COMPARISON OF CLEANROOM AND ISOLATOR ASEPTIC PROCESSING TECHNOLOGY FOR SMALL START-UP PARENTERAL FACILITIES

by

SHANNON LAMB BURTON

(Under the Direction of David Mullis, Ph.D.)

ABSTRACT

The sterility of drug products in the United States is of utmost importance when it comes to patient safety. Drug products, which cannot be subjected to terminal sterilization, must be brought together in their final form utilizing aseptic processing technologies such as cleanrooms and isolators. This thesis provided a comparison of cleanroom and isolator technologies relative to the current regulations (21 CFR 210 and 21 CFR 211) and applicable guidance documents (FDA Guidance for Industry Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice, ISO 14644 Cleanrooms and Associated Controlled Environments, ISPE Baseline Guide – Sterile Manufacturing Facilities) and a cost analysis to determine the overall financial impact to the manufacturer. The research demonstrated that isolator technology is more cost effective and advantageous for a small start-up parenteral facility and is therefore the superior technology.

INDEX WORDS: Aseptic Processing, Cleanroom, Isolator, 21 CFR 210, 21 CFR 211, FDA Guidance for Industry, ISO 14644, Controlled Environments,

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SHANNON LAMB BURTON

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SHANNON LAMB BURTON

Major Professor:	David Mullis, Ph.D.
Committee:	Frances Akelewicz
	Randall Tackett, Ph.D.

Electronic Version Approved:
Suzane Barbour
Dean of the Graduate School
The University of Georgia
May 2016

DEDICATION

This thesis is dedicated to my husband, Stuart Burton. Without his support and understanding this would have been an impossible journey. Also to my mother, Ella Arnold, who reminded me every day that I could do anything I set my mind to – no matter what.

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CHAPTER 1

INTRODUCTION

1.1 Purpose of Thesis

The purpose of this thesis was to present, compare and contrast cleanroom and isolator technologies for use in the United States and to determine how the current existing regulations apply to each technology. A cost analysis was performed for implementation and maintenance of each technology for a small scale, start-up parenteral manufacturer using prefilled syringes as the product example. While both aseptic processing technologies are currently in use by manufacturers throughout the United States, my thesis showed that while the isolation technology is newer and not as clearly defined in current regulations with some limited guidance, it is the superior processing technology for a small scale start-up facility.

The methodology used surveys of industry professionals with experience with aseptic processing and the technologies available. A total of twenty (20) experienced professionals were surveyed about the critical aspects of aseptic processing and the comparison of the use of cleanroom versus isolator technology. Prior to any data collection, all University of Georgia IRB requirements were met. All survey/questionnaire material was validated.

1.2 Overview of Aseptic Processing

The sterility of drug products is of utmost importance when it comes to patient safety. The sterility of parenteral drug products can be achieved via two manufacturing processes: terminal sterilization and aseptic processing. Terminal sterilization of drug products is performed by the product being manufactured in a controlled environment and then exposed to

a validated sterilization process which achieves the required sterility assurance level (SAL 10^{-6}) (Figure 1).

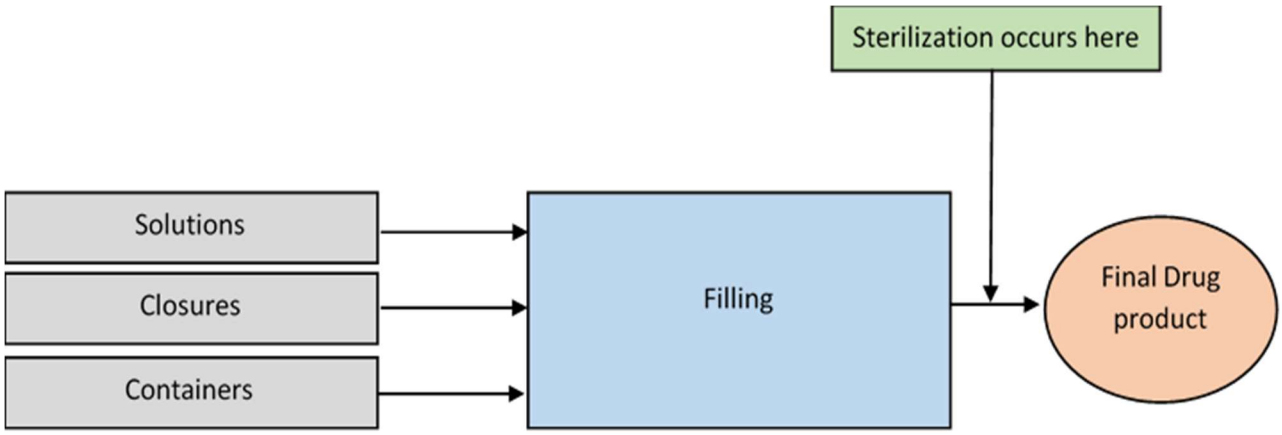

Figure 1. Terminal Sterilization

Most small volume parenteral products are unable to withstand terminal sterilization due to product instability and therefore, sterility must be assured by other means. These products must be manufactured through the use of aseptic processing, which consists of subjecting the drug product, container and closure to separate validated sterilization processes and then combining all in their final form using aseptic technique in a highly controlled quality environment (i.e. cleanroom or isolator) (Figure 2). Aseptic processing is more variable and results in lower and less predictable levels of sterility assurance (approximately SAL 10^{-3}).[1] This lower level of sterility assurance requires additional controls for the aseptic environment consisting of personnel practices and procedures, sterilization of equipment and components, sanitization practices and extensive environmental monitoring. The highly controlled quality environment necessary for aseptic processing has typically been achieved in a cleanroom, however, in the mid 1990's, advanced aseptic processing was introduced and consisted of the use of isolation technology.[2]

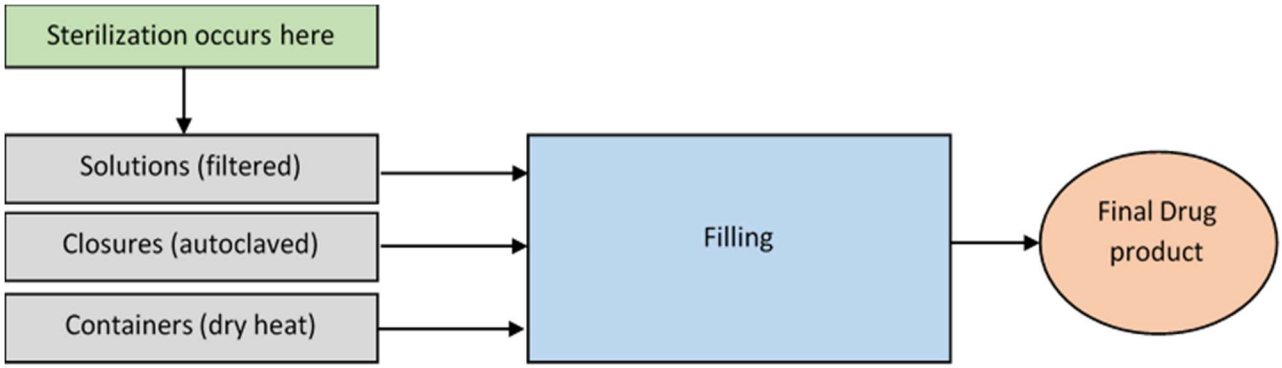

Figure 2. Aseptic Processing

In order to better understand aseptic processing, one must understand the sources of contamination. Sources of contamination for sterile products can come from the raw materials, environment, people, equipment, and from the nature of the process itself. People are the main source of contamination in an aseptic processing environment as shown in Table 1.1.[3] It is due to this particle generation, that personnel must be separated from the process. This separation can be achieved in cleanroom environments and isolators through the design of the areas, equipment and personnel gowning.

Table 1.1 Particle Generation through Personnel Movement[3]

Type of Personnel Movement	Particle/min. (>0.5µm)
Sitting without moving	100,000
Moving hands, arms, head	500,000
Active arm/hand movement, fast turning of the head	1,000,000
Standing up from a sitting position or vice versa	2,500,000
Rapid movement, climbing stairs, etc.	110,000,000

1.3 History of Aseptic Processing

Joseph Lister introduced aseptic techniques to the medical profession in the 1860's to better manage infection risk in patients undergoing surgery (Figure 3).[4] Lister's efforts changed

the way surgery was conducted by utilizing antiseptic techniques which over time, spread to the science of microbiology and ultimately to the manufacturing of sterile products.

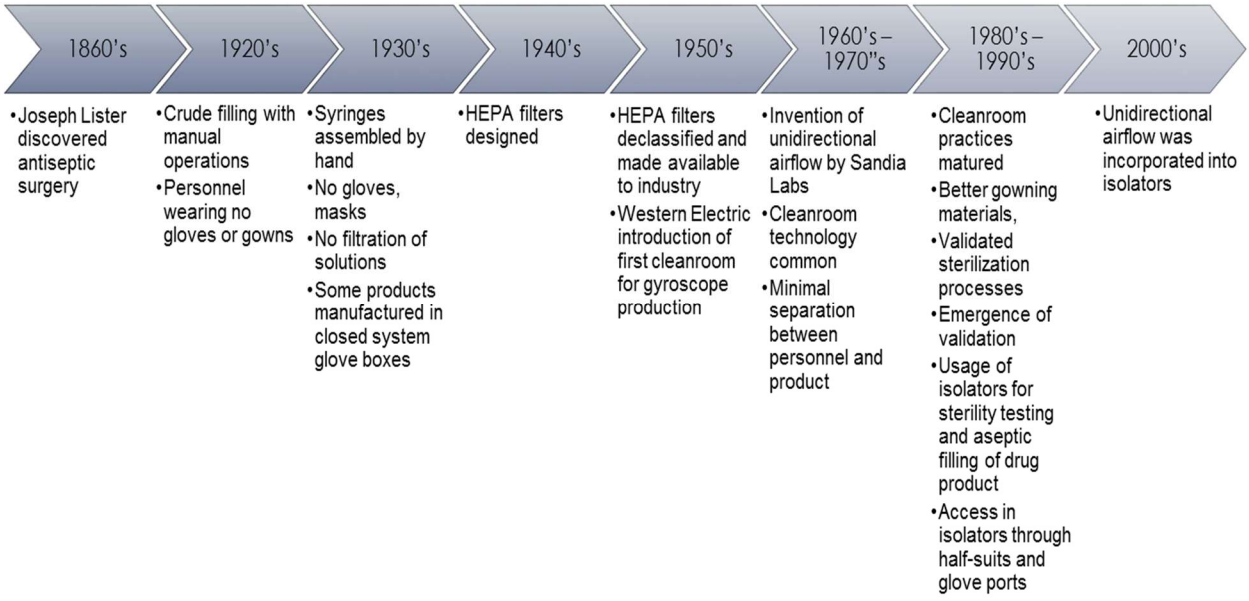

Figure 3 Evolution of Sterilization Technology

In the 1920's, filling of drug product was performed very crudely using manual operations with personnel wearing no gloves or gowns (Figure 4).[5] This was considered acceptable at the time. In the 1930's, syringes were assembled by hand with no gloves, masks and limited, generic, cotton gowning (Figure 5).[5] Solutions were not filtered. High Efficiency Particulate Air (HEPA) filtration did not yet exist.

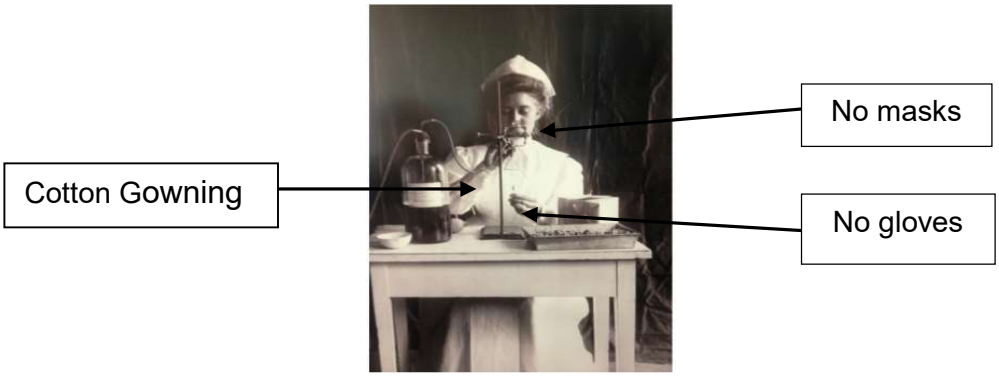

Figure 4 Aseptic Processing circa 1920[5]

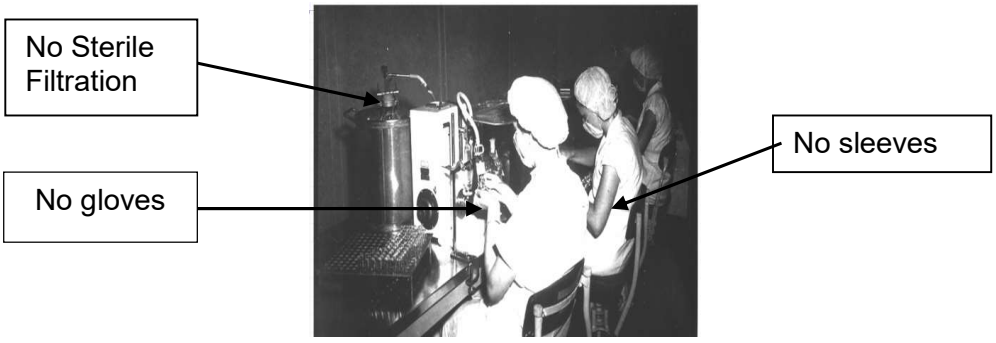

Figure 5 Aseptic Processing circa 1930[5]

During this pre-HEPA time period, operators were responsible for performing all tasks. Little or no equipment was involved, therefore, filling was completed at very slow speeds, labor intensive and all material transfers were relatively slow. During this time, some products were manufactured in a glove box (Figure 6).[5] This glove box featured a closed system in which the operators worked through gloves mounted in the lower walls. There were no HEPA filters, Rapid Transfer Ports (RTP) or Vaporized Hydrogen Peroxide (VHP) for glove box decontamination. Cleaning and disinfection of the glove box was accomplished through manual processes such as wiping the box glove between activities. The process was simply a manual assembly process performed by people but now the operators were separated from the product.

