ばならない。最初から無菌的プロセッシングをシミュレートする場合は、工程全体を管理することが、製品を保護するのに十分であることを示すべきである。これらのシミュレーションには、すべての製品操作、追加事項、製品が接触する表面が環境に露出する手順を組み込むべきである。シミュレーションは、最悪の条件、すなわち、開放作業に要する最大時間、および作業に従事するであろう最大数の人員を含むべきである。しかし、無菌的プロセッシングをシミュレートする場合は、製造作業中の操作を充分代表できるならば、すべての製造に要する時間をそのまま真似る必要はない。

無菌的プロセッシングをシミュレートする場合、製品の保管や他の製造エリアへの輸送をそのなかに組み込むこともまた重要である。たとえば、指定期間保管された原材料（バルク）の完全性は保証されなければならない。バルクを保存するタンクやその他の容器の輸送は、培地充填試験の一部として、シミュレーショトされるべきである。培地充填の模擬シミュレーションに関する、さらに多くの指針に関してはセクション IX. A を参照していただきたい。調製工程の無菌的プロセッシングのシミュレーションは、少なくとも年間２度行われるべきである。

B. 無菌的細胞プロセッシング

細胞治療に用いる細胞の作製は、作業全般が無菌的プロセッシングを必要とするものの代表的な例である。できるかぎり、治療用細胞の作製はクローズド・システムをもちいて行なうべきである。臨床用ヒト細胞の作製には、最終製品を製造する場合でも、各製造工程に要する時間は短いものでなければならない。臨床用ヒト細胞の場合、最終製品の無菌試験結果が明らかになる前に、患者に投与することはやむを得ない。臨床用ヒト細胞製品が投与される前に、最終の無菌試験結果が明らかではない状況において、追加のコントロール、及び検査を考慮しなければならない。たとえば、無菌試験は、製造の中間の段階、特に投与前の、製品の最終操作のすぐ後で行なうことができる。ほかの検査方法、たとえば顕微鏡検査、グラム染色法、及び、エンドトキシンテストのような微生物学的汚染を示すかもしれないものは、製品の出荷前に行われるべきである。

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用語解説

Air lock （エアーロック）

インターロック機能のついたドアを備えた小さな部屋であり、隣接した部屋（一般に異なる空気清浄度基準を備えた）間の室圧を維持するために設ける。無菌プロセスのエアーロックの目的は、下位の管理エリアからの微粒子や微生物汚染の進入を防ぐことである。

Alert Limit（警戒限界）

確立している微生物または微粒子の警戒レベルであり、正常な操作状態からの潜在的なずれに対して早期の警告を与えるものである。また、警戒限界は、潜在的な問題の適切な調査と追跡を開始するきっかけとなるものである。警戒限界は、常にアクション限界より低い。

Action Limit（アクション限界）

確立している微生物または微粒子のアクションレベルであり、そのレベルを超えた場合に、適切な調査とその調査に基づいた矯正アクションを起こすべきレベルである。

Action Process Facility（無菌操作設備）

クリーン・ルームの中で微生物や微粒子の汚染をコントロールするために、空気の供給、物質および設備が管理されているおり、その様なクリーン・ルームのある建物である。

Aseptic Processing Room（無菌生産室）

１つ以上の無菌操作またはプロセスが実行される部屋。

Asepsis（無菌）

無菌の作業エリアを用いること、暴露された無菌製品の微生物による汚染を防ぐ方法で行うことにより達成した管理状態。

Bioburden（生物学的負荷）

滅菌前の、特定アイテムと関連した微生物の総数。

Barrier（バリア）

周囲のエリアから部分的に分離することにより、無菌の製造ゾーンを守ることのできる物理的な仕切り。

Biological Indicator（BI）（生物学的インジケーター）

–適切な培地（たとえば、溶液、容器・栓）上に植え付けられた微生物の個体数であり、物理的または化学的なプロセスの滅菌サイクルの有効性を決めるために、適切な殺菌装置の負荷の場所に置かれた微生物の個体数である。曝露試験用微生物は所与のプロセスに対する抵抗力に基づいて選ばれ

る。入って来るロットのD値および微生物の総数は、BI の質を決める。

Clean Area（清浄区域）

微粒子や微生物の清浄度を規定した区域（たとえば、クラス 100。クラス 10,000。クラス 100,000）

Cleanroom（クリーン・ルーム）

薬に対する微粒子や微生物の汚染を防ぐように、設計、維持、管理された部屋。そのような部屋がクリーン・ルームに割り当てられており、その部屋は、再現性をもって、適切な空気清浄度区分を満たす。

