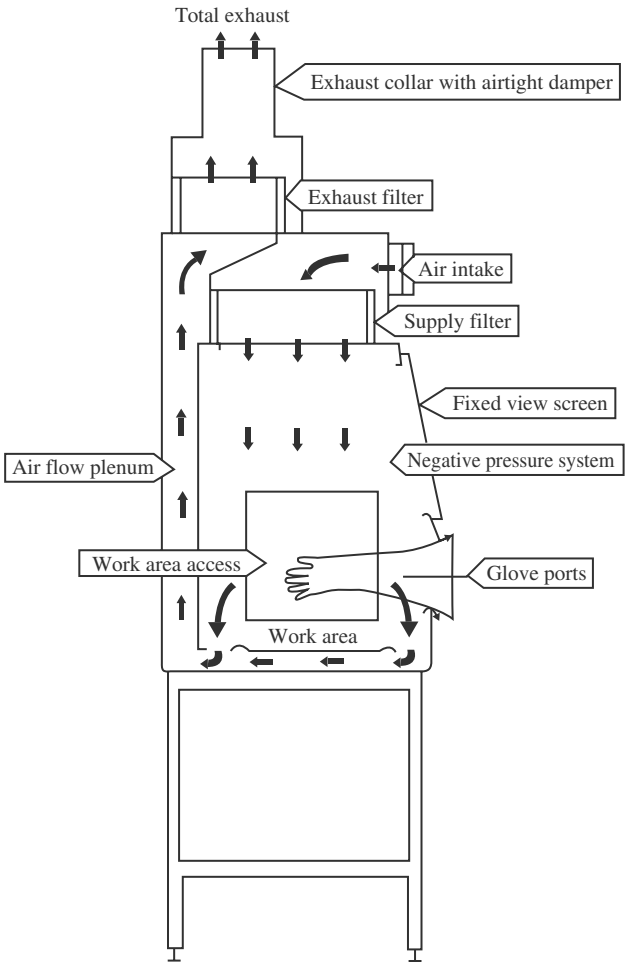

Fig. 9 Airflow patterns of the Class III laminar flow BSC. (Courtesy of the Baker Company, Sanford, Maine.)

Terminal HEPA Filtration Module

The terminal HEPA filtration module (TFM) is a self-contained HEPA filter and plenum unit (Fig. 11), which may be used to provide laminar or conventional airflow[q] to a clean space, or may be dedicated as a LAF workstation.[20] The TFM is available with a 10 in. (optional 12 inch) collar for connection by a circular supply duct to a central air handling system (Fig. 5A) or as a free-standing, fully powered unit containing a motor and blower. It is normally installed in a

[o]Although microbiologic decontamination of the BSC is not required, except as used in the manipulation of microbiologic agents, proper containment technique should be employed when refiltering or servicing these units.

[p]Current guidelines may recommend use of the Class 11 Type B2 (total exhaust) BSC in certain manufacturing and compounding applications, but proper operation of this unit is difficult to maintain because of non-interlocked operation of separate BSC supply and in-house exhaust air-handling systems. B2s in the configurations currently available frequently develop a supply–exhaust flow imbalance, which may readily compromise product or personnel protection. Until a reliable system for direct interlock of the supply and exhaust air handlers is available that synchronizes the operation of the components, facilitating changes in operation by either air handler being proportionately matched by the other, use of the Class-11 Type B2 BSC is not recommended for pharmaceutical manufacturing and pharmacy compounding applications as a containment LAFD.