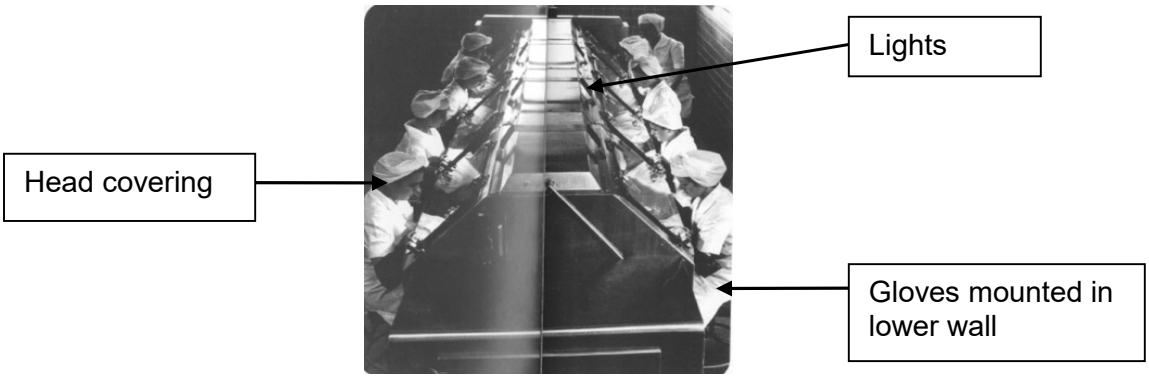

Figure 6. Aseptic processing in a glove box[5]

The manufacturing industries' ability to control microbiological contamination improved significantly with the government declassification of the HEPA filter. HEPA filters were originally designed in the 1940's under a classified government contract as part of the Manhattan Project, where the first atomic bomb was developed during World War II. Their development was considered a major advancement in air filtration technology. In the 1950's, when the filters were declassified and made available to industry, the first cleanrooms made their appearance.[5] The declassification of HEPA filters resulted in large volumes of air now being effectively free of microbial contamination and it became possible to dilute and/or remove the personnel related contamination that is considered the greatest contamination risk.

The availability of HEPA filtration made it possible for machines to perform much of the work associated with filling and sealing of product with operators present only to service the line as needed. HEPA filtration enabled the working room environment to be controlled and allowed manufacturers to reach levels of particle and microbial cleanliness not previously attainable through facility design and operating practices. These improvements encouraged manufacturers to increase automation in their processes and greatly reduced the risk of contamination.

In 1955, the first production cleanroom which recognized all of the basic requirements for a cleanroom was used for gyroscope production by Western Electric. Operators were now gowned in synthetic fabric clothing with a cap; they also had a locker room for changing clothes. Construction materials were chosen for ease of cleaning and to minimize the production of particles. Cracks and corners were minimized, the vinyl covered floors were coved onto the wall and the lighting was flush mounted to minimize dust accumulation. Pass-through windows were used for entry of materials into the area, air supply was conditioned and filtered through HEPA or 'absolute' filters that were capable of removing 99.95% of 0.3 µm particles, and the room was positively pressurized (Figure 7).[6]

Figure 7. Gyroscope Production Room at Western Electric[6]

A significant event that marked the turning point in the history of cleanroom technology was the invention, in 1960, of the 'unidirectional' or 'laminar air' concept of ventilation at the Sandia Laboratories, in Albuquerque, New Mexico. The room, constructed in 1961, was small. Instead of the air being supplied by ceiling diffusers and mixing with the room air in an uncontrolled manner, it was supplied by a bank of HEPA filters. This ensured that air moved in a unidirectional way from the filters, across the room, and out through the floor grills (Figure 8).[6]

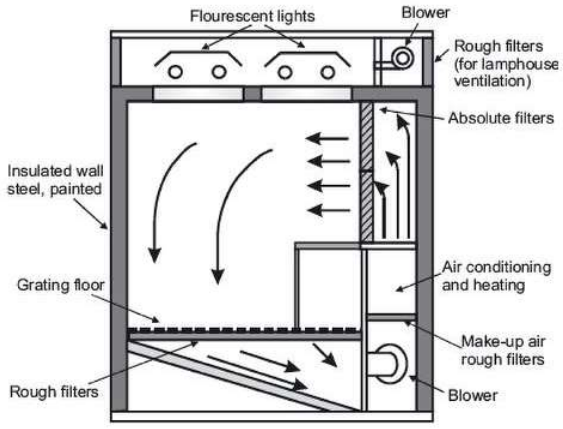

Figure 8. Original Unidirectional Airflow Cleanroom at Sandia Labs[6]

In the 1960's to 1970's, cleanroom technology was common but still consisted of a lot of personnel activity around open containers (Figure 9).[5] There was minimal separation between personnel and the product. In the 1980's to 1990's, cleanroom technology matured through a better understanding of the contamination control practices and a better understanding that the

personnel were the major contaminant source in aseptic processing. This led to improvements such as better gowning materials, the emergence of the concept and requirements for validation, validated sterilization processes, and technology advances.

Figure 9. Cleanroom 1960 – 1970 Design[5]

The technology advances consisted of the first isolator installations used for sterility testing in the 1980's. The isolator was essentially considered a highly evolved glove box which offered absolute separation between personnel and the drug product. This separation was made possible through the use of rapid transfer ports (RTP) and Vaporized Hydrogen Peroxide (VHP) generators. Early isolators used turbulent airflow, canister HEPA's, flexible walls, gloves (built in to the isolator) and were basically of crude design (Figure 10).[5]

Figure 10. Early Isolator Technology[5]

Isolators began being used for aseptic filling of drug product in the mid to late 1980's. The design was dramatically improved from the early crude design to consist of a rigid enclosure. The isolator now consisted of air inlets and outlets located above the isolator

chamber. Operators accessed the enclosure through the use of gloves and half-suits to perform interventions which allowed for complete separation of personnel and product (Figure 11).[5]

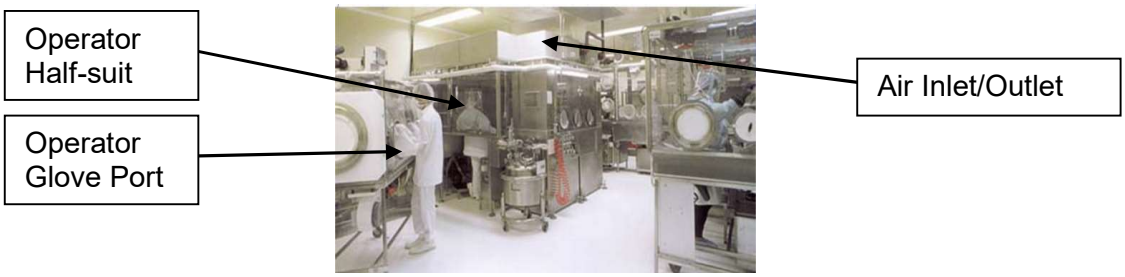

Figure 11. Isolator Filling Line - Circa 1988[5]

Isolator design was again improved around 2005. The improved isolators incorporated unidirectional airflow into the chambers and more closely resembled a cleanroom environment with regards to air passing over the product containers. The isolators typically resulted in a larger footprint, larger internal volume along with higher costs and higher levels of efficiency (Figure 12).[5]

Figure 12. Isolator Filling Line - Circa 2005[5]

In reading through Chapter 1, you see that the evolution of cleanrooms and isolators resulted in some significant advances for manufacturers using aseptic processing technology. The current regulations, guidance, and recommendations for cleanroom and isolator technologies will be discussed in Chapter 2.

CHAPTER 2

CURRENT REGULATIONS, GUIDANCE AND RECOMMENDATIONS FOR ASEPTIC PROCESSING

2.1 FDA Regulation 21 CFR 210

Current Good Manufacturing Practice, 21 Code of Federal Regulations (CFR) Part 210 addresses the general requirements for manufacturing, facilities, and controls for the manufacturing, processing, packaging or holding of a drug product. The sections for 21 CFR 210 is as follows:

- Sec 210.1 Status of current good manufacturing regulations
- Sec 210.2 Applicability of good manufacturing practice regulations
- Sec 210.3 Definitions

Section 210.1 specifies the minimum requirements for a company required to meet good manufacturing practices and covers the manufacturing, facilities, and controls for the manufacturing, processing, packaging and holding of a drug product. This section also states that failure to comply with these regulations will render the drug to be adulterated and the person responsible for the failure to comply will be subject to regulatory action. Section 210.2 describes the applicability of the regulations as they apply to drugs, biological products for human use, and tissue based products. Section 210.3 provides the definitions applicable to drug manufacturing throughout the various parts of the GMP regulations.[7]

2.2 FDA Regulation 21 CFR 211

Current Good Manufacturing Practice for Finished Pharmaceuticals, 21 Code of Federal Regulations (CFR) Part 211 is considered the basics of the GMP regulations as they apply to drugs intended for human use. The regulation covers all aspects of operations and is designed to be general in nature in order to provide flexibility to the variation of products and their specific manufacturing, packaging and storage requirements. The intent is to establish what drug manufacturers need to do, not how they need to do it. This regulation consists of various subparts that define specific requirements for personnel, facilities, equipment, component, process, packaging and labeling controls, laboratory controls, documentation, and an overall general scope.

Table 2.1 explains each of the subparts listed above that are applicable to the use of cleanrooms and isolators and the requirements of each subpart as they apply to good manufacturing practices for finished pharmaceuticals for human use. The table also briefly shows how the subparts support, or through associated guidance documents, tie into the use of cleanrooms or isolators. In reviewing the table, the reader can readily see how integrated the elements of a Quality System can impact the aseptic process and its respective technologies.[8]

TABLE 2.1 – 21 CFR 211, APPLICABLE SUBPART REQUIREMENTS

Subpart	Title	Requirements	Support finished product or aseptic processing requirements/technology
A	General provisions	Provides the minimum current GMP requirements for manufacturers who produce drug products for administration to humans or animals. Dictates the applicability of the definitions set forth in 21 CFR 210.3	• Sets the scope for the minimum current good manufacturing practices as they apply to drugs for human use
B	Organization and Personnel	Specifies the requirements for establishment of a quality control (QC) unit with adequate facilities for the responsibilities of testing, approving and rejecting all components, drug product containers, closures, in-process materials, packaging material, labeling and drug products processed within the manufacturer itself as well as with contract companies. Specifies the requirements for personnel qualifications as they apply to ensuring that personnel, including supervisors and consultants, have the education, training, and experience to be able to perform their assigned functions.	• Supports both through ensuring the appropriate knowledge, education, training and ongoing training of personnel and consultants. • Supports finished product through the establishment of a QC unit responsible for testing, approval and rejection of product.

TABLE 2.1 – 21 CFR 211, APPLICABLE SUBPART REQUIREMENTS

Subpart	Title	Requirements	Support finished product or aseptic processing requirements/technology
B	Organization and Personnel (Continued)	This includes training on cGMP's by a qualified individual on a routine basis. Also requires that there be an adequate number of personnel to perform and supervise activities. Provides the requirements for personnel responsibility as it applies to hygiene with regards to clothing and protective apparel required to protect the drug product from contamination. Also specifies practicing good sanitation and health practices for personnel and authorization for personnel entering limited access areas of buildings and facilities.	
C	Buildings and Facilities	Provides the requirements for manufacturers as it applies to buildings and facilities. Requires that the building be of suitable size and maintained to facilitate cleaning, maintenance, and operations. Also specifies the requirement that operations such as receipt, quarantine, and storage holding be defined to prevent contamination and/or mix-ups.	• Supports both through ensuring the facilities are designed appropriately for the aseptic operations including utilities, HVAC, surface cleanability, temperature and humidity controls, environmental monitoring and sanitization programs.

TABLE 2.1 – 21 CFR 211, APPLICABLE SUBPART REQUIREMENTS

Subpart	Title	Requirements	Support finished product or aseptic processing requirements/technology
C	Buildings and Facilities (Continued)	Requires separate facilities for the manufacture of penicillin and human drug products. Provides requirements for aseptic processing design of facilities including floors, walls, and ceilings which are smooth, hard and cleanable, environmental control of temperature and humidity, air filtration systems, environmental monitoring for microbiological and particulate contaminants, cleaning and disinfection programs and equipment maintenance. Specifies requirements for utility systems such as lighting, HVAC, plumbing, sewage, refuse, washing and toilet facilities, sanitation and facility maintenance.	• Supports both through appropriate practices, such as defined and segregated areas, to prevent cross-contamination and/or mix-ups. • Supports both through appropriate design for protection against pests which can lead to contamination. • Supports both through design measures which prevent unauthorized personnel from entering the sterile manufacturing areas.
D	Equipment	Provides the requirements for equipment design, size and location, construction, cleaning, maintenance, and automation. Provides requirements for equipment to ensure that the design, size, and location are appropriate for its intended use.	• Supports both through ensuring that equipment is designed, constructed, located, qualified and maintained to prevent product contamination such as bioburden and particulate.

TABLE 2.1 – 21 CFR 211, APPLICABLE SUBPART REQUIREMENTS

Subpart	Title	Requirements	Support finished product or aseptic processing requirements/technology
D	Equipment (Continued)	Provides requirements for construction of the equipment such that product contact surfaces are not reactive, additive or absorptive with the drug product. Also provides directives for written procedures to define the cleaning and maintenance of equipment to prevent contamination and equipment malfunctions. Also provides directives for the use of automated equipment provided that the equipment is routinely calibrated per a written program and all documentation is retained.	• Supports both through ensuring equipment surfaces that have product contact are not reactive, additive or absorptive such that they would adversely affect the product quality. • Supports both through ensuring equipment is identified so it is traceable.
E	Control of Components and Drug Product Containers and Closures	Provides the general requirements for receipt, identification, storage, handling, sampling, testing and approval or rejection of components, drug product containers/closures. Requires appropriate storage and handling to allow for cleaning and prevention of contamination. Provides requirements for identifying each lot of product upon receipt and identifying its status as quarantined, approved or rejected.	• Supports both through appropriate storage and handling to prevent contamination.

TABLE 2.1 – 21 CFR 211, APPLICABLE SUBPART REQUIREMENTS

Subpart	Title	Requirements	Support finished product or aseptic processing requirements/technology
E	Control of Components and Drug Product Containers and Closures (Continued)	Requires each lot to be examined upon receipt and stored under quarantine until testing and release have been performed. Sampling must be performed per approved procedures and testing for release should conform to approved specifications. Components, drug product containers and closures that meet specifications can be released for use while those that do not must be rejected.	
F	Production and Process Controls	Provides the requirements needed for production and process controls as it applies to written procedures, deviations, component charging, yield calculation, equipment identification, sampling and testing of in process materials, time limitations, microbiological contamination, and reprocessing. General requirement for written procedures to be followed and the execution of production and process control activities to be recorded at the time of completion.	• Supports both by establishing validated time limits for production phases that impact bioburden, endotoxin load, and maintenance of sterility. • Supports both through bioburden testing of aseptically manufactured products including products sterilized by filtration.