Clean Zone-Clean Area を参照。

Component（成分）

薬の製造に使用されるあらゆる原料であり、最終製品である薬に現れないものも含む。

Colony Forming Unit (CFU)

微生物の用語であり、微生物発育培地へ１つの（あるいはそれ以上の）微生物を接種後に、肉眼で見える一つのコロニー集落を形成することを示す。１つのコロニーを形成したユニットを１CFU と表現する。

Critical area（重要区域）

無菌材料の無菌性を維持するように設計された区域。滅菌された製品や容器・栓あるいは設備が、重要区域で露出されることがある。

Critical surfaces（重要な表面）

滅菌された製品あるいは容器・栓に接触するかも知れない、或いは直接影響を与えるかも知れない表面。重要な表面は、製造作業の開始前に、滅菌される。そして、無菌性は、操作中維持される。

Decontamination（汚染除去）

胞子を殺す化学物質の使用によって、生育できる生物学的負荷、バイオバーデン（生物学的負荷）を除去する操作。

Depyrogenation（発熱性物質除去）

発熱性物質（たとえば、菌体内毒素）の破壊または取り除くのに用いられる操作。

D value（D値）

所定の温度にさらされて、特定の微生物の個体数が１ log または 90%減少する時間、単位分。

Dynamic（動的）

通常の生産を行った時の、清浄区分に関連した条件。

Endotoxin（菌体内毒素）

バクテリアの細胞壁の中にある発熱性のある生成物（たとえば、リポ多糖類）。菌体内毒素は、注射を受けた患者の中に、発熱や時には死に至る様々な反応を引き起こすことがある。

Gowning Qualification（ガウニング適性）

個人が無菌的な方法で完全な無菌衣をきることが出来ることを、最初および定期的に、確立したプログラム。

HEPA filter（高性能エアーフィルター）

最小で0.3ミクロンの粒子で99.97%の捕集効率をもった高性能エアーフィルター。

HVAC–加熱、換気と冷房（Heating, Ventilation, Air Conditioning)。

Intervention(介在、介入)

重要なゾーンで生じる無菌操作または活動。

Isolator

HEPAまたはULPAで濾過された空気を供給して、汚染除去されたユニットであり、外部環境（たとえば、周囲のクリーン・ルームの空気や技術員）からそのユニット内部を徹底して、連続的に隔離するものである。

Laminarity（層流性）

微粒子を重要な操作または検査エリアから一様に吹き流すのに十分な速度の一方向の気流。

Operator（技術員）

ラインのセット・アップや充填、メンテナンスを含めた無菌操作に関与するすべての人、あるいは無菌ラインの活動に関連するその他の人。

Overkill sterilization process（オーバーキル滅菌工程）

少なくとも1分のD値を持った微生物を少なくとも12 logの菌数減少おこなうのに十分な工程。

Pyrogen（発熱性物質）

患者の中の発熱性の反応を引き起こす物質。

Sterilizing grade filter（滅菌グレードフィルター）

適切にバリデートされている時に、流体から全ての微生物を除去し、無菌の流れを作り出すフィルター。

Terminal sterilization（最終滅菌）

あらかじめきめられた、通常 10^6（すなわち、100 万のうち 1 個以上が非滅菌である可能性）未満である滅菌性の保証水準を成し遂げるために、密封された最終製品に対して提供される滅菌処理。

ULPA filter（ULPA フィルター）

最小で 0.3 ミクロン粒子で 99.999%の捕集効率をもったフィルター。

Validation（バリデーション）

文書化された証拠を確立することであり、その証拠は、特定のプロセスが前もって定義した仕様および品質に合致した製品を一貫して生産するだろうということに対して高度な保証を与えるものである。

Worst case（最悪のケース）

標準の操作手順内の条件も含めて、プロセスの最大限や最小限および周囲環境を含んだ条件の組み合わせであり、工程や製品の失敗（理想的な条件と比較した場合に）を引き起こす可能性が大いにある条件である。そのような条件は、必ずしも製品やプロセスの失敗を引き起こす物ではない。

Preliminary Concept Paper
Not for Implementation

Sterile Drug Products Produced by Aseptic Processing Draft

Preliminary Concept Paper
Not for Implementation

Sterile Drug Products Produced by Aseptic Processing
Draft

I. INTRODUCTION

II. BACKGROUND

There are basic differences between the production of sterile drug products by aseptic processing and by terminal sterilization.