[q]Laminar-airflow room is defined as a cleanroom in which filtered air entering the room makes a single pass through the work area in a parallel-flow pattern, with a minimum of turbulent flow areas. Laminar-flow rooms must have HEPA filter coverage of at least 80% of the ceiling (as vertical flow), or one wall (as horizontal flow), producing a uniform and parallel airflow (net filter medium face area versus gross area = 0.80)

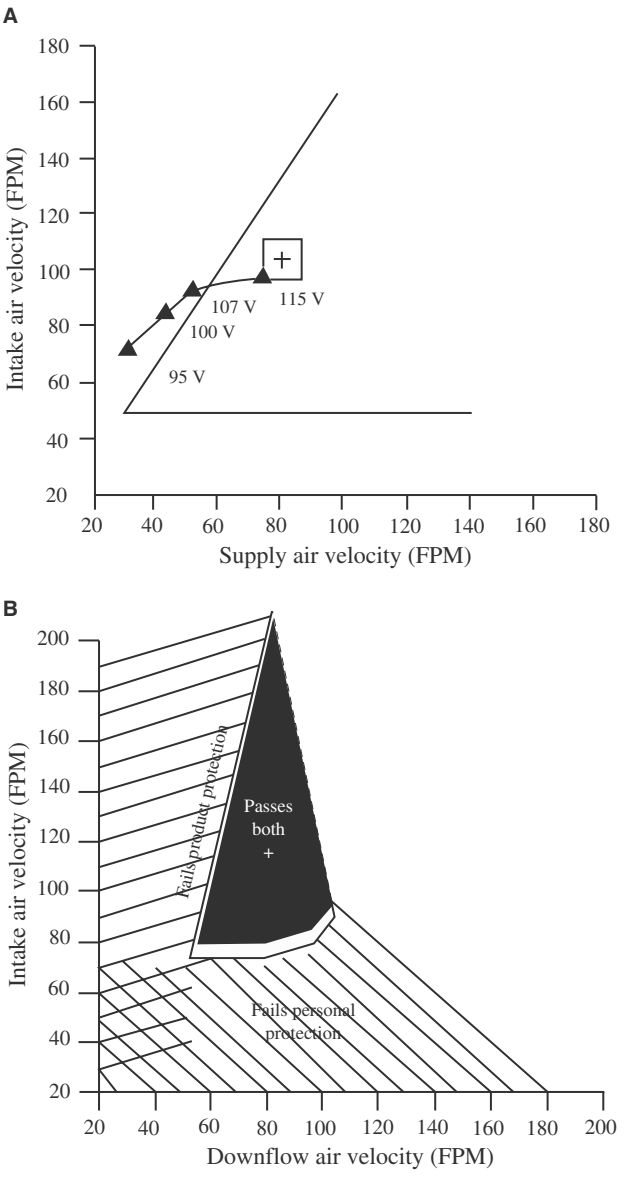

Fig. 10 (A) Effects of voltage variation on cabinet performance; National Sanitary Foundation (NSF) range, +: Normal setpoint; —: Performance envelope; ▲—▲ Airflow balance. (B) Performance envelopes for Class II BSCs determined by conducting a series of microbiological aerosol tests at a variety of airflow settings. (Courtesy of the Baker Company, Sanford, Maine.)

''T-bar'' grid ceiling system, suspended by seismic restraints from the architectural ceiling or building supports (Fig. 5B), which constitutes the inner clean space ceiling. Permanently installed or modular air handling systems are available that provide treatment (heating, air conditioning, dehumidification, etc.) of recirculated and make-up air to the clean space. Self-powered TFMs do not provide supply air treatment, and care should be taken in installing this type of unit because of high noise level and heat output factors,

Table 2 Protection provided by various BSC designs

Design	Personnel	Product	Environmental
Clean benches		•	
Class I	•		•
Class II			
Type A	•	•	•
Type B1	•	•	•
Type B1	•	•	•
Type B1	•	•	•
Class III	•	f(design)[a]	•

[a]Characteristic a function of design.

which may fatigue operative personnel or adversely affect temperature-sensitive stored drug products.