TABLE 2.1 – 21 CFR 211, APPLICABLE SUBPART REQUIREMENTS

Subpart	Title	Requirements	Support finished product or aseptic processing requirements/technology
F	Production and Process Controls (Continued)	Production records should be designed to allow assurance that the drug product is manufactured to provide 100% of the specified active ingredient. Specifies the requirement that all equipment be identified to indicate contents. Requires in-process sampling and testing to assure batch uniformity and integrity of drug product throughout the manufacturing process. Provides the requirement for time limitations on production phases. Requires written procedures to prevent objectionable microorganisms be established and followed. For sterile products, all aseptic and sterilization processes for microbial control must be validated.	• Supports both through requiring validation of all sterilization processes used for microbial control.
I	Laboratory Controls	Provides the general requirements for the establishment of specifications, standards, sampling plans, and test procedures to ensure product quality. Specifies requirements for calibration of laboratory equipment.	• Supports both through the requirements defined for testing and release of each batch of drug product, acceptance criteria and validated test methods.

TABLE 2.1 – 21 CFR 211, APPLICABLE SUBPART REQUIREMENTS

Subpart	Title	Requirements	Support finished product or aseptic processing requirements/technology
I	Laboratory Controls (Continued)	Provides requirements for testing and release of each batch of drug product, adequate acceptance criteria and validated test methods. Provides the requirements for a written stability program including the necessary sample size, storage conditions, testing requirements designed to assess the storage conditions and expiry of drug product. Special testing requirements for sterility or pyrogenicity, particulates, and controlled release are dictated for applicable drug products. Requires keeping reserve samples representative of each lot in quantities sufficient enough to allow performing all release testing twice as necessary. Samples should be stored under conditions consistent with product labeling and retained per the required retention time.	• Supports sterile finished product through the testing for sterility and pyrogenicity (endotoxin testing) and particulates.

TABLE 2.1 – 21 CFR 211, APPLICABLE SUBPART REQUIREMENTS

Subpart	Title	Requirements	Support finished product or aseptic processing requirements/technology
J	Records and Reports	Provides requirements for keeping equipment cleaning and use logs, along with component, container, closure, and labeling records. Requirement to have a standard operating procedure for master production and control records and that these records be maintained. Specifies that batch production and control records must be used for manufacturing and these records must be maintained. Requires records to be reviewed/approved by quality control unit and include complete data derived from all tests necessary to assure compliance.	• Supports both through documentation of processing steps, cleaning and maintenance of equipment used in the manufacturing of the drug product. • Supports both through the use of laboratory testing records for drug product release testing.

In reading through Table 2.1, one can see that the items apply to both cleanroom and isolator technologies. There is no distinction in the regulations for how to meet the requirements, just that they must be met.

2.3 FDA Guidance for Industry

Current Good Manufacturing Practices, 21 CFR 210 and 21 CFR 211 broadly define the requirements of the Food, Drug & Cosmetic Act and US laws/regulations. In addition, there are specific guidance documents for aseptic and sterilization processing and testing, which are designed help manufacturers by providing clear, consistent communications of regulatory expectations and aid in promoting voluntary compliance throughout industry. The Guidance for Industry - Sterile Drug Products Produced by Aseptic Processing describes the FDA's current thinking on sterile drugs produced by aseptic processing in the context of current good manufacturing practice (cGMP) regulations for drug and biological products. This guidance document provides recommendations for manufacturers on how to meet the intent of the regulations and covers an array of topics including buildings and facilities, personnel, validation of aseptic processes and sterilization, laboratory controls, and sterility testing.[9] The applicability of the guidance document will be discussed in additional detail in chapter 3 of this document.

2.4 ISO 14644 Cleanrooms and Associated Controlled Environments

The International Organization for Standardization (ISO) has developed a series of cleanroom standards. These standards consist of ten (10) documents which cover a wide variety of important cleanroom issues such as classification, design, testing, operation and biocontamination. The parts of ISO 14644 and their applicability to cleanrooms and isolators are described in Table 2.[10]

Table 2.2 ISO 14644 Cleanrooms and Associated Controlled Environments Parts and Overview

Standard #	Title	Overview	Application to Cleanrooms and/or Isolators
14644-1	Classification of Air Cleanliness	Part 1 provides the airborne particle limits for different classes of cleanrooms. It also gives the methods that should be used to measure the airborne particle concentration when testing a cleanroom to determine its class.	Supports both by defining the procedure for determining the concentration of airborne particles and classification of areas.
14644-2	Specifications for testing and monitoring to prove continued compliance with ISO14644-1	Part 2 provides information, including time intervals, for testing a cleanroom to show that it complies with the ISO 14644–1 standard.	Supports both by defining the frequency of periodic testing to prove operations continue to comply with 14644-1.
14644-3	Test methods	Part 3 provides a description of the methods that should be used to test the cleanroom to show it is working correctly.	Supports both by describing the test methods that can be used to characterize a cleanroom.
14644-4	Design, construction, and start-up	Part 4 provides general guidance as to how a cleanroom should be designed, constructed and made ready for handing over to the user.	Supports both through laying out the requirements for the design and construction of cleanroom facilities including requirements for start-up and qualification

Table 2.2 ISO 14644 Cleanrooms and Associated Controlled Environments Parts and Overview

Standard #	Title	Overview	Application to Cleanrooms and/or Isolators
14644-5	Operations	Part 5 provides general advice on how to run a cleanroom.	Supports both through requirements for operational systems, cleanroom clothing, personnel, materials and equipment, and cleaning.
14644-6	Vocabulary	Part 6 provides a compilation of all the definitions of terms that are listed in the individual parts of the ISO cleanroom standards	
14644-7	Separative enclosures (clean air hoods, glove boxes, isolators and mini environments)	Part 7 provides information on enhanced clean air devices such as isolators and minienvironments.	Supports isolators by specifying the minimum requirements for design, construction, installation, testing and approval.
14644-8	Classification of airborne molecular contamination	Part 8 provides a classification scheme for airborne concentrations of specific chemical substances (by individual, group or category) and gives test methods.	

Table 2.2 ISO 14644 Cleanrooms and Associated Controlled Environments Parts and Overview

Standard #	Title	Overview	Application to Cleanrooms and/or Isolators
14644-9	Classification of surface particle cleanliness	Part 9 provides a classification scheme and other information on surface particle contamination.	
14644-10	Classification of surface chemical cleanliness	Part 10 provides a classification scheme and other information on surface chemical contamination.	

2.5 ISPE Baseline Guide – Sterile Manufacturing Facilities

The International Society for Pharmaceutical Engineering (ISPE) Baseline Pharmaceutical Guide, Sterile Manufacturing Facilities, was designed to assist pharmaceutical manufacturers in the design and construction of new and renovated facilities that are required to comply with the requirements of the FDA. The guide provides manufacturers assistance with the design, construction, commissioning and qualification of new aseptic or sterile manufacturing facilities.[11] The applicability of this guide will be discussed in additional detail in chapter 3 of this document.

CHAPTER 3

APPLICATION OF THE REGULATIONS, GUIDANCE DOCUMENTS AND STANDARDS TO ASEPTIC PROCESSING TECHNOLOGIES

As stated in Chapter 1, aseptic processing consists of subjecting the drug product, container, and closure to separate validated sterilization processes and then combining all in their final form using aseptic technique in a highly controlled quality environment (i.e. cleanroom or isolator). To ensure this is completed effectively and in compliance with the regulations defined in 21 CFR 210 and 21 CFR 211, guidance documents and standards have been developed to assist manufacturers with the design, control, and maintenance of aseptic processing environments. The following sections provide more detail regarding these when utilizing cleanroom technology versus isolator technology.

3.1 Cleanroom Technology

Cleanrooms are defined as controlled areas that when combined with the facility design and infrastructure, create an environmental envelope for performing aseptic processing operations. This environmental envelope consists of a complex combination of physical rooms and areas which utilize High Efficiency Particulate Air (HEPA) filters to create unidirectional airflow patterns as described in section 3.3.2. In addition, positive pressure is maintained between rooms in conjunction with constant air changes to ensure each room's generated particulates remain within the room as discussed in section 3.3.3. All of these controlled areas operate with constant environmental monitoring (EM) and a qualified sanitization program as defined in section 3.3.8.[12]

3.2 Isolator Technology

The Parenteral Drug Association (PDA) defines an isolator as “a structure that is sealed or is supplied with air through a microbially retentive filtration system (HEPA) and may be reproducibly decontaminated. When closed, it uses only decontaminated interfaces or rapid transfer ports (RTPs) for materials transfer. When open, it allows for ingress and/or egress of materials through defined openings that have been designed and validated to preclude the transfer of contamination by maintaining the pressure gradient at all times. This is done by the isolator’s design, which ensures that the internal amount of pressure created by air exchanges is greater than the exterior of the isolator. The isolator can be used for aseptic processing activities, for containment of potent compounds, or simultaneously for both asepsis (absence of microorganisms) and containment”.[13]

There are two types of isolators: open and closed. Closed isolators are typically used for containment purposes when dealing with toxic materials. They can also be used in aseptic processing when ingress and/or egress of materials are not required. Open isolators are typically used for aseptic filling of finished pharmaceuticals and allow for continuous ingress and/or egress of materials during operation. Although open, the isolator is still maintaining protection over the internal environment through the use of positive pressure and reproducible, validated decontamination cycles. Open isolators are closed during decontamination and then opened during processing.

3.3 Critical Elements for Aseptic Processing

The requirements for cleanrooms and isolators used in the manufacture of sterile drug products are the same in principle. It is about controlling inputs (i.e. materials, personnel, equipment) to get the required output (controlled areas suitable for aseptic processing). Therefore, the requirements for both are taken from the cGMP regulations set forth in the Code

of Federal Regulations at 21 CFR 210 and 21 CFR 211 as discussed in Chapter 2 as well as several key guidance documents and standards which have been developed by different organizations. These are:

- The FDA, in order to aid manufacturers in interpreting the regulations, has issued the Guidance for Industry Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice. This guidance document provides current good manufacturing practice recommendations for manufacturers on how to meet the intent of the regulations as they apply to facility design, equipment suitability, process validation, and quality control.
- The International Organization for Standardization (ISO) 14644-1 Cleanrooms and Associated Controlled Environments provides a standard method for categorizing cleanrooms of any classification (ISO Class 1 – ISO Class 9). While this standard is not a guidance document, it is considered by the FDA as a recognized standard.
- In addition, the International Society for Pharmaceutical Engineering (ISPE) has developed the Baseline Pharmaceutical Engineering Guide for Sterile Manufacturing Facilities. This document covers the engineering aspects of building new sterile manufacturing facilities and modification of existing facilities. This document is not considered an FDA regulation however is useful in the design of such facilities.

In order for a manufacturer to successfully meet the intent of the regulations, guidance documents, and standards, there are essential elements that must be considered when developing an aseptic processing environment, which are illustrated in Figure 13.

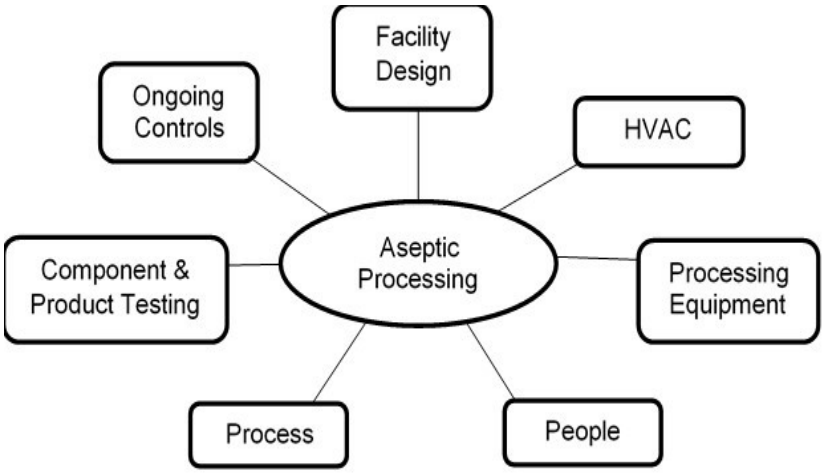

Figure 13. Critical Elements for Aseptic Processing

3.3.1 Aseptic Process - General

For the purpose of this thesis, a filled syringe will be the final drug product. Filling of the syringe using aseptic processing is the step that has the highest likelihood of compromising the sterility of the final sterile product. At this point in the process, the sterile filtered product is filled into the syringe. The containers are then closed by insertion of the plunger. The filling operation is typically the only operation after sterile filtration where the drug product is exposed to the environment. It is for this reason that filling must always be performed in a Class 100/ISO 5 area with unidirectional airflow. Therefore, the airflow volume and direction for the working environment must be properly defined, delivered and controlled to ensure that contamination in the form of viable (contains one or more living microorganisms[14]) and non-viable (does not contain a living microorganism but acts as transportation for viable particles[14]) particulates is not introduced to the filling product. The factors, other than the facility design discussed in section 3.3.2, are:

- The capacity for the cleanroom or isolator as a result of the number of pieces of equipment; and

- The design (construction and functionality) of the equipment which impacts the airflow direction and volumes from the equipment such as fan exhaust, equipment movement, etc.); and
- The number of people and their movement patterns during filling; and
- The amount of product components (how crowded will the physical space become which impacts the airflow patterns)

3.3.2 Facility

Facilities for the manufacture of sterile products must be designed and maintained to minimize the potential for introduction of viable and non-viable contamination into the manufacturing process. The proper design of the facility is determined through consideration of the overall production process along with people and material flows, effective cleaning and decontamination practices, effective maintenance programs, and adequate ventilation including air pressure and volume, temperature, humidity, and particulate and microbial controls. ISO 14644 Cleanrooms and Associated Controlled Environments is the standard commonly used for the design, classification, and testing of cleanrooms and isolators.

Materials of construction

Materials of construction for aseptic processing facilities should be appropriate for the operations occurring in the specific area. In general, materials should be non-shedding and designed to withstand the necessary and extensive sanitization/disinfection processes and allow for the necessary level of environmental control. The surfaces should be durable, smooth and easily cleanable (non-porous). The floors, ceiling and walls should be continuous, such as coved flooring where there is no seam present where the wall meets the floor, with any necessary fixtures flush mounted. Surfaces should not be designed in such a way that would

allow for particulate accumulation or ingress from interior wall areas. Table 3.1 indicates the appropriate types of materials for each technology and finishes based off of area classification.