Terminal sterilization usually involves filling and sealing product containers under conditions of a high quality environment; the product, container, and closure in most cases have low bioburden but are not sterile. The environment in which filling and sealing is performed is of high quality in order to minimize the microbial content of the in-process product, and to help ensure that the subsequent sterilization process is successful. The product in its final container is then subjected to a sterilization process such as heat or radiation.

In aseptic processing, the drug product, container, and closure are subjected to sterilization processes separately, as appropriate, and then brought together.[1] Because there is no further processing to sterilize the product after it is in its final container, it is critical that containers be filled and sealed in an environment of extremely high quality. Manufacturers should be aware that there are more variables associated with aseptic processing than terminal sterilization. Before aseptic assembly, different parts of the final product are generally subjected to different sterilization processes, such as dry heat for glass containers, moist heat sterilization for rubber closures, and sterile filtration for a liquid dosage form. Each of the processes of the aseptic manufacturing operation requires thorough validation and control. Each also introduces the possibility of error that might ultimately lead to the distribution of contaminated product. Any manual or mechanical manipulation of the sterilized drug, components, containers, and closures prior to or during aseptic assembly poses a risk of contamination and thus necessitates careful control. The terminally sterilized drug product, on the other hand, undergoes a single sterilization process in a sealed container, thus limiting the possibilities for error.[2]

Manufacturers should have a keen awareness of the public health implication of distributing a non-sterile drug purporting to be sterile. Poor CGMP conditions at a manufacturing facility can ultimately pose a life threatening health risk to a patient.

[1] Due to their nature, certain products are aseptically processed from an earlier stage in the process, or in their entirety. Cell-based therapy products are an example. All components and excipients for these products are rendered sterile, and release of the final product is contingent on determination of sterility. See Appendix III.
[2] Nearly all drugs recalled due to Non-sterility or Lack of Sterility Assurance in the period spanning 1980-2000 were produced via aseptic processing.

III. SCOPE

This document discusses only selected issues and thus does not address all aspects of aseptic processing. Finished drug product CGMP issues are primarily addressed, with only limited guidance regarding upstream bulk processing steps. Updates relative to the 1987 document include guidance on: personnel qualification, clean room classifications under dynamic conditions, room design, quality control, environmental monitoring, and review of production records. The aseptic processing isolator is also discussed.

Although this document discusses CGMP issues relating to the sterilization of components, containers, and closures, terminal sterilization of the drug product is not addressed. It is a well-accepted principle that sterile drugs should be manufactured by aseptic processing only when terminal sterilization is not feasible. However, unacceptable degradation of the product can occur as a result of terminal sterilization, or the market presentation can afford some unique and substantial clinical advantage not possible if terminal sterilization were employed. In such cases, adjunct processing steps (e.g., heat exposure conditions which provide some F_0) to increase the level of sterility confidence should be considered.

A list of references, which may be of value to the reader, is included at the conclusion of this document.

IV. BUILDINGS AND FACILITIES

> Section 211.42 (design and construction features) requires, in part, that aseptic processing operations be "performed within specifically defined areas of adequate size. There shall be separate or defined areas for the firm's operations to prevent contamination or mixups." Aseptic processing operations must also "include, as appropriate, an air supply filtered through high efficiency particulate air (HEPA) filters under positive pressure," as well as systems for "monitoring environmental conditions..."and "maintaining any equipment used to control aseptic conditions."
>
> Section 211.46 (ventilation, air filtration, air heating and cooling) states, in part, that "equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing or holding of a drug product." This regulation also states that "air filtration systems, including pre-filters and particulate matter air filters, shall be used when appropriate on air supplies to production areas."

In aseptic processing, there are various areas of operation which require separation and control, with each area having different degrees of air quality depending on the nature of the operation. Area design is based upon satisfying microbiological and particulate standards defined by the equipment, components, and products exposed, as well as the particular operation conducted, in the given area.

Critical and support areas of the aseptic processing operation should be classified and supported by microbiological and particulate data obtained during qualification studies. While initial clean room qualification includes some assessment of air quality under as-built and static conditions,

the final room or area classification should be derived from data generated under dynamic conditions, i.e., with personnel present, equipment in place, and operations ongoing. The aseptic processing facility monitoring program should assess conformance with specified clean area classifications under dynamic conditions, on a routine basis.

The following table summarizes clean area air classifications (Ref. 1).