The TFM may also be used to provide a Class 1–100 work surface of almost any size, and may be installed in the ceiling (vertical downflow), or in a wall (horizontal flow). Using this design, shrouded laminar flow Class 1–100 ''first air'' is provided directly to the critical worksurface in the same quantity and quality as by a LFCB. Outflow from the critical worksurface is used to treat the general space, in combination with additional room ''buffer'' HEPA filtration, thus providing both the highly-controlled critical worksurface, and the less-controlled general room area. Several inexpensive concept designs are available to develop reliable worksurfaces and buffer areas, which support both pharmacy and pharmaceutical manufacturing operations.[20]

In-duct HEPA filtration

In this type of filtration the HEPA filter is placed within the supply duct system, providing Class 100

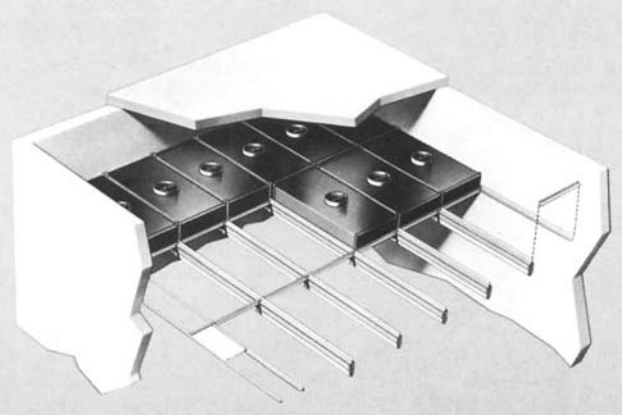

Fig. 11 Self-contained terminal HEPA filtration modules installed in a T-bar suspended plenum ceiling in a laminar-flow application. (Courtesy of American Air Filter, Inc., Louisville, Kentucky.)

air from the point immediately downstream of the filter to the supply diffusers within the general clean space. This arrangement is used where a comparatively small volume of supply air is required for the clean space operation, when filter handling and disposal is critical (requiring remote ''bag in/out'' containment isolation or other special handling considerations), or where space limitations prevent the installation of TFMs. Induct HEPA filtration provides conventional airflow and is recommended as secondary or ''buffer'' filtration in clean spaces where critical work zones are treated using an LAFD. In-duct HEPA filtration is not recommended for LAF applications to provide required Class 1–100 conditions at critical worksurfaces, where uninterrupted ''first air'' is necessary to achieve the highest levels of contamination control.

The plenum ceiling

The plenum ceiling is an arrangement of ductless terminal HEPA filter modules which, in a manner similar to TFMs, are installed in a ''T-bar'' grid system. These filter modules are not connected directly to an air handling system by means of ducts. The uniform flowofair through all modules results rather from a pressurized common space or ''plenum'' immediately above the entire T-bar ceiling assembly. This plenum is supplied directly by an air handler, eliminating the need for extensive ductwork. The plenum ceiling is normally used in overhead space-limited LAF applications.

The cleanroom

The cleanroom is a dedicated clean space with exacting as-built, at-rest, and operational specifications of airborne and surface cleanliness, temperature, relative humidity, and lighting and noise levels, in which specific critical operations are carried out.[11] The cleanroom may be designed to provide vertical or horizontal LAF throughout the entire room for large-scale operations requiring extended critical work zones (sterile conveyors, sterile fill operations, etc.), or may be designed as a conventionally-supplied, controlled secondary or ''buffer'' area, housing one or more smaller LAFD for aseptic processing steps requiring comparatively limited critical work zones.

The cleanroom is normally constructed in an existing building or structure as a core unit, surrounded by supporting access and staging anterooms, service chases, and machine rooms necessary to support the aseptic operation, supply working materials, and remove finished products and waste materials without cross-contamination or interference with the critical work stream.

TESTING AND CERTIFICATION OF LAF SYSTEMS

Thorough, periodic testing of LAF equipment is necessary to optimize performance and demonstrate compliance with established operating procedures and industry standards.

Certification

The term ''certification'' is widely used in connection with this type of testing. Certification may, however, only be provided by a registered testing or metrology laboratory, or other organization that derives its certification authority directly from a legitimate regulatory agency (FDA, EPA, AIHA, etc.) and which is subject to review. For a test procedure to qualify as a performance certification, the procedure must be performed and documented in accordance with the current good laboratory practices.[21] All on-site testing of this nature constitutes a laboratory field certification of performance, with each test report accession-numbered in the laboratory test notebook as an actual laboratory test procedure. If the vendor of this service does not have such regulatory oversight, the buyer must qualify the vendors adequacy of experience, equipment, and efficacy of all test procedures to be performed,[22] regardless of the vendor's professional affiliations or memberships.