Table 3.1 Architectural Materials/Finishes Guide [11,13]

Element	Class 100,000/ISO 8	Class 10,000/ISO 7	Class 100/ISO 5 for Cleanroom	Class 100/ISO 5 for Isolator
Floors	Sealed concrete, epoxy coatings, VCT seamless tile, chemically resistant coatings, and terrazzo, capped floor drains	Sheet vinyl and epoxy floor systems, Coved wall bases integral with the floor system, floor drains not permitted.	Sheet vinyl and epoxy floor systems, Coved wall bases integral with the floor system, floor drains not permitted.	304 L or 316 L Stainless Steel
Interior walls	Concrete Masonry Unit (CMU), gypsum board, metal panels (finished with epoxy paint), resinous coatings, metal or PVC type cladding	Gypsum board finished with chemically resistant coatings, sheet vinyl or sprayed on wall finishes, panel systems with metal or vinyl surface finishes, Curved/rounded corners	Gypsum board finished with chemically resistant coatings, sheet vinyl or sprayed on wall finishes, panel systems with metal or vinyl surface finishes, Curved/rounded corners	316 L Stainless Steel for rigid wall, Polyvinyl Chloride (PVC) for flexible wall
Ceilings	Sealed suspended grid systems (Mylar, FRP, metal or other cleanable, nonporous surfaces), gypsum board, metal panels clipped in place to hold room pressure	Gypsum board finished with chemically resistant coatings, sheet vinyl or sprayed on wall finishes, panel systems with metal or vinyl surface finishes, Fixtures (lights and diffusers) flush mounted with no horizontal surfaces exposed below the ceiling, sprinkler heads should be recessed and capped, not caulked.	Gypsum board finished with chemically resistant coatings, sheet vinyl or sprayed on wall finishes, panel systems with metal or vinyl surface finishes, Fixtures (lights and diffusers) flush mounted with no horizontal surfaces exposed below the ceiling, sprinkler heads should be recessed and capped, not caulked.	Fixtures (lights and diffusers) flush mounted with no horizontal surfaces exposed below the ceiling

Table 3.1 Architectural Materials/Finishes Guide [11,13], continued

Element	Class 100,000/ISO 8	Class 10,000/ISO 7	Class 100/ISO 5 for Cleanroom	Class 100/ISO 5 for Isolator
Junction Details (Floor/wall, wall/wall, wall/ceiling)	Coved/splayed integral floor bases suggested, rounded wall/wall and wall/ceiling preferred	Coved and splayed integral floor bases, wall/wall and wall/ceiling covings	Coved and splayed integral floor bases, wall/wall and wall/ceiling covings	Joints should be fully welded, hygienic construction, crack and crevice free
Doors and Windows	Metal with painted finish, FRP in corrosive areas, Windows may be glass, Plexiglas, Lexan® or equivalent. Horizontal surfaces should be easily accessible for cleaning.	Metal, vinyl, PVC, Windows may be glass, Plexiglas, Lexan®, or equivalent, Stainless steel can be used for door, hardware, and kick plates.	Metal, vinyl, PVC, Windows may be glass, Plexiglas, Lexan®, or equivalent, Stainless steel can be used for door, hardware, and kick plates.	Tempered glass, polycarbonate (Lexan®), or acrylic plastics
Hardware	Plated metals or stainless steel	Recessed and concealed, accessible for cleaning, plated metals or stainless steel	Recessed and concealed, accessible for cleaning, plated metals or stainless steel	Stainless steel, gasket material must be compatible with decontamination agents
Gloves/ Sleeves	Not applicable	Not applicable	Not applicable	Hypalon®, Neoprene®

Manufacturing Zones

For aseptic processes used in the manufacture of sterile syringes, very specific environmental conditions are required.[10] A basic element of the facility design to ensure that the appropriate environmental conditions are achieved is zoning or classification of the areas. Zoning consists of implementing defined areas of operation that can be controlled to meet the air quality required for the nature of the operations performed in the particular area.

The air quality is determined by assessing particulate and microbial data during qualification activities which consist of static (non-operational) and dynamic (operational) conditions. The typical classification configuration used in an aseptic processing environment is shown in Figure 14.

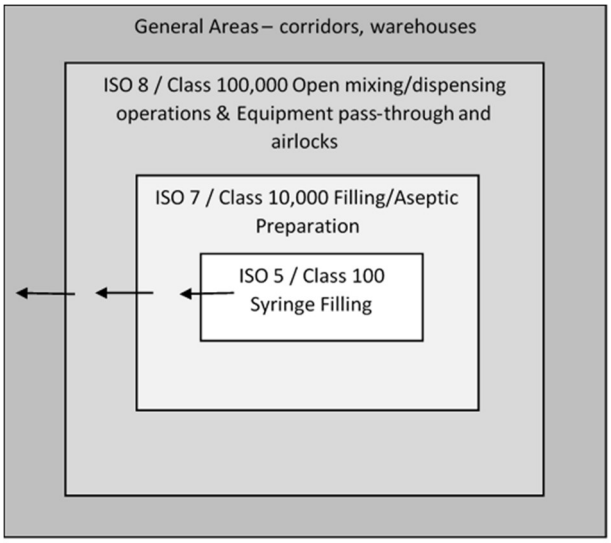

Figure 14. Aseptic Manufacturing Zones

For cleanroom applications, the areas immediately adjacent to the Class 100/ISO 5 areas are considered Class 10,000/ISO 7 and are the background environments for Class 100/ISO 5 aseptic preparation and filling areas. The entire aseptic processing area is surrounded by Class 100,000 /ISO 8 environments which are acceptable for less critical activities such as preparation of solutions that will be sterile filtered, gowning, and equipment cleaning/preparation. For isolator applications, the isolator itself is considered Class 100/ISO 5

and because the isolator is sealed, the surrounding environment is not as critical and is recommended to be Class 100,000/ISO 8.

Air Classifications

The International Organization for Standardization (ISO) 14644-1 Cleanrooms and Associated Controlled Environments provides a standard method for categorizing cleanrooms of any classification (ISO Class 1 – ISO Class 9). While the standard was created to address cleanrooms, the Class 100/ISO 5 air classification has been applied to isolator technology as well. The clean air classifications that are applicable to each zone illustrated in Figure 14, along with the recommended action levels of microbial quality are indicated in Table 3.2 below.

Table 3.2. Air Classifications[a,10]

Clean Area Classification (0.5 µm particles/ft^3)	ISO Designation[b]	≥ 0.5 µm particles/m^3	Microbiological Active Air Action Levels[c] (cfu/m^3)	Microbiological Settling Plates Action Levels[c,d] (diam. 90mm; CFU/4 hrs.)
100	5	3,520	1[e]	1[e]
1,000	6	35,200	7	3
10,000	7	352,000	10	5
100,000	8	3,520,000	100	50

a- All classifications based on data measured in the vicinity of exposed materials/articles during periods of activity.

b- ISO 14644-1 designations provide uniform particle concentration values for cleanrooms in multiple industries. An ISO 5 concentration is equal to Class 100 and approximately equals EU Grade A.

c- Values represent recommended levels of environmental quality. You may find it appropriate to establish alternate microbiological action levels due to the nature of the operation or method of analysis.

d- The additional use of settling plates is optional.

e- Samples from Class 100 (ISO 5) environments should normally yield no microbiological contaminants.

For parenteral manufacturing, those operations which expose the product to potential modes of contamination such as aseptic connections and operator interventions must be performed in Class 100/ISO 5 areas. In these areas, it is important that the product not be put

at risk by exposure to contamination. This is accomplished through multiple environmental controls such as air handling systems, differential pressures and HEPA filtration.

3.3.3 HVAC

The air system contributes to maintaining the pressure differential to ensure room integrity. These systems if not properly designed and maintained cannot maintain room integrity and therefore, can lead to the contamination of the rooms through insufficient pressure differentials or insufficient air circulation for filtration.

The design of the Heating, Ventilation and Air Condition (HVAC) system is critical to the control of classified areas. These systems are complex, extensive and provide the environmental control (temperature and humidity), air exchanges and positive pressure necessary to maintain aseptic conditions. Airflow should be provided through High Efficiency Particulate Filtration (HEPA) filters, should be of sufficient velocity to sweep particles away from critical areas, and should be unidirectional in nature. The ductwork system typically utilizes aluminum or stainless steel (SS304) ducting to provide the supply air to the cleanroom or isolator and to return air to the system. These ducts are located in the interstitial space and are sealed using plasma welding to ensure the system is leak tight. The joints should be angle flanged to allow for limited but necessary movement of the ductwork due to air movement & volume. The design of the filtration system will also typically include the use of pre-filters to filter out particles which are greater than 1.0 micron. These pre-filters are usually located in a separate area with access after the supply air fan discharge to enable cleaning and changing of the filters without disturbing the rest of the filtration system.

Air quality, including airflow, is another critical aspect of the design of the aseptic manufacturing process and both should be designed in order to prevent potential contamination risks. Due to the classifications varying in adjacent areas, it is important that the air quality is

maintained to prevent contamination. In cleanrooms, this is achieved through establishing the proper airflow from areas of higher cleanliness to adjacent less clean areas through the use of differential pressures. Differential pressures provide separation between the classified areas. This is achieved by ensuring that the area has a minimum of 0.05 inches water gauge (12.5 Pascals) between air classes. When defining the differential pressures, items such as the ability to measure the differentials, acceptable changes due to door opening, duration of doors opening and response to pressure alarms should be considered.

In isolators used for aseptic processing, the isolator is maintained at significant overpressure relative to the surrounding environment in order to meet the design requirement of separating the interior environment from the external environment.[11] This high overpressure essentially forms an invisible wall with the external environment. In an isolator designed with an egress hole, the overpressure is maintained significantly above 0.05 inches water gauge (typically 1.0" or more). This overpressure must be supported by data and qualified.[11] Due to the over-pressurization of the isolator, leak testing of the system must be performed prior to sanitization and aseptic processing operations. The nature of the decontamination agent also requires additional ductwork to be installed to safely vent the unit after decontamination. When using an open isolator, the effects of personnel movements and other activities outside of the opening should be considered during the design.

Airflow can be specified either as the average air velocity within the room or as air changes per hour. Both air velocity and air changes are important factors in maintaining the air quality in cleanrooms and isolators. The air velocity is dependent on the level of cleanliness that you want to achieve. The primary objective is to maintain airflow in parallel flow streams that serve two purposes. The first is to dilute particle concentrations that may have formed in the room due to personnel or process activity and the second, to carry away particles or contaminants generated within the room.[15] Air change rate is a measure of how quickly the air in an interior space is replaced by outside (or conditioned) air.[15] The air change rate is an

indication of the air-tightness of a room. The number of air changes must be related to the size of the room, the type and amount of equipment, and the total personnel present in the room during routine production operations in order to maintain the air quality by continuously removing particulates. While there is no clear consensus on an optimum air change rates/air velocity, table 3.3 shows the cleanroom industry design criteria commonly followed.

Table 3.3 Cleanroom Industry Design Criteria [16]

Cleanroom Class	Airflow Type	Avg. Airflow Velocity, fpm	Air Changes per hour
100 / ISO 5	Unidirectional	50-90	300-480
10,000 / ISO 7	Mixed	25-40	60-120
100,000 / ISO 8	Mixed	10-30	10-40

As stated previously, air filtration is accomplished through the use of High Efficiency Particulate Air (HEPA) filters. The filters are typically located in the ceiling, above the work area, and the returns are located at a point much lower in the room. This helps to facilitate the capture of the unidirectional airflow patterns by carrying potential contaminants down and away from the work area. For Class 100/ISO 5 and Class 10,000/ISO7 areas, these filters must meet a minimum efficiency of 99.97% for particulates greater than 0.3 microns in diameter. In addition, they must also pass a leak integrity test using a limit of less than 0.01% leakage of particles. For cleanroom applications in Class 100/ISO 5, there should be 100% HEPA filter coverage of the ceiling in the area. For Class 10,000/ISO 7, this HEPA filter coverage should be 10-15%.[15]

These HVAC systems require extensive testing and maintenance to ensure the quality of the cleanroom environment. If not maintained properly, the effect on the cleanroom can be very detrimental to the quality of the drug product being manufactured. This testing consists of verification of air exchange rates, verification of room pressures, HEPA filter integrity testing, verification that duct leakage is within acceptable limits and demonstrating acceptable airflow

patterns through the use of smoke pattern studies. The testing must reflect the room “at rest” as well at maximum use conditions (people, equipment, and product volume).

Personnel & Equipment Flow

Understanding the people and equipment flows within the aseptic processing area is another important aspect of facility design. The fact that personnel are the largest contamination source in aseptic processes requires that these processes be isolated from personnel access doors and pathways. This is accomplished through the use of gowning and material airlocks, which require ingress of people/materials in order of increasing cleanliness (i.e. ISO 8 > ISO 7 > ISO 5). The personnel and equipment flows should also not allow “backtracking” into areas of less cleanliness and should not cross potentially contaminated pathways. Additionally, the process of gowning which has a distinct order for the steps must be qualified per person on a periodic basis to ensure that this critical control is not compromised. Additionally, this qualification also will detect if the individual has had a change in their personal bioburden level (amount and type of contamination) which can also impact the cleanroom’s ability to control contaminants.

People and material flows, while still important, are not as critical in isolator facility design due to the isolators being fully enclosed and sealed units with HEPA filtered air supplied in a unidirectional manner. They offer complete separation between the drug product and personnel, which provides a more effective aseptic processing environment than the cleanroom. All access by personnel into the isolator is completed through the use of glove ports. Any items introduced into the process are pre-sterilized and introduced using sterile transfer systems such as rapid transfer ports (RTP’s).

3.3.4 Equipment

The equipment used in aseptic processing must be designed in a way to ensure that the equipment does not compromise the production process or contribute particulates and other contamination into the environment. To aid in accomplishing this, ergonomics should be considered in the equipment layout to optimize the comfort and movement of the operators. The location of the equipment in the cleanroom or isolator should also be designed such that unidirectional airflow is not disturbed and horizontal ledges or surfaces that could accumulate dust are avoided. The equipment design should also consider particulate generation, mechanical seal performance, capability to maintain pressure, suitability of connections (i.e. no screw threads), capability to maintain pressure, where necessary, and corrosion resistance. Processing equipment and systems must be equipped with sanitary fittings and valves.[17] For example, ball valves may not be suitable for use in certain applications due to difficulty in sterilizing all surfaces.

For aseptic processes, all product contact equipment and components must be sterilized using a validated process demonstrating a sterility assurance level of 10^{-6} or better.[17] This sterilization can be achieved through filtration, moist heat, and dry heat.

3.3.5 People

Personnel are necessary in aseptic processing to perform required operations. Due to personnel being the main source of contamination in this environment, it is important that the facility ensures that the risk of potential contamination is limited. This is accomplished in part by ensuring that personnel understand the importance of their role in ensuring the safety of the product. Additionally, it is important that personnel who will perform activities within a cleanroom or isolator receive appropriate training and if required, gowning qualification. This training should consist of aseptic technique, appropriate aseptic behavior, basic microbiology,

hygiene, and gowning requirements (if expected to enter classified areas). Upon completion of the initial training, all personnel should participate regularly in an ongoing training program.

Training on aseptic technique should describe the appropriate techniques to utilize to minimize/eliminate potential contamination. These techniques consist of basic methods or behaviors such as the individual having minimal intervention with the process and when intervention is necessary, utilizing sterile tools and/or instruments. Sterile tools should always be used when performing manual interventions during production. These tools should be maintained under Class 100/ISO 5 conditions and maintained to minimize potential contamination. Personnel should move in a slow and deliberate fashion to avoid creating turbulence in the area which they have the potential to disrupt the unidirectional airflow and increase the amount of bioburden in the area from the personnel themselves.