TABLE 1- Air Classifications[a]

Clean Area Classification	≥ 0.5 um particles/ft^3	≥ 0.5 um particles/m^3	Microbiological Limit[b]	
			cfu/10 ft^3	cfu/m^3
100	100	3,500	<1[c]	<3[c]
1000	1000	35,000	≤ 2	≤7
10,000	10,000	350,000	≤ 5	≤ 18
100,000	100,000	3,500,000	≤25	≤ 88

a- All classifications based on data measured in the vicinity of exposed articles during periods of activity.
b- Alternate microbiological standards may be established where justified by the nature of the operation. c- Samples from class 100 environments should normally yield no microbiological contaminants.

Two clean areas are of particular importance to sterile drug product quality: the critical area and the supporting clean areas associated with it.

A. Critical Area (Class 100)

A critical area is one in which the sterilized drug product, containers, and closures are exposed to environmental conditions designed to preserve sterility. Activities conducted in this area include manipulations (e.g., aseptic connections, sterile ingredient additions) of sterile materials prior to and during filling and closing operations.

This area is critical because the product is not processed further in its immediate container and is vulnerable to contamination. In order to maintain product sterility, the environment in which aseptic operations are conducted should be of appropriate quality throughout operations. One aspect of environmental quality is the particulate content of the air. Particulates are significant because they can enter a product and contaminate it physically or, by acting as a vehicle for microorganisms, biologically. Particle content in critical areas should be minimized by effective air systems.

Air in the immediate proximity of exposed sterilized containers/closures and filling/closing operations is of acceptable particulate quality when it has a per-cubic-foot particle count of no more than 100 in a size range of 0.5 micron and larger (Class 100) when counted at representative locations normally not more than one foot away from the work site, within the airflow, and during filling/closing operations. Deviations from this critical area monitoring parameter should be documented as to origin and significance.

Measurements to confirm air cleanliness in aseptic processing zones should be taken with the particle counting probe oriented in the direction of oncoming airflow and at specified sites where sterilized product and container-closure are exposed. Regular monitoring should be performed during each shift. Nonviable particulate monitoring with a remote counting system is generally less invasive than the use of portable particle counting units and provides the most comprehensive data. See Section X.D, "Particulate Monitoring."

Some powder filling operations can generate high levels of powder particulates that, by their nature, do not pose a risk of product contamination. It may not, in these cases, be feasible to measure air quality within the one foot distance and still differentiate "background noise" levels of powder particles from air contaminants. In these instances, air should be sampled in a manner that, to the extent possible, characterizes the true level of extrinsic particulate contamination to which the product is exposed. Initial certification of the area under dynamic conditions without the actual powder filling function should provide some baseline information on the non-product particle generation of the operation.

Air in critical areas should be supplied at the point of use as HEPA filtered laminar flow air at a velocity sufficient to sweep particulate matter away from the filling/closing area and maintain laminarity during operations. The velocity parameters established for each processing line should be justified, and appropriate to maintain laminarity and air quality under dynamic conditions within a defined space (Ref. 2).[3]

Proper design and control should prevent turbulence or stagnant air in the aseptic processing line or clean zone. Once relevant parameters are established, airflow patterns should be evaluated for turbulence. Air pattern or "smoke" studies demonstrating laminarity and sweeping action over and away from the product under dynamic conditions should be conducted. The studies should be well-documented with written conclusions. Videotape or other recording mechanisms have been found to be useful in assessing airflow initially as well as facilitating evaluation of subsequent equipment configuration changes. However, even successfully qualified systems can be compromised by poor personnel, operational, or maintenance practices.

Active air monitoring of critical areas should normally yield no microbiological contaminants. Contamination in this environment should receive investigative attention.

B. Supporting Clean Areas

Supporting clean areas include various classifications and functions. Many support areas function as zones in which non-sterile components, formulated product, in-process materials, equipment, and container/closures are prepared, held, or transferred. These environments should be designed to minimize the level of particulate contaminants in the final product and control the microbiological content (bioburden) of articles and components that are subsequently sterilized.

The nature of the activities conducted in a supporting clean area should determine its classification. An area classified at Class 100,000 would be used for less critical activities (such

[3] A velocity from 90 to 100 feet per minute is generally established, with a range of plus or minus 20% around the setpoint. Higher velocities may be appropriate in operations generating high levels of particulates.

as initial equipment preparation). The area immediately adjacent to the aseptic processing line should, at a minimum, meet Class 10,000 standards (see Table 1) under dynamic conditions. Depending on the operation, manufacturers can also classify this area as Class 1000 or maintain the entire aseptic filling room at Class 100.