Vendor Qualification

Although large manufacturers often have in-house personnel and facilities available to carry out LAF equipment testing, this task is frequently performed byan outside testing contractor, whose procedures and findings are relied upon without question by the buyer. Because the pharmaceutical manufacturer and pharmacy practitioner bear the ultimate responsibility to regulatory groups for ensuring compliance with all testing standards and requirements, it is essential that they select a qualified testing contractor. The buyer should interview the prospective contractor and reviewall aspects of the tester's training and experience, the test procedures and equipment to be used, equipment calibration and traceability, and the proposed documentation.[22] The prospective contractor should be prepared to provide both company and individual resumes of qualifications, including at least three references of clients for whomthe contractor has recently provided similar services.[20]

Test Equipment Calibration and Traceability

The LAF equipment tester should have the equipment necessary to carry out the required challenge of the LAF system.[20] This equipment should be in good working order and calibrated to a National Institute of Standards and Testing (NIST)-traceable[r] standard at least annually, or more often as indicated by the manufacturer's specifications or equipment performance.[23] NIST-traceable calibration ensures the uniformity, accuracy, and serviceability of all test equipment as well as proper maintenance and care by the user. The NIST-traceability of equipment calibration is substantiated by a detailed calibration certification letter, issued by the calibrating authority for each piece of equipment.

Certification Standards

The primary standard for testing LAF equipment is a standard operating procedure (SOP), unique to the equipment or system. This SOP is normally established by the using organization to define the calibration and testing requirements of a specific LAF system, and should include the scope, intent, and frequency of testing; the equipment to be used in conducting the test; test equipment calibration; test methods and performance criteria; documentation of results; and corrective actions and acceptance. The SOP should cite the applicable references and industry standards from which it has been derived. In the absence of an organizational SOP, LAF equipment should be tested in accordance with industry standards applicable to the specific LAF application or area of operation (Table 3). In this case, regulatory groups will defer to these standards for proof of proper LAF system function and serviceability.

Test Reports

A comprehensive report should be issued upon completion of the test procedures, which should include all values measured for compliance, a listing of all test equipment, calculations, conversions, and all appropriate statistical justification along with comments pertaining to system function and operation. A dated test-completion or certification sticker should be affixed to the LAF unit referring any examining authority to the completed test report. All reports should include floor plans or maps of the clean space, which identify sample locations, probe heights, unusual performance characteristics, system adjustments, and repairs.

[r]Formerly the National Bureau of Standards (NBS), Washington, D.C.

Test Procedures

Air velocity

Measurement of air velocity and laminar profile quality is the first step in LAF system testing. Using the appropriate instrument and measurement technique,[4,11,18] the velocity of the laminar airstream for all LAFDs, and conventional buffer supply airflow volume for all controlled areas should be measured and adjusted to conform with pertinent SOPs or industry standards, consistent with the system manufacturers specifications and limitations.[20]

HEPA filter performance

Following verification of the proper velocities, the HEPA filter should be aerosol-challenged in accordance with industry standards.[4,11,18] Because this challenge is based upon the effectiveness of the filter in retaining aerosols, the upstream concentration of test aerosol should be verified before commencing this test and should not be assumed to be adequate, regardless of the circumstances.

Particle counting

Only through discrete particle counting can air cleanliness be verified, and the cleanliness class of the sampled environment established.[4] Periodic in-process monitoring of workstations, buffer rooms, anterooms, production areas, and any other area about which a definitive air cleanliness statement is made or reasonably assumed, should be carried out in accordance with SOPs or industry standards.[4,11] A discrete particle counter (DPC) with an adequate sampling rate, calibration features, and dynamic range should be used for sample acquisition, based on the specified air cleanliness level.[4,17]

Noise levels

Noise in excess of recommended levels within the LAF environment or clean space may cause operator discomfort and premature fatigue, and may indicate HEPA filter failure, or a malfunction of the LAFD or clean space air handling unit.[20,24] Cabinet pressure integrity and vibration analysis are recommended for all biological safety cabinets.