A critical aseptic technique requirement is to ensure that personnel in the area always maintain the concept of “First Air”. This term is used to define the first air that your product contact sterile equipment surfaces, container closures and product should see. When personnel place their bodies in the path of the unidirectional airflow, the disruption of this airflow can pose a risk to product sterility. Although personnel are separated from the process in isolators, the concept of “first air” is still applicable.

Personnel should also have an understanding about behaviors that are appropriate in the cleanroom, isolator, or aseptic areas. These behaviors start with understanding the personnel flow in the area. Personnel should not travel from lesser controlled areas to more controlled areas without taking some measures to eliminate potential contamination. Additional behaviors include minimizing communication (i.e. talking), standing rather than sitting, maintaining glove sterility and minimizing movement (i.e. moving slowly and deliberately). All of these behaviors, when applied consistently, can serve to reduce the potential for contamination being entered into the cleanroom.

Personnel working in aseptic processing environments should also have an understanding of basic Microbiology. This helps personnel to understand the types of microorganisms and their growth requirements, sources of microorganisms (i.e. people, dirt/soil, etc.), the importance of identification, and most importantly the different modes of microorganism transport. Personnel with a basic understanding of microbiology will better understand why using good aseptic technique and following good cleanroom behavior is critical to sterile product success.

Good personal hygiene is also critical for personnel working in a cleanroom environment. Basics of good personal hygiene consist of showering/washing hair daily, wearing clean clothes and washing your hands properly. In addition to the above practices to promote and/or preserve health, 21 CFR 211.28(d) requires personnel to be excluded from contact with product/components if unhealthy.[8] This requires personnel to tell their supervisor if they are ill including colds, flu, stomach issues, rashes, open sores, etc.

The objective of aseptic gowning is to reduce the risk of human borne microorganisms contaminating the aseptic environment. This is accomplished by donning the gown and other sterile garments by handling the item from the inside surfaces only. Personnel must demonstrate the ability to aseptically gown through completion of gowning qualification. Initial qualification programs typically consist of the following:

- an overview of aseptic technique/aseptic gowning; and
- demonstration of gowning procedure by a qualified person, and
- practice gowning under trainer guidance, and
- qualification (typically 3X) with surface sampling, the results of which should be satisfactory prior to entry into the Class 100/ISO 5 and Class 10,000/ISO 7 areas.

Routine qualification should occur on an annual basis with a successful 1X demonstration of gowning by all aseptic personnel.

Personnel should remove all makeup, jewelry, nail polish, etc. prior to initiating gowning activities. A site approved uniform or scrubs should be donned. Hair, including facial hair, should be covered using a hair net or beard cover. Plant dedicated shoes should be worn and hands should be washed with soap and water or other approved hand sanitizers.

Personnel gowning must serve as a barrier between personnel's body and product/materials used in manufacturing. The gowning must be sterile and made of non-shedding materials. Typically gowning will consist of coveralls, hood, boots, mask, goggles and gloves. There must be detailed procedures for proper gowning which include the order in which to gown, overlapping gown components and sanitization of hands and components at each step of the gowning process. Procedures should also include instructions for personnel that if the gown is compromised (i.e. torn or defective) or potentially contaminated, it should be changed immediately.

3.3.6 Process

Aseptic processing operations, whether completed in cleanrooms or isolators, must be validated. This is completed by substituting a growth medium, such as Tryptic Soy Broth (TSB), to product contact surfaces, container closure systems, critical environments, and process interventions to simulate the actual process. This validation process is completed through process simulations (i.e. media fills).

Process simulations must be designed to include those operations or interventions which pose the greatest risk to the product, including worst-case activities. The rationale for these conditions must be clearly defined and documented. The process simulation must include the following elements:

- Factors associated with the longest permitted run on the processing line that can pose contamination risk
- Representative number, type, and complexity of routine interventions that occur with each run, as well as non-routine interventions and events
- Designation of maximum hold times
- Aseptic assembly of equipment
- Number of personnel and their activities
- Representative number of additions or transfers
- Shift changes, breaks, and gown changes
- Aseptic equipment disconnections and connections
- Where multiple units of the same equipment exist, representative units are used for each process simulation, but use of units must be rotated to include all units over a defined period of time
- Aseptic sample collections
- Line speed and configuration
- Weight checks
- Container closure systems
- Specific provisions in written procedures related to aseptic processing[17]

The initial validation of the process, should consist of individual full-length process simulations that must be performed a minimum of three consecutive, successful times to ensure results are consistent and meaningful. After initial validation is completed, routine validation can be performed on a semi-annual basis and should take into consideration shifts and process interventions in order to provide an ongoing evaluation of the state of control of the aseptic process.

Changes or events that have the potential to affect the ability of the aseptic process to exclude contamination from the sterilized product must be assessed to determine if additional process simulations are required. Examples of such changes include facility and equipment modifications, line configuration changes, significant personnel changes, etc. The number of runs is dependent on the scope of the changes made. Major changes may require three separate runs.

The duration of the process simulation must be determined by the time it takes to incorporate manipulations and interventions as well as appropriate consideration of the duration of the actual aseptic operation. Initial validation should, however, cover all operating shifts and represent the full duration of the longest process on the line. If the process utilizes manual filling or closing, or extensive manual manipulations, the duration of each process simulation must be no less than the length of the actual manufacturing process to best simulate contamination risks posed by operators.[17]

The size of the process simulation runs should be based on the contamination risk for the process and must be sufficient to accurately simulate activities that are representative of the manufacturing process. The minimum starting point for run size is between 5,000 and 10,000 units.[17,18] The process simulation should also incorporate the range of line speeds utilized during production.

All integral media filled units using clear containers with identical physical properties to the drug product container should be incubated under conditions appropriate to detect microorganisms that are present in the normal flora of the facility. The incubation time should not be less than 14 days, seven days at 20-25°C followed by seven days at 30-35°C.[17] This is done to optimize conditions for different, but typical contaminants such as yeast and mold. Upon completion of incubation, 100% inspection should be completed on all filled units by qualified personnel. Any suspect units should be brought to the immediate attention of supervision.

The acceptance criteria for assessing the state of the aseptic process control are as follows:

- If filling less than 5,000 units, no contaminated units may be detected. One contaminated unit is cause for revalidation (three consecutive runs) following an investigation.
- If filling 5,000 – 10,000 units, one contaminated unit must result in an investigation, including a consideration of a repeat process simulation. Two contaminated units are considered cause for revalidation (three consecutive runs), following an investigation.
- If filling more than 10,000 units, one contaminated unit must result in an investigation. Two contaminated units are considered cause for revalidation (three consecutive runs) following an investigation.[17]

Process simulations, whether completed in a cleanroom or an isolator, have the same requirements and acceptance criteria to consider the process validated.

3.3.7 Component and Product Testing

Quality Control (QC) testing of products manufactured through aseptic processing consists of environmental monitoring (discussed in section 3.1.4), bioburden testing, and sterility testing. These tests will provide an indication that the process and all of its elements functioned appropriately and will ensure that the product is sterile.

Bioburden Testing

Bioburden must be controlled throughout the manufacturing process. This can be achieved by controlling the environment, incoming materials, and the process to minimize opportunities for microbial growth. Evaluation of the bioburden load contributed by materials and processing must be performed at specified time points, which are determined by potential risk to the product. These time limits, once established, should be controlled and validated for

each phase of aseptic processing, which has the potential to impact bioburden and affects maintenance of sterility. These time limits can include the following:

- The time between washing and sterilization,
- The time between sterilization and the use of equipment,
- The period between the start of product compounding and its filtration, and
- The filtration processes and product exposure while on the processing line.

Sterility Testing

The sterility test is applied to drug products which are purported to be sterile. Sterility testing is carried out for drug products under the guidelines provided in the United States Pharmacopoeia <71>. The sterility test procedures utilized in USP <71> are not by themselves designed to ensure that a batch of product is sterile or has been sterilized. This is accomplished primarily by validation of the sterilization process or of the aseptic process.[19] The tests are limited in their ability to detect contamination due to the small sample size required. A satisfactory result is only indicative that no contaminating microorganism has been found in the sample examined under the conditions of the test.

For sterility testing, each lot of drug product must be tested prior to being released. The samples collected for testing must be representative of the entire process (i.e. beginning, middle and end of fill). Testing should be conducted in a laboratory environment, which is comparable to the aseptic processing facility in order to minimize the possibility of false positive results.

3.3.8 Control and Verification

In aseptic processing environments, control of the areas is typically measured through the use of environmental monitoring (EM) and personnel monitoring (PM). One of the most important indicators of control is the site's environmental monitoring program. The

environmental monitoring program is used to evaluate the effect of the controls (i.e. gowning, etc.) on the manufacturing environment. The program also allows for assessment of the cleanroom, isolator, and other controlled areas. The regulatory guidelines for the environmental monitoring program requirements are found in the FDA Guidance for Industry, the United States Pharmacopeia (USP) <1116>, and the International Organization for Standardization (ISO) 14644. Table 3.4 shows the requirements for the environmental monitoring program per the regulations.

Table 3.4. Environmental Program requirements[20]

Standard	ISO-14644-1	US Aseptic Processing Guidance 2004	USP <1116>
Classification	ISO 5	ISO 5/ Class 100	100
Frequency	Not stated (dynamic assumed)	Each production shift Gloves monitored on a daily basis or in association with each lot. Establish frequency for other gown locations.	Each operating shift
Total Particulate Count	3,520/m^3 (<0.5 µm)	3,520/m^3 (<0.5 µm)	100/ft^2 (.0.5 µm)
	29/m^3 (>5 µm)	Recommends remote counting system	3,530/m^3 (<0.5 µm)

The EM program consists of several components such sample site selection, cleaning/disinfection program, frequency of testing, establishing alert/action limits, and investigations for out of specification results. The sample site selection should consist of sites, which provide meaningful interpretable data. Selection should be based on factors such as where contamination is most likely to adversely affect product, areas where cleaning and sanitization may be difficult, and frequently touched surfaces or equipment. The Environmental Monitoring (EM) should ensure that cleanroom or isolator remains of the quality necessary for manufacture of sterile product.

An appropriate cleaning/disinfection/sanitization program is a vital piece of the EM program and should be developed with the purpose to control microbial contamination. The program should address cleaning/disinfection as it applies to corrective actions as a result of viable and non-viable excursions during EM monitoring. The program should also be used as a method of preventing contamination from entering the cleanroom environment. Cleanroom sanitization/disinfection requires the use of qualified cleaning and disinfection agents. In cleanroom environments, these agents typically consist of phenolics, 70% sterile Isopropyl Alcohol (IPA), Quaternary Ammonium, and Sodium Hypochlorite.

Cleaning and sanitization of isolators is accomplished by using Hydrogen Peroxide (H_2O_2) vaporized through the use of a generator. The generator, which vaporizes the peroxide, uses an automated sequence to inject the peroxide. This sequence requires validation to ensure that it is consistent and repeatable. Although automated decontamination is performed, a manual cleaning of the isolator is still required on a routine basis. Many manufacturing processes can result in residue which, if allowed to accumulate, can mask contamination and make it impenetrable by the decontamination agent. Like in cleanroom applications, the agents used for manual cleaning of the isolator must be qualified and appropriate for the microbial flora of the facility determined during your baseline assessment.

It is important that the selected sanitization/disinfection agents are appropriate for the microbial contaminants recovered within the manufacturing facility during baseline monitoring to establish the normal bioburden and over time as the environment changes (people, equipment, volume and type of work and products, and aging of the physical building structures). The sanitization process, when performed in cleanrooms, requires full sterile gowning of personnel who have been trained in the use of proper aseptic technique.

The EM process consists of viable sampling of surfaces such as walls, floor, equipment and viable and non-viable monitoring of air. Surface sampling should consist of product and non-product contact surfaces. These samples are commonly collected through the use of

contact plates and /or swabs. The method chosen for surface monitoring should be suitable to the surface being sampled. Contact plates have a convex surface and are easy to use when sampling smooth surfaces. Swab samples are used for irregular surfaces and equipment and require additional processing prior to incubation.

Air sampling consists of viable and non-viable sampling of air. Viable air monitoring is critical to monitoring air quality. The sample sites are selected as indicated previously with methods which can be active achieved through inertial impaction or centrifugal force equipment or passive through the use of settle plates. Non-viable sampling for particulates (0.5 and 5 micron) is the basis for the areas classification. Non-viable monitoring should be performed, at a minimum, with each production shift. Continuous monitoring is recommended for ISO 5 areas.

EM must occur during periods when critical operations are being performed where sterile product is exposed to the environment. The required frequency of the monitoring and methods used to perform EM must be specified. The suggested frequency per USP <1116> is outlined in table 3.5.

A program for microbiological assessment of personnel performing cleanroom aseptic operations must also be established. This program consists of initial and on-going qualification as described in the Personnel section of this document. In addition, an on-going personnel monitoring program must be established. Sampling should consist of all personnel who are present where sterilized product or components are exposed. Monitoring must occur at least once per day or in association with each batch by obtaining glove and gown monitoring samples. The gown sample sites should be selected through an assessment of where the operator's movements are most likely to result in contamination (i.e. chest, forearms, etc.). Prior to sampling, gloves should not be sanitized as sanitization can prevent recovery of microorganisms that may have been present when performing aseptic tasks.

Table 3.5: Suggested Frequency of Sampling for Aseptic Processing Areas[21]

Sampling Area/Location	Frequency of Sampling
Critical Zone (ISO 5 or better)	
Active Air Sampling	Each Operational Shift
Surface Monitoring	At the end of the operation
Aseptic Area adjacent critical Zone	
All Sampling	Each Operating shift
Other nonadjacent aseptic areas	
All Sampling	Once per day

A personnel monitoring program is not required for isolator operations as the gowning for personnel working in isolators meets the requirements for the classification of the area surrounding the isolator (i.e. ISO 8). Gowning typically would consist of a coverall over a plant uniform, hairnet, shoe covers, beard covers (if applicable), and gloves. Some facilities may require the use of double gloves prior to entering the isolator gloves as a best practice.

For the environmental monitoring and personnel monitoring programs, the appropriate required alert and action levels must be established. These levels must be established based on historical data but should not exceed the levels set forth in the applicable regulatory requirements. Excursions resulting from an exceeded alert and action level must be evaluated for its impact to the operations.

In reading through Chapter 3, one can see that the guidance documents and standards can be applied to both cleanroom and isolator technologies. Although applied somewhat differently, they provide manufacturers the necessary details to assist with the design, control and maintenance of these aseptic processing environments.

CHAPTER 4

COST ANALYSIS OF ASEPTIC PROCESSING TECHNOLOGIES

As discussed in Chapter 3, there are differences when comparing cleanroom technology and isolator technology for maintaining sterility assurance. These differences are shown in Table 4.1.