C. Clean Area Separation

Adequate separation is necessary between areas of operation to prevent contamination (211.42). In order to maintain air quality in areas of higher cleanliness, it is important to achieve a proper airflow and a positive pressure differential relative to adjacent less clean areas. Rooms of higher classification should have a positive pressure differential relative to adjacent lower classified areas of generally at least 0.05 inch of water (with doors closed). When doors are open, outward airflow should be sufficient to minimize ingress of contamination (Ref. 3). Pressure differentials between clean rooms should be monitored continuously throughout each shift and frequently recorded, and deviations from established limits investigated.

An adequate air change rate should be established for a cleanroom. For Class 100,000 supporting rooms, airflow sufficient to achieve at least 20 air changes per hour is typically acceptable.

Facility monitoring systems should be established to rapidly detect atypical changes that can compromise the facility's environment. Operating conditions should be restored to established, qualified levels before reaching action levels. For example, pressure differential specifications should enable prompt detection (i.e., alarms) of any emerging low pressure problem in order to preclude ingress of unclassified air into a classified room.

D. Air Filtration

1. Membrane (Compressed Gases)

A compressed gas should be of appropriate purity (e.g., free from oil and water vapor) and its microbiological and particulate quality should be equal to or better than air in the environment into which the gas is introduced. Compressed gases such as air, nitrogen, and carbon dioxide are often used in clean rooms and are frequently employed in operations involving purging or overlaying.

Membrane filters allow for the filtration of compressed gases to meet an appropriate high quality standard, and can be used to produce a sterile compressed gas. A sterile-filtered gas is used when the gas contacts a sterilized material. Certain equipment also should be supplied with a sterile-filtered gas. For example, sterile bacterial retentive membrane filters should be used for autoclave air lines, lyophilizer vacuum breaks, vessels containing sterilized materials, and hot air sterilizer vents. Sterilized tanks or liquids should be held under continuous overpressure to prevent microbial contamination. Safeguards should be in place to prevent a pressure change that can result in contamination due to back flow of non-sterile air or liquid.

Gas filters (including vent filters) should be dry. Condensate in a gas filter can cause blockage or microbial contamination. Frequent replacement, heating, and use of hydrophobic filters prevent moisture residues in a gas supply system. These filters also should be integrity tested upon installation, and periodically thereafter (e.g., including at end of use). Integrity test failures should be investigated.

2. High Efficiency Particulate Air (HEPA)[4]

An essential element in ensuring aseptic conditions is the maintenance of HEPA filter integrity. Integrity testing should be performed at installation to detect leaks around the sealing gaskets, through the frames or through various points on the filter media. Thereafter, integrity tests should be performed at suitable time intervals for HEPA filters in the aseptic processing facility. For example, such testing should be performed twice a year for the aseptic processing room. Additional testing may be needed when air quality is found to be unacceptable, or as part of an investigation into a media fill or drug product sterility failure. Among the filters that should be integrity tested are those installed in dry heat depyrogenation tunnels commonly used to depyrogenate glass vials.

One recognized method of testing the integrity of HEPA filters is use of a dioctylphthalate (DOP) aerosol challenge. However, alternative aerosols may be acceptable. Poly-alpha-olefin can also be used, provided it meets specifications for critical physicochemical attributes such as viscosity. Some alternative aerosols are problematic because they pose a risk of microbial contamination of the environment being tested. Firms should ensure that any alternative does not promote microbial growth.

An intact HEPA filter is capable of retaining at least 99.97 percent of particulates greater than 0.3 micron in diameter. It is important to ensure that the aerosol used for the challenge has a sufficient number of particles of this size range. Performing an integrity test without introducing particles of known size upstream of the filter is ineffective for detecting leaks. The DOP challenge should introduce the aerosol upstream of the filter in a concentration of 80 to 100 micrograms/liter of air at the filter's designed airflow rating. The downstream side of the filter is then scanned with an appropriate photometer probe at a sampling rate of at least one cubic foot per minute. Scanning should be conducted on the entire filter face and frame at a position about one to two inches from the face of the filter. This comprehensive scanning of HEPA filters should be fully documented. While vendors often provide these services, the drug manufacturer is responsible for ensuring that these essential certification activities are conducted satisfactorily. A single probe reading equivalent to 0.01 percent of the upstream challenge should be considered as indicative of a significant leak and should result in replacement of the HEPA filter or perhaps repair in a limited area. A subsequent confirmatory re-test should be performed in the area of any repair.