Table 3 Regulations and guidelines pertaining to LAF systems[a,b]

	Guidelines						
	ASHP (Proposed)	EN ISO 14644-1 TO 6	IES-RP-CC-001-86 (Testing HEPA Filters)	IES-RP-CC-006-84-T (Testing cleanrooms)	IES-RP-CC-018.2 (Cleanroom Housekeeping operating and monitoring)	NSF 49	USP 1074 (Proposed)
Pharmacy (IV/TPN)	•						
Pharmacy (CYTA)	•					•	
Home health care (IV/TPN)			•	•	•		•
Home health care (CYTA)			•	•	•	•	•
Nursing home (IV/TPN)							
Nuclear pharmacy	•	•				•	
Pharmaceutical manufacturing		•	•	•	•		
Nuclear pharmaceutical manufacturing		•	•	•	•	•	
Pharmaceutical repackaging		•	•	•	•	•	

	Regulations									
	FED. STD. 209c	CGMP-CFR	CGLP-CFR	JCAHO	Regional Pharmacy Practice Acts	Regional Department of Public Health	OSHA 8.1.1	NRC. FEDERAL	NRC. STATE	Municipal Codes
Pharmacy (IV/TPN)	•			•	•	•				•
Pharmacy (CYTA)				•	•	•	•			•
Home health care (IV/TPN)				•	•	•				•
Home health care (CYTA)				•	•	•	•			•
Nursing home (IV/TPN)	•			•	•	•	•			
Nuclear pharmacy	•			•	•	•		•	•	•
Pharmaceutical manufacturing	•	•	•			•				•
Nuclear pharmaceutical manufacturing	•	•	•			•		•	•	•
Pharmaceutical repackaging	•	•				•		•	•	•

[a]Courtesy Lab Safety Corp., Chicago.
[b]Reactor products on site: non-agreement states.
TPN: Total parenteral nutrition; CYTA; Cytotoxic agent; CGMP: Current Good Manufacturing Practices; CGLP: Current Good Laboratory Practices; CFR: Code of Federal Regulations; NRC: Nuclear Regulatory Commission.

Visible and ultraviolet light levels

Visible light levels should be monitored for operator comfort and total visibility of the worksurface.[20,22] Ultraviolet germicidal light should be measured for effectiveness in all LAFDs having this feature.[18]

LAMINAR FLOW CLEAN SPACE PROJECT DEVELOPMENT

As an engineering control, the demands normally placed upon an LAF system should not exceed the system's ability to provide a sterile, aerosol-free work area in which to conduct the desired aseptic operations with a high degree of confidence. Neither should a facility be overbuilt; unnecessary complication of clean space operation to achieve control levels that provide no demonstrable improvement in the process or finished product is counterproductive and an expensive waste of resources. To develop a system that is adequate for the aseptic processing task at minimum expense, a definitive, phased approach to design and implementation of the LAF system should be taken, regardless of the size or complexity of the system. The method described below ensures that any project, from a simple hood installation to a complex process cleanroom, will have the most comprehensive development and planning, thus maximizing the probability of a successful outcome.

Conceptualization

As the initial step, a thorough and complete conceptualization of the process, and the steps that will be taken to achieve the desired results should be defined in a protocol. This document is to be used as the basis of communication with design and mechanical engineers in developing specifications for an effective and workable design, to be constructed, validated, and operated within existing cost constraints.