Table 4.1. Comparison Isolator/Cleanroom for Aseptic Manufacturing

Element	Isolator	Cleanroom
Facilities (Manufacturing Zones)	Class 100/ISO 5 (for interior of Isolator) & Class 100,000/ISO 8 (for external) environments required	Class 100/ISO 5 (for interior of Cleanroom), Class 10,000/ISO 7 background environment, & Class 100,000/ISO 8 external environment required
Personnel & Equipment Flow	Complete separation of drug product and personnel, very low risk of contamination	Personnel present in the area, higher risk of contamination
	All personnel access is through glove ports and equipment is pre-sterilized and introduced through rapid transfer ports (RTP's)	Requires airlocks from lesser to higher classification for introduction of personnel and materials
People	Aseptic technique not as critical but still required	Well executed aseptic technique is critical
	Class 100,000/ISO 8 gowning required	Class 100/ISO 5 cleanroom gowning required
Control and Verification	Personnel Monitoring not required	Personnel monitoring of personal bioburden, gloves and gown required
	Decontamination performed with vaporized hydrogen peroxide (VHP)	Disinfection/Sanitization performed using qualified agents
Sterility Assurance Level (SAL)	SAL 10^{-6}	SAL 10^{-3}

Although there are clear advantages for sterility assurance regarding isolator technology, there are also initial capital and operating costs that must be considered by a start-up parenteral facility. These include initial equipment (syringe filler and facility), validation, and operating

costs. Evaluation of the costs associated with the two technologies has been performed by many companies. A comparison performed by Ferreira, et al. presented at the ISPE annual meeting in 2009, compared the initial capital and operating costs for aseptic manufacturing facilities utilizing cleanroom and isolator technology.[21] For the purpose of the evaluation, a model process facility was designed to aseptically fill biopharmaceutical products. The basis of the model consisted of a single formulation area serving two filling lines; one for liquid and lyophilized vials, and a second for liquid syringes.[21] For the purpose of this cost analysis, focus will be on the costs of the filling for liquid syringes.

Design of Comparison Evaluation

For the evaluation, an equipment list and a conceptual layout were developed for cleanroom and isolator technology selections to serve as a basis for cost comparison. Each of the unit operations were estimated separately and can be viewed as a stand-alone operation. In order to understand the full impact of each technology selection, the analysis took into consideration the following:

- support areas such as parts preparation,
- sterilization, and
- clean utilities were considered in the analysis.

The total cost comparison for each technology option consisted of other costs including:

- support facilities,
- validation cost, and
- operations cost was included.

As mentioned in chapter 3, aseptic filling of syringes, whether performed in a cleanroom or isolator, must take place in a Class 100/ISO 5 environment to protect the product from particulate and microbiological contamination. For the cost analysis, a common application

used in existing facilities of an integrated syringe filling line running approximately 300 units/min on nested 1 mL presterilized syringes was used as the basis for the evaluation.[21] Plungers are supplied in bags as RTS (ready to sterilize). Once autoclaved, the bags of sterilized components are transferred to the filling line. The following assumptions were made as part of the evaluation:

- Wetted path components (those exposed to product) are cleaned and sterilized external to the aseptic filling environment.
- Syringes will be received presterilized by gamma-irradiation, ready to use (RTU), inside packed tubs (100 syringes/tub).
- Syringe tubs will be loaded onto the filling line via different technologies.[21]

Filling of the syringes in a cleanroom consists of the following:

- racks of presterilized syringes would enter from a lesser controlled Class 100,000/ISO 8 (at rest), into a Class 100,000/ISO 8 material staging room,
- the tubs are placed into gravity conveyors that transfer the tubs into the Class 10,000/ISO 7 fill room, and
- once inside the Class 100/ ISO 5 area, the tub is manually placed into the filling line and syringe filling begins.

Filling of the syringes in an isolator consists of the following:

- Syringe tubs are placed in an e-beam sterilizer for surface sterilization prior to automatically entering the isolator enclosure for the filler, which provides a Class 100/ ISO 5 environment,
- RTP bags containing presterilized plungers are docked to the isolator to allow for the plungers to be manually dumped into the hopper, and
- Inside the isolator, product syringes are filled, plungers inserted, and then the syringes are replaced into the tubs.

Comparison of Cost

The cost comparison for the aforementioned filling lines consisted of:

1. initial capital for facility and equipment design and construction,
2. validation, and
3. general operating costs.

Initial Capital

For the evaluation of the filling design mentioned above, table 4.2 illustrates the relative core facility sizes and table 4.3 illustrates the costs for each of the technology selections.

Table 4.2. Syringe Filling Area[21]

Area Classification	Cleanroom	Isolator	
	Size (base case)	Size	% of Base
Class 100/ISO 5	430 ft^2	Via isolator	NA
Class 10,000/ISO 7	1840 ft^2	0 ft^2	0
Class 100,000/ISO 8	1210 ft^2	2190 ft^2	181
Class 100,000/ISO 8 (at rest)	100 ft^2	100 ft^2	100
Total	3580 ft^2	2290 ft^2	64

Table 4.3. Syringe Filling Costs[21]

Direct Costs	Cleanroom	Isolator	
	Cost (Base case)	Cost	% of Base
Equipment	$3,421,000	$7,907,000	231
Facility	$3,395,000	$1,941,000	57
Total	$6,816,000	$9,848,000	144

These tables indicate that the isolator facility core design costs are significantly higher with equipment costs being 231% of the base cost of a cleanroom core facility. This increased cost is due to the initial capital costs required for the isolator equipment.

The costs for the support areas of the facility were also evaluated. The support area costs were based on the following:

- plunger handling,
- cleaning and preparation of filler wetted path components,
- RTP canister handling and utility systems.

The following assumptions were made for the support facility costs:

- Plunger handling consisted of the use of component processors to wash, sterilize, and dry the plungers.
- The plungers are transferred into a RTP canister for component delivery to the filling line.
- Cleaning and preparation of filler-wetted path components must be removed from the filling room for cleaning, wrapping, and sterilization.
    - For a cleanroom, the filler-wetted components are washed, wrapped under HEPA filtration (i.e. unidirectional hood), and autoclaved.
    - For an isolator, all filler-wetted components must exit the autoclave in an RTP or a sealed autoclave bag.
- The costs of lifts and transfer carts were included.

For the evaluation of the support facility areas above, table 4.4 illustrates the relative facility sizes and table 4.5 illustrates the costs for each of the technology selections.

Table 4.4 Support Facility Areas (Equipment Wash/Preparation Areas)[21]

Area Classification	Cleanroom	Isolator	
	Size (base case)	Size	% of Base
Class 100/ISO 5	350 ft^2	0 ft^2	0
Class 10,000/ISO 7	440 ft^2	0 ft^2	0
Class 100,000/ISO 8	930 ft^2	1530 ft^2	165
Class 100,000/ISO 8 (at rest)	930 ft^2	930 ft^2	100
Total	2650 ft^2	2460 ft^2	92

Table 4.5. Support Facility Costs[21]

Direct Costs	Cleanroom	Isolator	
	Cost (Base case)	Cost	% of Base
Equipment	$2,888,000	$2,998,000	104
Facility	$2,178,000	$1,888,000	87
Total	$5,066,000	$4,896,000	97

While table 4.3 showed that there were higher costs associated with the initial capital for the filling isolator, table 4.5 indicates that costs required for the support facilities are reduced when compared to cleanroom applications.

Validation

Validation consists of commissioning and qualification of the facility or isolator and the equipment followed by validation of the various processes that control the environment, clean the facility and equipment, and the filling and sealing process. All of these are impacted by the selection of the technology a manufacturer chooses to use. For the cleanroom, the filling machine will be checked for basic functionality at the factory and then verified by the site. As discussed in chapter 3, the filling room is required to meet Class 100/ISO 5 classifications. Due to the manual nature of the process, the following must be completed:

- An environmental monitoring program which satisfies the requirements of ISO 14644-1 must be developed for Class 100/ ISO 5 and Class 10,000/ ISO 7 areas,
- HEPA filters must be certified,
- A cleaning and sanitization program must be developed for the facility,
- Standard operating procedures (SOP's), test protocols for qualification, and training program for operators must be developed.

For the isolator, the equipment is more complex and requires more testing at the factory. In addition, once received on site and installed, there is site acceptance testing (SAT) that is required. The validation of the isolator filling line is somewhat more complex as it is supplied with separate air handling equipment and is designed for automatic decontamination. The air system is tested for functionality including pressure control, temperature control, air distribution, and leak tightness. In addition, smoke testing needs to be conducted. Testing and qualifying the VHP delivery system (i.e. generator) must be performed. This testing includes cycle development to develop the cycle that will allow for adequate gas distribution. The gas distribution is proven through the use of chemical indicators. In addition, aeration studies are required to ensure residual peroxide is removed prior to starting operations. The cycle is proven effective through the use of biological indicators.

The costs associated with validation of cleanroom versus isolator technology are shown in table 4.6.

Table 4.6 Validation Cost Impact [21]

Direct Costs	Cleanroom	Isolator	
	Cost (base case)	Cost	% of Base
IQ/OQ Isolator/Decontamination System	$0	$150,000	NA
PQ Decontamination	$0	$300,000	NA
Facility Qualification	$200,000	$0	0
Total Cost	$200,000	$450,000	225

The costs relative to the IQ/OQ/PQ for the isolator are significantly higher for the isolator. This is due to the isolator technology requirements for testing and qualification of the equipment whereas for a cleanroom, only testing of the facility is required (i.e. HVAC, cleaning/sanitization program).

Operating Cost

While the initial capital costs associated with the syringe filler, support facility, and validation are higher for the use of isolator technology, the operating costs have the greatest, long-term cost impact. After the initial facility (cleanroom or isolator) qualification is complete and the facility is operational, there are continuing costs associated with the following:

- utilities,
- personnel gowning,
- testing and revalidation, and
- maintenance

For the operating cost analysis, data presented by Edwards and Chester, presented at ISPE 2006 was used.[21] This included representative costs for gowning, testing, revalidation and utilities were used. The calculations were based on the following assumptions:

- Two filling lines were running in a single shift;
- Lines were running 5 days a week for 45 weeks;
- Utilities are required year round;
- Gowning for supervision and cleaning staff were not included;
- Glove testing was based on weekly replacement with leak testing required; and
- Thirty-six (36) gloves were maintained.

Based on the assumptions above the annual operating costs are summarized in table 4.7.

Table 4.7. Annual Operating Costs [21]

Direct Costs	Cleanroom	Isolator	
	Cost (Base case)	Cost	% of Base
Aseptic gowning	$300,000	$0	0
Glove Testing	$0	$150,000	NA
Annual Revalidation			
HEPA recertification	$25,000	$0	0
Gas (VHP) System	$0	$30,000	
Environmental Monitoring	$2,700,000	$1,400,000	52
Utility Costs	$1,171,000	$511,000	44
Total	$4,196,000	$2,091,000	50

Once the annual operating costs were determined, the data was used to project the total operating costs for a ten-year facility life. The impact of this cost is shown in table 4.8.

Table 4.8. Facility Costs [21]

Direct Costs	Cleanroom	Isolator	
	Cost (Base case)	Cost	% of Base
	$41,960,000	$20,910,000	50

The annual operating costs for isolators are reduced due to the isolator being located in a Class 100,000/ ISO 8 environment where aseptic gowning is not required. The focus shifts to isolator gloves and consists of glove integrity testing and routine glove change procedures.

As a result of this cost analysis, it can be seen that when adding overall operating costs to the analysis, the isolator moves from being the most costly technology to the least costly, when compared to a cleanroom. The increased level of sterility assurance associated with isolators comes at the expense of the initial capital costs. However, this cost is offset over the life of the facility through the reduced annual operating costs.

A summary of the cost analysis for cleanroom versus isolator technology and which items are more cost effective are shown in table 4.9.

Table 4.9 Summary of Cost Analysis

Cost Element	Cleanroom	Isolator	Comments
Initial Capital - Filling Machine	√		Cleanroom saves >$3 Million
Initial Capital - Facility		√	Cleanroom costs ~ $170K
Validation	√		Cleanroom saves ~ $250K
Operating Costs			
Gowning		√	Cleanroom costs ~ $300K
Glove Testing	√		Cleanroom saves ~ $150K
Utilities		√	Cleanroom costs ~ $660K
Annual Revalidation	√		Cleanroom saves ~ $5K
Environmental Monitoring (including personnel monitoring)		√	Cleanroom costs ~ $1.3 Million

As indicated in the table, the initial capital costs for an isolator versus a cleanroom are significantly higher with cleanroom technology saving approximately $3 million. It is for this reason that a manufacturer considering isolator technology should carefully consider all options. While the initial capital investment is significant, the overall operating costs associated with isolators are significantly lower (approximately $2.3 million) and can essentially be recovered over the life of the facility.

CHAPTER 5

METHODOLOGY AND RESULTS

5.1 Methodology

Purpose

The purpose of this thesis was to collect and systematically analyze the information about aseptic processing utilizing cleanroom technology versus isolator technology in support of the thesis that for small start-up parenteral facilities the isolator technology is superior when compared relative to cost and sterility assurance outcomes. A study was conducted comparing cleanroom and isolator aseptic processing technology. The research was comprised of three different analyses; a literature review of regulations, guidance documents, and standards, a review of costs analysis data, and a survey of experts to obtain opinions from experienced professionals about aseptic processing and the use of cleanrooms and isolators.

Parameters

For the purpose of this thesis, a small start-up parenteral facility was defined using the following points:

- Organizational size of <500 employees,
- New facility being designed, and
- Product is a new launch for a sterile injectable.

The criteria for the costs comparisons included:

- facility and equipment design and construction,
- qualification and validation activities, and
- general operating costs to include utilities, personnel gowning, testing and revalidation, and maintenance.

The criteria for the advantages of isolator technology included:

- sterility assurance
- ease of use, and
- application of the guidance's.

For the first part of the analysis, a literature review was conducted to collect information on regulations, guidance documents, and standards applicable to aseptic processing utilizing cleanrooms and isolators. Current Good Manufacturing Practices, 21 CFR 210 and 21 CFR 211 were reviewed to determine the regulations required for aseptic processing. The Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing was reviewed to describe the FDA's current thinking on sterile drugs produced by aseptic processing. In addition, various standards and guides, such as ISO 14644-1 and ISPE's Baseline Pharmaceutical Engineering Guide for Sterile Manufacturing Facilities, were also reviewed and provided useful details about classification of cleanrooms and their design. Internet research was also conducted on journals, engineering standards, and published materials which provided information regarding aseptic processing. For the second part of the analysis, a review of cost analysis data was reviewed from the literature and various presentations from conferences within the pharmaceutical industry.

Survey Design and Validation

The third part of the analysis consisted of collecting opinions of experienced professionals with knowledge of aseptic processing and the use of cleanrooms and isolators through the use of an Internet survey. In order to conduct the survey, approval was received by the Institutional Review Board (IRB) from the University of Georgia in compliance with Title 45 Code of Federal Regulations Part 46. The approval for the study was granted on July 6, 2015, under the IRB ID STUDY00002250.