There is a major difference between filter integrity testing and efficiency testing. The purpose of regularly scheduled integrity testing is to detect leaks from the filter media, filter frame and seal. The challenge is a polydispersed aerosol usually composed of particles ranging in size from one

[4] The same broad principles can be applied to ULPA filters.

to three microns. The test is done in place and the filter face is scanned with a probe; the measured downstream leakage is taken as a percent of the upstream challenge. The efficiency test, on the other hand, is a test used only to determine the rating of the filter.[5]

HEPA filter integrity testing alone is not sufficient to monitor filter performance. This testing is usually done only on a semi-annual basis. It is important to conduct periodic monitoring of filter attributes such as uniformity of velocity across the filter (and relative to adjacent filters). Variations in velocity generally increase the possibility of contamination, as these changes (e.g., velocity reduction) can have an effect on the laminarity of the airflow. Airflow velocities are measured six inches from the filter face or at a defined distance proximal to the work surface for each HEPA filter. For example, velocity monitoring as frequently as weekly may be appropriate for the clean zone in which aseptic processing is performed. HEPA filters should be replaced when inadequate airflow (e.g., due to blockage) or non-uniformity of air velocity across an area of the filter is detected.

E. Design

Section 211.42 requires that aseptic processing operations be "performed within specifically defined areas of adequate size. There shall be separate or defined areas for the firm's operations to prevent contamination or mixups."

Section 211.42 states that "flow of components, drug products containers, closures, labeling, in-process materials, and drug products through the building or building shall be designed to prevent contamination." HEPA filtered air as appropriate, as well as "floors, walls and ceilings of smooth, hard surfaces that are easily cleanable" are some additional requirements of this section.

Section 211.63 states that equipment "shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance."

Section 211.65 states that "equipment shall be constructed so that surfaces that contact the components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements."

Section 211.68 includes requirements for "automatic, mechanical and electronic equipment."

Section 211.113 states that "appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed."

An aseptic process is designed to minimize exposure of sterile articles to dynamic conditions and potential contamination hazards presented by the operation. Limiting the duration of open container exposure, providing the highest possible environmental control, and designing equipment to prevent entrainment of lower quality air into the Class 100 zone are essential to this goal (Ref. 3).

[5] The efficiency test uses a monodispersed aerosol of 0.3 micron size particles, relates to filter media, and usually requires specialized testing equipment. Downstream readings represent an average over the entire filter surface. Therefore, the efficiency test is not intended to test for leakage in a filter.

Any intervention or stoppage during an aseptic process can increase the risk of contamination. Personnel and material flow should be optimized to prevent unnecessary activities that increase the potential for introducing contaminants to exposed product, container-closures, or the surrounding environment. The layout of equipment should provide for ergonomics that optimize comfort and movement of operators. The flow of personnel should be designed to limit the frequency with which entries and exits are made to and from the aseptic processing room and, more significantly, its critical area. In order to prevent changes in air currents that introduce lower quality air, movement adjacent to the critical area should be limited. For example, personnel intervention can be reduced by integrating an on-line weight check device, thus eliminating a repeated manual activity within the critical zone. It is also important to minimize the number of personnel in the aseptic processing room.

Transfer of products should be performed under appropriate clean room conditions. For example, lyophilization processes include transfer of aseptically filled product in partially-sealed containers. To prevent contamination, partially-closed sterile product should be staged and transferred only in critical areas. Facility design should assure that the area between a filling line and the lyophilizer, and the transport and loading procedures, provide Class 100 protection.

The sterile product and container-closures should also be protected from activities occurring adjacent to the line. Carefully designed curtains, rigid plastic shields, or other barriers should be used in appropriate locations to partially segregate the aseptic processing line.

Airlocks and interlocking doors facilitate better control of air balance throughout the aseptic processing area. Airlocks should be installed between the aseptic processing area entrance and the adjoining uncontrolled area. Other interfaces such as personnel entries, or the juncture of the aseptic processing room and its adjacent room, are also appropriate locations for air locks.

Clean rooms are normally designed as functional units with specific purposes. A well-designed clean room is constructed with material that allows for ease of cleaning and sanitizing. Examples of adequate design features include seamless and rounded floor to wall junctions as well as readily accessible corners. Floors, walls, and ceilings are constructed of smooth, hard surfaces that can be easily cleaned (211.42). Ceilings and associated HEPA filter banks should be designed to protect sterile materials from contamination. Clean rooms also should not contain unnecessary equipment, fixtures, or materials.

Processing equipment and systems should be equipped with sanitary fittings and valves. Drains are not considered appropriate for rooms in classified areas of the aseptic processing facility.

When applicable, equipment must be suitably designed for ease of sterilization (211.63). The effect of equipment layout and design on the clean room environment should be addressed. Flat surfaces or ledges that accumulate dust and debris should be avoided. Equipment should not obstruct airflow and, in critical zones, its design should not perturb airflow.