Protocol and Project Management

The protocol should be developed under the supervision of a project manager, selected on the basis of experience and understanding of the product, existing and intended markets, regulatory issues, the intended aseptic process, the engineering controls normally required for such a process, and the design, construction, validation, operational, and maintenance methods to be employed.[25] The manager represents the owners' interests, and acts as liaison in all dealings with outside vendors and contractors. He or she should seek direct input from key personnel and representatives of all groups having direct involvement with the planned clean space[26] in meetings and discussions, as the concept evolves, with appropriate sign-off by the participants on the finished protocol. This method prevents after-the-fact, unforseen demands upon system operation, or dissatisfaction with system performance by essential personnel. Conceptualization is based upon the following considerations:

- Space constraints vs. process requirements.
- Product or process quality statements.
- Output capacity and growth expectations.
- Industry standards and regulatory issues (Table 3).
- Cleanliness class(es) required. Identification of critical work zones and areas requiring LAF, rather than mere characterization of these areas as Class 100.
- Work streaming. Inclusion of the necessary QA/QC steps in the overall process.
- Necessary process equipment (Table 4).
- Identification of all process steps requiring an LAF environment to facilitate the desired cleanliness class. What facility and equipment performance alert and action limits are necessary, and how are these to be monitored?
- Process equipment portability and flexibility requirements. Will the process(es) be expanded or modified at some time in the future? What equipment must be permanently installed and ''hard wired'' within the clean space?
- Process equipment service and maintenance requirements.
- Number of personnel required.
- Personnel disciplines. What type and arrangement of anterooms are required for scrubbing, gowning, and storage of barrier materials?
- Process materials staging and waste management.
- Health and safety requirements.
- Facility housekeeping and maintenance procedures.
- Facility validation, testing, and recertification.
- Documentation, i.e., the necessary process records, logs, labels, etc., and how, when, and where these documents are produced and used.

Regulatory Issues

Operation of LAF systems in the course of pharmaceutical manufacturing and pharmacy compounding operations is ultimately scrutinized by several regulatory and quasi-regulatory groups responsible for the control and oversight of these industries. Because these regulatory groups require, almost without exception, operation of manufacturing or compounding systems

Table 4 Equipment features and performance[a,b,c]

	Cleanliness Class-Fed Std 209°C					Applications				
	Class 10	Class 100	Class 1,000	Class 1000,000	Pharmacy IV corresponding	TPN (HA) compounding	CYTA compounding	Product protection	Personal protection	Technology, screening
LFCB	2	1			1	1	3	1		
LFBSC Class I									1	1
LFBSC Class IIA	2	1			1	1	1	1	1	1
LFBSC Class IIB		1	1[d]				2	2	1	1
LFBSC 3 glovebox	2	1						1	1	1
In-duct HEPA filter			2	1	4	4		4		
Terminal HEPA filter module (TFM)	2	2	1		4	4		4		
Filter plenum ceiling	2	1					2			

	Applications					Airflow and Equipment Configuration						
	Microbiology	Sterility testing	Work station	Cleanroom	Leminar flow	Conventional flow	First air work station	Terminal filtration	In-duct filtration	Ventable to room	Direct connection	Thimble unit
LFCB		1	1		1		1			1		
LFBSC Class I	3		1						1		1	
LFBSC Class IIA	1	1	1		1		1			1	1	1
LFBSC Class IIB	1		1		1		2				1	
LFBSC 3 glovebox	1		1		2	1			1		1	
In-duct HEPA filter		4		1		1			1	1		
Terminal HEPA filter module (TFM)		4	2	1	2	1	2	1		1		
Filter plenum ceiling			1	1		2	1					

[a]See also Appendix B.
[b]1: Primary engineering control; 2: With optimization or modification; 3: Pbsolete application; 4: Secondary or ''buffer'' control.
[c]Courtesy Lab Safety Corp., Chicago.
Early designs.

in accordance with "current industry standards," the distinction between regulations and guidelines has become unclear. Guidelines, as a reflection of the most current application of any technology, often take on the weight of regulations as determinants of industry standards. As such, operation in accordance with specific industry guidelines is often required to demonstrate compliance with non-specific or generalized regulations—i.e., current good manufacturing practices (cGMPs) or Joint Commission on Accreditation of Health Care Organizations (JCAHO) Standards. Table 3, although not intended to be all inclusive, provides a list of regulations and guidelines that are pertinent to the operation of LAF systems in several different pharmaceutical manufacturing and pharmacy-compounding applications.