A survey was developed to ask questions of professionals experienced in aseptic processing on the use of cleanroom technology and isolator technology. The survey was conducted with individuals who met the inclusion criteria of the study. The inclusion criteria required that the participants were:

- Professionals knowledgeable and experienced in aseptic processing using cleanrooms and isolators.

The total population included individuals from:

- Former FDA,
- Industry experts (based on professional credentials, publication background, past corporate experience),
- Internal industry experts responsible for sterilization/aseptic processing,
- QC personnel responsible for environmental monitoring, bioburden, etc., and,
- Others such as project engineering, regulatory consultants, and technical advisors.

The first questions within the survey were created to screen the participants for demographics such as current position, number of years' experience (education and working) with aseptic processing, knowledge of cleanroom technology and requirements, and knowledge of isolator technology and requirements. The survey was designed to eliminate in the initial screening, any participants who either:

- Did not consider themselves knowledgeable about cleanroom technology and requirements, or
- Did not consider themselves knowledgeable about isolator technology and requirements.

The remaining questions were used to gain knowledge on participants' opinions on the use of aseptic processing in cleanrooms versus isolators.

An assessment of the Internet survey tool Qualtrics was performed in order to determine if it would be suitable for the survey. The tool needed to be accessible through the internet, and

provide security of the participant's information. Based on these criteria, Qualtrics was used to develop and distribute the survey.

The survey was validated by using five (5) participants to answer the validation questions. The participants, which had knowledge and experience with aseptic processing, included individuals from:

- Quality Control
- Quality Assurance
- Internal industry experts responsible for validation and engineering

The number of participants was based on Juran's[23] concept of a minimum of 5 data points to establish a concise summary of the distribution of observations. The validation questions were designed to ensure that the survey questions were understood and not leading or biased. The survey consisted of 26 questions for each respondent with some questions having subsections. The first four questions were designed to screen the participants to determine the population characterization and the participants' knowledge in both cleanroom aseptic processing and isolator technology processing. For validation, this portion required completion and verification that the questions were appropriately definitive to achieve these purposes. The remaining 22 questions, were designed to challenge the identified parameters that were being measured as previously discussed in this section. The questions were designed to result in binomial data points to remove any ambiguity in the respondents' answer. The validation questions consisted of a total of twenty-two questions for each respondent for a total of 110 responses. The success criteria were set at 90% for the remaining 110 responses. Of the 110 responses, 106 met the predefined response criteria equaling 96.3%, therefore the validation passed. Of the four responses answered as no, minor wording clarifications were made to the survey to better define/clarify the question.

The first page of the survey was for the informed consent; if the participant answered that they did not agree to participate, the survey ended. Responses were received in real time and saved in the Qualtrics system. The Qualtrics survey tool provided a reporting section with statistical analysis tools for use in analyzing the data, however, the choice was made to download the data into Excel® for ease in analysis.

Per the study protocol, if any data was collected from individuals who later decided to withdraw from the study, that data would be collected, up to the point of withdrawal, and kept as part of the study and continued to be analyzed. No participants in the survey requested the removal of their data or participation. Anonymity was maintained for the participants in the survey as no personal or identifiable information about the participants was collected. The raw data will only be visible to the principle investigator and researcher and the results were only provided in summary form for the thesis.

Sample Size

The sample size was set at 20 with a requirement of a 90% participant response factor. The criteria for determining the sample size was established based on the binomial probability with an error rate of 20%, where if 16 participants agreed then the results would be detectably different than strictly chance. Former FDA personnel were approached for participation based on their knowledge of the regulations and industry expertise. Industry experts (external and internal) were approached based on their expertise. Other participants such as QC, project engineering, technical advisors, and regulatory consultants were approached based on their working knowledge of environmental monitoring, testing, and facility design. The sample size reached the researcher's requirement of a participant response factor of ≥ 90%.

5.2 Recruitment

Recruitment began on July 6, 2015. Experienced professionals contact information was obtained through professional networks and through public record review (such as industry publications, web pages, etc.) and through various industry contacts such as consulting companies. Industry and subject matter experts were contacted via telephone or email and asked about participation. Once they agreed, the approved survey was emailed to the individual through the use of or Qualtrics. The survey was made available for 3 weeks. At the end of the data collection period, the survey was closed and final data were extracted. At the end of the recruitment period, there were 20 respondents (100% response) to the survey

5.3 Data Analysis

The data from the literature review and survey was evaluated for the cost comparison. The literature review consisted of current FDA regulations, guidance documents, applicable standards, technical journals, and published literature. The information taken from the literature review is represented in detail in Chapters 2, 3, and 4.

The survey results were analyzed to determine if the responses supported the hypothesis of the isolator being the superior technology using the identified parameters in section 5.1. Within each parameter, the data was further analyzed to determine if an individual's demographics potentially influenced their responses.

By combining the literature review, cost comparison, and survey results, this study intended to answer the original questions as to the superiority of isolator technology. The answers were based on advantages of isolators for sterility assurance, ease of use, and application of the regulations. In addition, isolator cost effectiveness was based on facility and equipment design and construction, qualification and validation activities, and general operating costs to include utilities, personnel gowning, testing and revalidation, and maintenance.

5.4 Results

Following the execution of the study, the data were compiled from the literature research, cost analysis, and survey responses. The following provides the results for each of these components of the research study.

Literature Review Results

A literature review was conducted to answer the question of isolator technology superiority compared with cleanroom technology for aseptic processing. Current Good Manufacturing Practices, 21 CFR Part 210 and 21 CFR Part 211, FDA Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing, ISO 14644-1, and ISPE's Baseline Pharmaceutical Engineering Guide – Sterile Manufacturing Facilities were reviewed to determine the requirements for a manufacturer who uses aseptic processing.

The FDA documents, 21 CFR 210 and 21 CFR 211, provide the requirements for a drug manufacturer who intends to manufacture commercial drugs for human use. These documents establish what drug manufacturers need to do, but not how they need to do it. Current Good Manufacturing Practice, 21 CFR 210 addresses the general requirements for manufacturing, facilities, and controls for the manufacturing, processing, packaging, and holding of a drug product. Current Good Manufacturing Practice, 21 CFR 211 covers all aspects of operations. It is general in nature to allow the manufacturer flexibility due to the variation of products and their specific manufacturing, packaging, and storage requirements. The various subparts which support aseptic processing through the use of cleanroom and/or isolator technology are shown in Table 2.1 of this thesis.

To assist manufacturers in interpreting the broadly defined 21 CFR 210 and 21 CFR 211 documents, guidance documents and standards have been developed to assist manufacturers in meeting the requirements for aseptic processing. The most widely used guidance document is the FDA Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing. This guidance document describes the FDA's current thinking on aseptic processing and provides

the manufacturer recommendations on how to meet the intent of the regulations. The International Organization Standardization (ISO) developed standard ISO 14644 Cleanrooms and Associated Controlled Environments, which addresses important issues such as classification, design, testing, operation and biocontamination of cleanrooms. Each of these documents provides the manufacturer with useful information regarding facility design, classification, qualification, and operation for the implementation of aseptic processing technologies.

The review of these documents indicated that isolator technology has the following advantages when compared to cleanrooms:

- Significantly increased sterility assurance levels,
- Complete separation of personnel from drug product,
- Decreased facility footprint and less stringent background classifications,
- Decreased levels of personnel gowning, and
- Validated decontamination (VHP) cycles.

Cost Analysis of Aseptic Processing Technologies Results

Cost analysis data was collected from literature and various presentations from conferences within the pharmaceutical industry. Industry opinions on the cost of cleanroom and isolator technology were also collected through the Internet survey of experienced professionals. The cost analysis, described in detail in chapter 4, demonstrated that when considering overall operating costs, the isolator moved from the most costly technology to the least costly, when compared to a cleanroom.

Aseptic Processing Industry Responses

Demographics of Industry Participants

Twenty experienced professionals provided their opinions on aseptic processing using cleanrooms versus isolators. Figure 15 depicts the participants' current position within the industry.

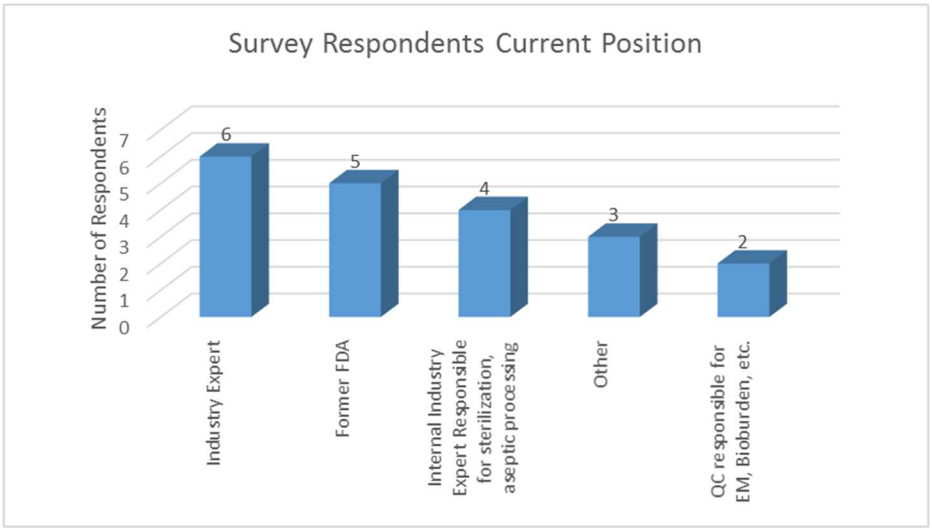

Figure 15. Survey Participants Current Position

Three participants selected other as the description of their current position. These individuals consisted of the following: a project engineer responsible for the design/delivery of new isolator based formulation/fill facility, a regulatory consultant that has worked within the sterile industry in the past, and a technical advisor, including sterility assurance, for veterinary vaccines.

To determine the participants' experience (education and working) with aseptic processing, the survey requested the number of years' experience of each participant. Figure 16 summarizes the responses with regards to years of experience with aseptic processing.

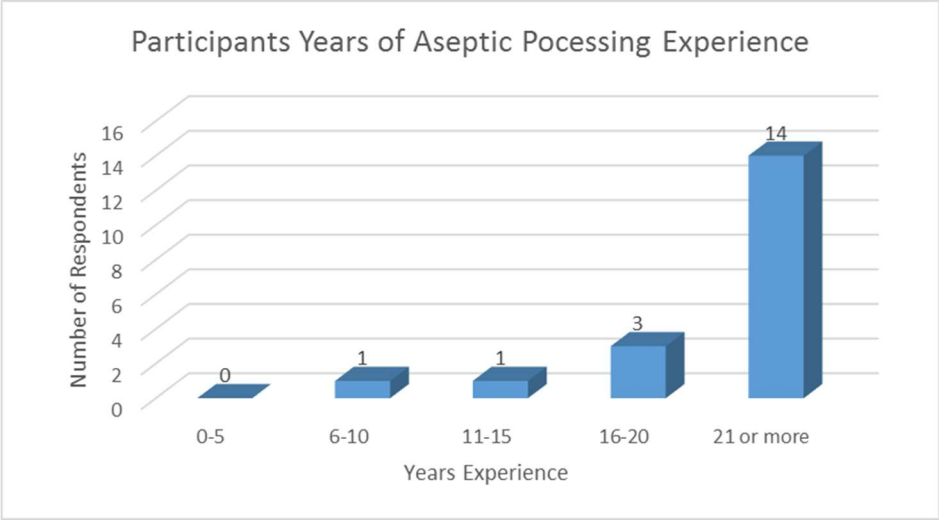

Figure 16. Participants Years of Experience with Aseptic Processing

Of note was that 70% (14) of the participants had 21+ years of experience, which indicated approximately 294+ combined years of aseptic processing experience. The demographics of these participants indicated a wide range of job responsibilities, which translated into a population whose opinions were representative of all aspects of aseptic processing as shown in Figure 17.

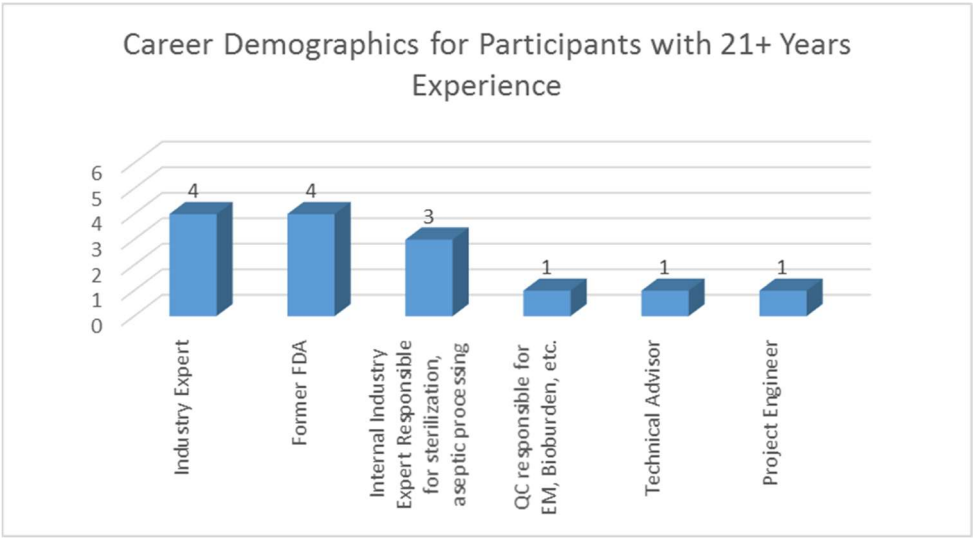

Figure 17. Participants Demographics for 21+ Years of Experience

For the participants to be able to complete the survey, it was required that they be knowledgeable about both cleanroom and isolator technology. Questions 3 and 4 of the survey were designed so that if any participant did not consider themselves knowledgeable about either technology, the survey would end. Of the twenty participants, all considered themselves knowledgeable about both technologies and their requirements as shown in Figure 18.