V. PERSONNEL TRAINING, QUALIFICATION, & MONITORING

Sections 211.22 states that "the quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product."

Section 211.113(b) addresses the procedures designed to prevent microbiological contamination, stating that "appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed."

Section 211.25, Personnel Qualifications requires that "each person engaged in manufacture, processing, packing or holding of a drug product shall have education, training and experience, or any combination thereof, to enable that person to perform the assigned functions...Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to perform assigned functions in such a manner as to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess." This section also requires "an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing or holding of each drug product." Section 211.25 also requires that continuing training in CGMP "shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them." The training "shall be in the particular operations that the employee performs and in current good manufacturing practice (including the current good manufacturing practice regulations in this chapter and written procedures required by these regulations), as they relate to the employee's functions."

Section 211.28, Personnel Responsibilities states, that "personnel engaged in the manufacture, processing, packing or holding of a drug product shall wear clean clothing appropriate for the duties they perform." It also states that "personnel shall practice good sanitization and health habits" and specifies that "protective apparel, such as head, face, hand, and arm coverings, shall be worn as necessary to protect drug products from contamination." It also states that "any person shown at any time (either by medical examination or supervisory examination) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of drug products. All personnel shall be instructed to report to supervisory personnel any health conditions that may have an adverse effect on drug products."

This section also addresses restrictions on entry into limited access areas: "Only personnel authorized by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas."

Section 211.42 requires the establishment of a "system for monitoring environmental conditions."

A. Manufacturing Personnel

A well-designed aseptic process minimizes personnel intervention. As operator activities increase in an aseptic processing operation, the risk to finished product sterility also increases. It is essential that operators involved in aseptic manipulations adhere to the basic principles of aseptic technique at all times to assure maintenance of product sterility.

Appropriate training should be conducted before an individual is permitted to enter the aseptic processing area and perform operations. For example, such training should include aseptic technique, clean room behavior, microbiology, hygiene, gowning, and patient safety hazard posed by a non-sterile drug product, and the specific written procedures covering aseptic processing area operations. After initial training, personnel should be updated regularly by an ongoing training program. Supervisory personnel should routinely evaluate each operator's conformance to written procedures during actual operations. Similarly, the quality control unit

should provide regular oversight of adherence to established, written procedures and basic aseptic techniques during manufacturing operations.

Adherence to basic aseptic technique is a continuous requirement for operators in an aseptic processing operation. Some of these techniques aimed at maintaining sterility of sterile items and surfaces include:

1. *Contacting sterile materials only with sterile instruments.* Sterile instruments (e.g., forceps) are should always be used in the handling of sterilized materials. Between uses, instruments should be placed only in sterilized containers. These instruments should be replaced as necessary throughout the operation.

After initial gowning, sterile gloves should be regularly sanitized to minimize the risk of contamination. Personnel should not directly contact sterile products, containers, closures, or critical surfaces.

2. *Moving slowly and deliberately.* Rapid movements can create unacceptable turbulence in the critical zone. Such movements disrupt the sterile field, presenting a challenge beyond intended cleanroom design and control parameters. The principle of slow, careful movement should be followed throughout the cleanroom.

3. *Keeping the entire body out of the path of laminar air.* Laminar airflow design is used to protect sterile equipment surfaces, container-closures, and product. Personnel should not disrupt the path of laminar flow air in the aseptic processing zone.

4. *Approaching a necessary manipulation in a manner that does not compromise sterility of the product.* In order to maintain sterility of nearby sterile materials, a proper aseptic manipulation should be approached from the side and not above the product (in vertical laminar flow operations). Also, speaking when in direct proximity to an aseptic processing line is not an acceptable practice.

Personnel who have been qualified and permitted access to the aseptic processing area should be appropriately gowned. An aseptic processing area gown should provide a barrier between the body and exposed sterilized materials, and prevent contamination from particles generated by, and microorganisms shed from, the body. Gowns need to be sterile and non-shedding, and should cover the skin and hair. Face masks, hoods, beard/moustache covers, protective goggles, elastic gloves, clean room boots, and shoe overcovers are examples of common elements of gowns. An adequate barrier should be created by the overlapping of gown components (e.g., gloves overlapping sleeves). If an element of the gown is found to be torn or defective, it should be changed immediately.