Design

Based upon the protocol, the facility and process design is the next step. Whether a simple hood installation to an existing space, an upgrade retrofit of an existing space, or construction of a totally new space, the design responsibility has to be assigned and a designer chosen. The designer's obligations are considerable and should be thoroughly understood by the individual or firm retained to provide the clean space design.[20]

Construction

Following completion of the design, the building contractor is chosen. The construction phase is normally carried out with the input and assistance of the designer in conducting vendor audits for the selection of contractors with sufficient experience and facilities to complete the building tasks efficiently. Materials and workmanship audits should be carried out periodically by the project manager and the designer.

Validation and certification

Validation is described as proof that the system performs as stated. As an engineering control, the LAF system must demonstrably support the intended aseptic or controlled process. Validation of the aseptic manufacturing process and the LAF systems that support terminal sterilization in pharmaceutical manufacturing applications should be carried out in accordance with industry standards.[1,27–31] Such validation should be accomplished in three phases, consisting of installation qualification (IQ), operational qualification (OQ), and process qualification (PQ), with full and detailed documentation of all activities and outcomes.[20]

Cleanroom Construction and Validation: A Low-Cost Approach

The following is a consolidation of steps leading to the construction and operation of a low-cost clean space of the type required for small- and intermediate-size drug repackagers, home health care pharmacies, and small pharmaceutical manufacturers.

Cleanroom design

The cleanroom should be conceptualized, designed, constructed, validated, operated, and maintained in a manner that supports the aseptic process. A construction plan, including reasonable time frames for the acquisition of labor and materials should be developed, followed, and updated. All work and materials should comply with local building codes and safety ordinances.

HEPA Filtration

Computation of the air change rate (AC) necessary for the desired cleanliness class is the initial step in determining the ceiling module filter density required for the clean space, and should be calculated accurately, with sufficient redundancy to assure the required airflow and resulting cleanliness levels.[20,32,33]

Air Handling

Air handling requirements should be calculated, and air handler type and capacity should be matched to the AC rate, heating, cooling, and dehumidification requirements of the facility,[34] as calculated from the reflected ceiling plan. At almost any intended level of processing, low cost, "turn-key" air handling systems are available with a minimum of lead time. They are easily installed, operated, and maintained. The installation of a modular air handler of this type provides conditioned air, allowing operation of the core and anteroom areas as an independent facility, without dependence upon a central building air handling apparatus for process control. This type of low-cost, modular air handler, in a single-or multiple-unit installation, facilitates complete treatment and conditioning of the supply air to be provided in quantities adequate to maintain the most stringent air cleanliness classes for workstations and general room air, as well as temperature and relative humidity at recommended core and anteroom internal operating pressures. In addition, several manufacturers of this type of unit have experienced, on-staff mechanical engineers qualified to assist the buyer in determining the exact air treatment and handling requirements for a specific

application at no additional charge. Qualification of the knowledge and experience of all individuals involved in the conceptualization and design phases is necessary, and references should be obtained and checked by the buyer.

Differential Pressurization

The cleanroom facility should be carefully designed to control the ingress of contaminants, and be positively pressurized to the surrounding area in accordance with industry standards. The core and anterooms are positively pressurized by varying the amount of incoming ''make-up'' air.[20] In the case of ''soft wall'' clean space facilities, such pressurization (potential outflow) is not possible, and a sufficient amount of constant, active outflow (kinetic outflow) should occur to prevent ingress of contaminants.

Lighting and Electrical

Electrical service should be provided in the normal fashion in accordance with local building and electrical codes. Clean space service requires no special treatment, and should provide a 25–50 A surplus over worst-case processing demands, to allow for additional electrical equipment and source power fluctuations. Fixture types, sealable outlets, and hard-wiring of processing equipment should be selected and carried out in accordance with industry standards and electrical codes.[20]

Walls and Windows

Walls should be typical 5/8-in. drywall over metal studs at 16-in. centers, and may be insulated or not as deemed appropriate. The inner clean space wall should be finished with enameled panels (available at most building supply outlets) that are butted and sealed with RTV silicone, to provide gas-tight seams between the wall panel, ceiling T-bar, and floor base junctions. (Clear RTV silicone is recommended, neatly and sparingly ''mopped in,'' with all residues cleared away while still wet; this method creates an invisible, water-tight seal facilitating long term serviceability and ease of cleaning.) The outer walls should be painted with cleanable epoxy enamel or suitably covered, and a long, narrow observation window (recommended aspect 1 : 8–10, without ledge), or a series of double-pane, ledgeless windows should be installed and finished to provide complete observation of the operational process by prospective clients, supervisory personnel, and others.

Floor

The anteroom and core flooring should be an attractive, highly durable, one-piece vinyl or other suitable floor material, providing a minimum of seams. This flooring should ideally radius in a cove at the wall base and continue upward to a height of 8 in. to 1 ft above the floor. At that point it should be capped with a suitable beading, sealed by RTV silicone, neatly ''mopped in,'' and allowed to dry. No drain or other floor opening should be permitted in the core; a small, single drain may be permitted in the anteroom in the event carts or other materials are to be cleaned and staged in that area. The floor should be routinely cleaned by a wet-vac recovery of a spread floor cleaning solution (with hose and head located within the clean space, with pass-through connection to a vacuum source located and vented outside the clean space).

Ceiling

The anteroom and core ceilings should be of typical 1.5 in. T-Bar construction, with seismic restraints adequate to support the HEPA terminals, lighting fixtures, and ceiling panels. The panels may be obtained from clean space suppliers in the form of finished ''cleanroom'' ceiling panels, or by reduction of additional enameled wall panels to 2×4 ft (nominal) panels, affixed by permanent adhesive to standard, plain face (non-textured), fire-rated, 0.5 inches. commercial ceiling panels, which are easily installed and RTV silicone-sealed inplace. This allows installation of a permanent, gas-tight ceiling, washable like the walls and floor, and attractive in that it provides visual continuity of the wall material.

Doors and Pass-Throughs

Doors and pass-throughs should facilitate easy, integral entry and exit of personnel and working materials.[20]

Construction

Construction of the facility should be based upon the completed design and incorporate normal construction methods, tools, and techniques. Special preparation of components is necessary, including a general cleaning and protection of components and equipment from potential sources of contamination during the construction phase. The working materials should be protected from atmospheric dust, sawdust, grease, aerosols of oil, and other residues, which may be

encountered during construction, using ''clean construction'' methods.[20]

Validation

Following completion of all testing and certification of the facility, documentation should be developed and retained, which may be used as proof of performance in accordance with the protocol in the as-built configuration.[4,11] Periodic retesting and monitoring at specified intervals in the at-rest and operational modes[4,11] should be carried out to maintain operation of the facility in accordance with SOPs or industry standards.

Operation

Operation of the facility in accordance with validation conditions, through the use of appropriate SOPs and industry standard quality management parameters[28] should be commenced following validation, incorporating the necessary alert and action limits, monitoring procedures and maintenance steps to be carried out andincluded in the production cycle documentation. All microbiologic monitoring of the clean space anterooms, core, worksurfaces and personnel barriers should be carried out in a systematic manner by experienced personnel.[35]

Personnel Selection and Validation

Because the effectiveness of operative personnel is potentially the greatest variable in any controlled process, a selection, training, examination, and grading system should assure the suitability of candidates, the adequacy of training, and the ultimate uniformity and consistency of clean space operating procedures.[12,14,15,36]

Maintenance

Clean space maintenance SOPs and documentation should be developed and followed in strict accordance with industry standards[13] to ensure the consistency of operation in accordance with validation conditions.

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