There should be an established program to regularly assess or audit conformance of personnel to relevant aseptic manufacturing requirements. An aseptic gowning qualification program should assess the ability of a cleanroom operator to maintain the sterile quality of the gown after performance of gowning procedures. Gowning qualification should include microbiological surface sampling of several locations on a gown (e.g., glove fingers, facemask, forearm, chest, other sites). Following an initial assessment of gowning, periodic requalification should monitor

various gowning locations over a suitable period to ensure the consistent acceptability of aseptic gowning techniques. Semi-annual or yearly requalification is acceptable for automated operations where personnel involvement is minimized.

To protect exposed sterilized product, personnel are expected to maintain sterile gown quality and aseptic method standards in a consistent manner. Written procedures should adequately address circumstances under which personnel should be retrained, requalified, or reassigned to other areas.

B. Laboratory Personnel

The basic principles of training, aseptic technique, and personnel qualification in aseptic manufacturing are equally applicable to those performing aseptic sampling and microbiological laboratory analyses. Processes and systems cannot be considered to be in control and reproducible if there is any question regarding the validity of data produced by the laboratory.

C. Monitoring Program

Personnel can have substantial impact on the quality of the environment in which the sterile product is processed. A vigilant and responsive personnel monitoring program should be established. Monitoring should be accomplished by obtaining surface samples of each aseptic processing operator's gloves on an at least a daily basis, or in association with each batch. This sampling should be accompanied by an appropriate sampling frequency for other strategically selected locations of the gown (Ref. 7). The quality control unit should establish a more comprehensive monitoring program for operators involved in operations which are especially labor intensive, i.e. those requiring repeated or complex aseptic manipulations.

Asepsis is fundamental to an aseptic processing operation. An ongoing goal for manufacturing personnel in the aseptic processing room is to maintain contamination-free gloves throughout operations. Sanitizing gloves just prior to sampling is inappropriate because it can prevent recovery of microorganisms that were present during an aseptic manipulation. When operators exceed established levels or show an adverse trend, an investigation should be conducted promptly. Follow-up actions may include increased sampling, increased observation, retraining, gowning requalification, and in certain instances, reassignment of the individual to operations outside of the aseptic processing area. Microbiological trending systems, and assessment of the impact of atypical trends, are discussed in more detail under Section XI., Laboratory Controls.

VI. COMPONENTS AND CONTAINER/CLOSURES

A. Components

Section 210.3(b)(3) defines a "component" as "any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product."

Section 211.80, General Requirements, requires, in part, the establishment of written procedures "describing in sufficient detail the receipt, identification, storage, handling, sampling, sampling, testing, and approval or rejection of components ar drug product containers and closures...Components and drug product containers and closures shall at all times be handled and stored in a manner to prevent contamination."

Section 211.84, Testing and approval or rejection of components, drug product containers, and closures, requires that "eac lot of a component, drug product container, or closure that is liable to microbiological contamination that is objectionable view of its intended use shall be subjected to microbiological tests before use."

A drug product produced by aseptic processing can become contaminated by use of one or more components (e.g., active ingredients, excipients, Water for Injection) that are contaminated with microorganisms or endotoxins. It is important to characterize the microbial content of each component liable to contamination and establish appropriate acceptance/rejection limits based on information on bioburden. Knowledge of bioburden is critical in assessing whether the sterilization process is adequate.

In aseptic processing, each component is individually sterilized or several components are combined, with the resulting mixture sterilized.[6] There are several methods to sterilize components (see relevant discussion in Section IX). A widely used method is filtration of a solution formed by dissolving the component(s) in a solvent such as USP Water For Injection (WFI). The solution is passed through a sterilizing membrane or cartridge filter. Filter sterilization is used where the component is soluble and is likely to be adversely affected by heat. A variation of this method involves subjecting the filtered solution to aseptic crystallization and precipitation of the component as a sterile powder. However, this method involves more handling and manipulation and therefore has a higher potential for contamination during processing. If a component is not adversely affected by heat, and is soluble, it may be made into a solution and subjected to steam sterilization, typically in an autoclave or a pressurized vessel.

Dry heat sterilization is a suitable method for components that are heat stable and insoluble. However, carefully designed heat penetration and distribution studies should be performed for powder sterilization because of the insulating effects of the powder.

Ethylene oxide (EtO) exposure is often used for surface sterilization. Such methods should be carefully controlled and validated if used for powders to evaluate whether consistent penetration of the sterilant is achieved and to minimize residual ethylene oxide and by-products.

Parenteral products are intended to be non-pyrogenic. There should be written procedures and appropriate specifications for acceptance or rejection of each lot of components that might contain endotoxins. Any components failing to meet endotoxin specifications should be rejected.

B. Containers/Closures

[6] See Appendix III for discussion of certain biologic components that are aseptically handled from the start of the process.