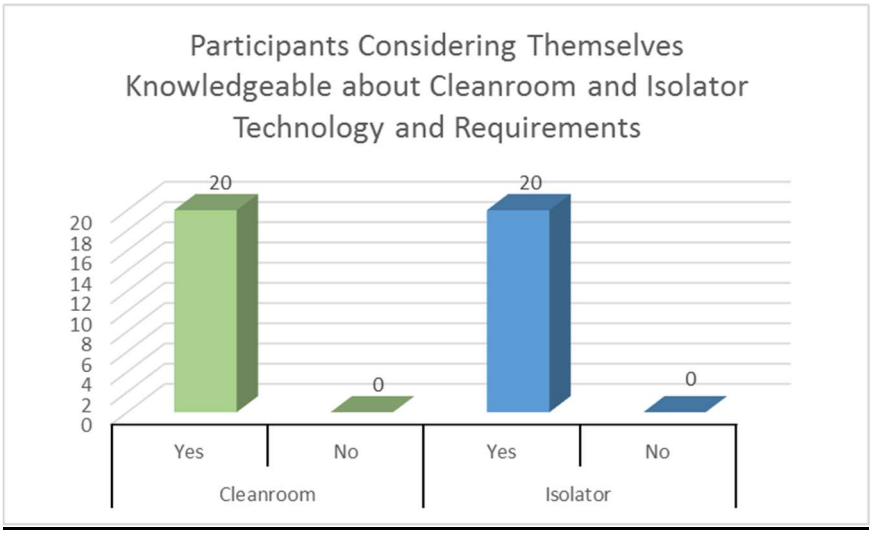

Figure 18. Participants Considering Themselves Knowledgeable about Cleanroom and Isolator Technology and Requirements

Cost Effectiveness of Isolator Technology

Five of the survey questions were designed to obtain the participants' opinions on the costs associated with cleanroom versus isolator technology. The survey data was used to support the hypothesis that the use of isolator technology is more cost effective for use by a small, startup parenteral facility and thus, is the superior technology. The results were based on facility and equipment design and construction, qualification and validation activities, and general operating costs to include utilities, personnel gowning, testing and revalidation, and maintenance.

Facility and Equipment Design

Survey questions 10 and 11 obtained the participants' opinions on costs associated with facility and equipment design when comparing cleanrooms versus isolators. These aspects consisted of the following:

- Facility footprint
- Classification of background environment for isolator

Survey question 10 asked participants if they felt that isolators reduced the facilities' footprint (amount of space within the facility) when compared to a cleanroom. Figure 19 shows that 75% (15) of the participants felt that isolators reduced the facilities' footprint when compared to a cleanroom, while 20% (4) of participants did not.

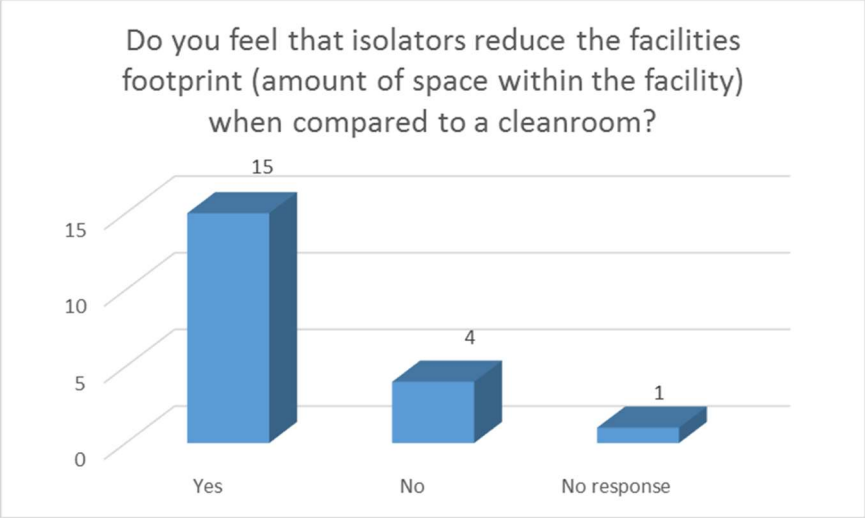

Figure 19. Participants' Opinions on Isolators Reducing the Facility Footprint

Survey question 12 asked participants if they felt that a Class 100,000/ISO 8 classification background is sufficient for the area surrounding an isolator. Figure 20 shows that 70% (14) of participants felt that the Class 100,000/ISO 8 background was sufficient for the area surrounding an isolator, while 30% (6) did not.

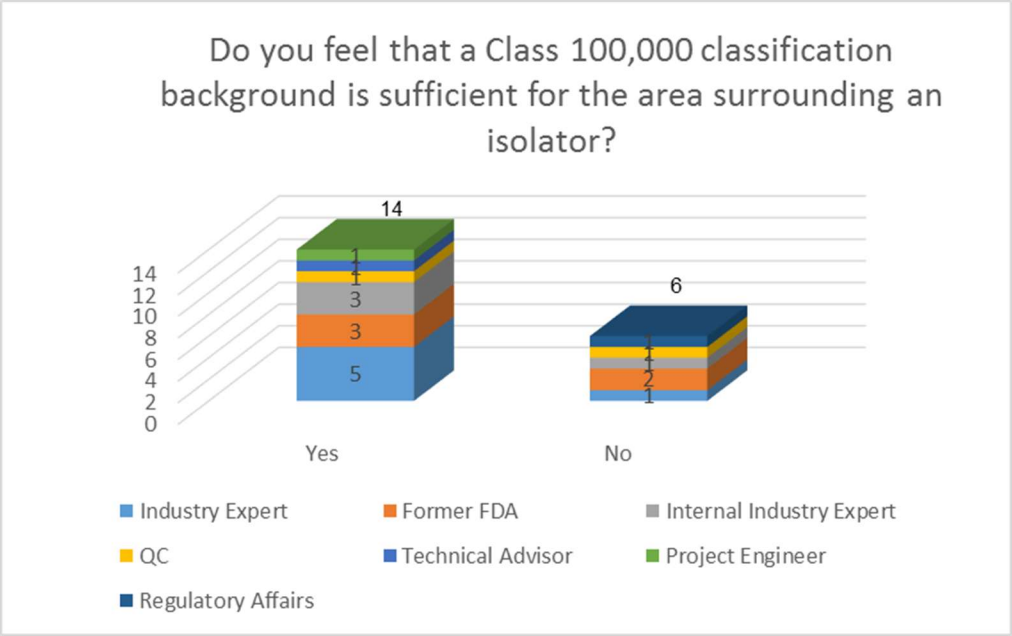

Figure 20. Participants' Opinions and Demographic Breakdown on Class 100,000/ISO 8 Background for an isolator.

The opinions of those surveyed were higher when considering the facility design aspects of facility footprint and classification. The industry opinions further support the literature review (chapters 3 and 4) which indicated the following:

- the square footage required for the syringe filling and support areas for isolators was less than required for cleanrooms, and
- the Class 100,000/ISO 8 background is sufficient for the surrounding environment for isolators.

Decreased facility footprint and lower background classifications lead to decreased square footage required for the facility and therefore lower costs saving $170K. This supports the hypothesis that the isolator is more cost effective when compared to cleanrooms due to the design and engineering requirements.

Qualification and Validation Activities

Survey question 11 was designed to obtain the participants' opinions regarding the qualification duration of isolators versus cleanrooms. Participants were asked if they felt that the qualification duration of isolators was similar to that of cleanrooms. Figure 21 shows that 70% (14) of participants indicated that they felt the qualification duration of isolators was similar, while 30% (6) did not.

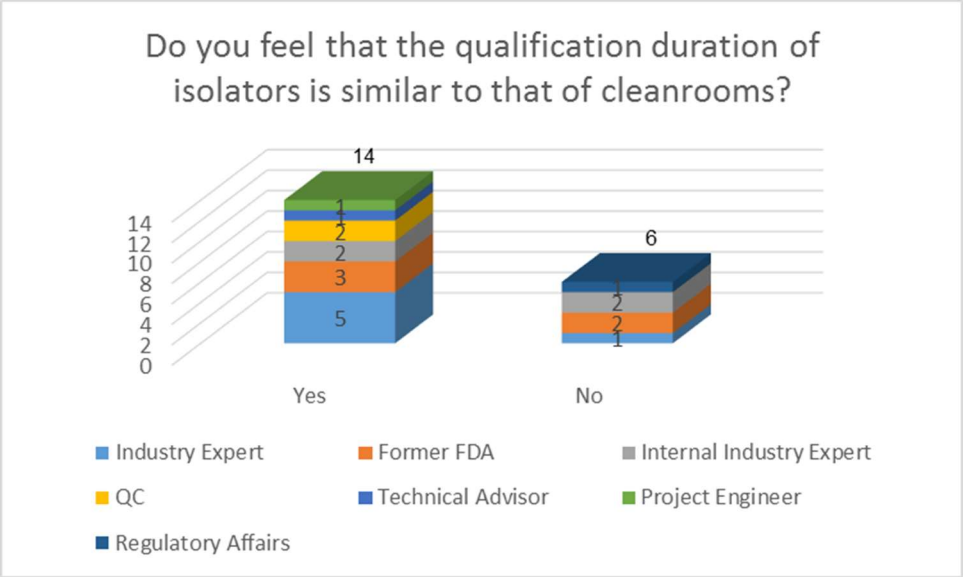

Figure 21. Participants' Opinions and Demographics on Qualification Duration of Isolators Being Similar to that of Cleanrooms

The similar qualification duration is further supported by literature which indicated that the qualification duration for cleanrooms and isolators is typically 6-9 months.[24] While the qualification duration of the technologies is similar, the costs associated with qualification are not. The cleanroom costs for qualification, as indicated in chapter 4, are approximately $250K less than the costs for isolators. The cost difference is due to the isolator technology requirements for testing and qualification of the equipment, whereas for a cleanroom, only testing of the facility is required.

Operating Costs

Survey questions 9 and 13 were designed to obtain the participants' opinions on operating costs when comparing cleanrooms versus isolators. These aspects consisted of the following:

- General operating costs
- Productivity

Survey question 9 asked participants if they feel that isolators have lower operating costs when compared to cleanrooms. Figure 22 shows that 85% (17) of participants indicated they felt isolators had lower operating costs, while 10% did not.

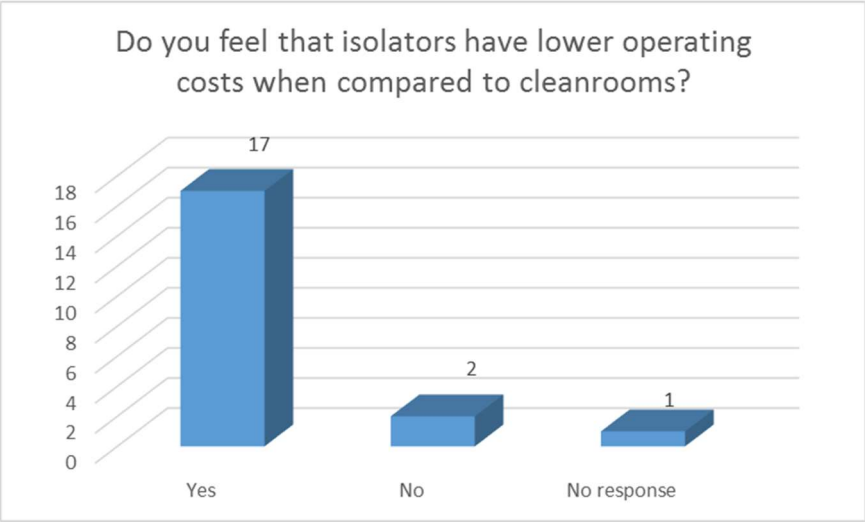

Figure 22. Participants' Opinions on Isolator Operating Costs

The participants' opinions show that isolator routine operating costs such as utilities, personnel gowning, testing and revalidation, and maintenance are considered to be lower than cleanrooms. This is further supported through the literature review as described in chapter 4.

Survey question 13, which was designed to determine the impact on productivity, asked participants if they felt that isolator operations take longer due to access restraints by operators. Figure 23 shows that 37% (7) of participants indicated that they felt isolator operations took longer due to access restraints, while 63% (12) indicated they did not.

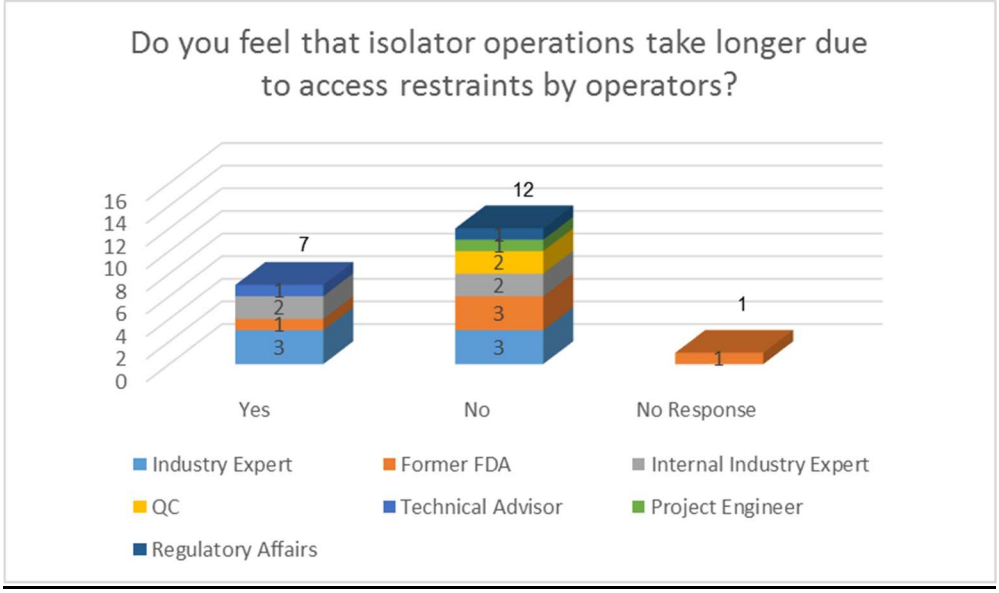

Figure 23. Participants' Opinions and Demographic Breakdown on Isolator Operations Taking Longer due to Access Restraints

Of note is that of those surveyed, the results for industry experts and internal industry experts responsible for sterilization/aseptic processing were equally split. The results indicate that there are differing opinions on the accessibility of isolators to perform interventions. If the isolator is designed properly, gloves should allow access to all areas of the isolator. This would make all areas accessible through the gloves for performing any interventions with no impact to productivity. Interventions could have the potential to take longer due to the loss of dexterity of performing activities with gloves.

The opinions of those surveyed were higher when considering the operating costs of the aseptic processing technologies. The opinions further support the literature review (chapters 3 and 4) which indicated the following:

- That isolator routine operating costs such as utilities, personnel gowning, testing and revalidation, and maintenance are considered to be lower than cleanrooms, and
- The productivity of isolators is similar to that of cleanrooms relative to performing of interventions.

This supports the hypothesis that the isolator is more cost effective when compared to cleanrooms due to the design and engineering requirements.

Advantages of Isolator Technology

The remaining seventeen questions were designed to obtain the participants' opinions on cleanroom versus isolator use. The superiority of the isolator was demonstrated based on advantages relating to overall sterility assurance, ease of use, and application of the guidance documents.

Sterility Assurance

Survey questions 7, 8, 17, 18, 20 and 21 were designed to obtain the participants' opinions on certain aspects of sterility assurance when comparing cleanrooms versus isolators. These aspects consisted of the following:

- Complete separation of personnel from the process
- Increased sterility assurance levels
- Detection of Microbial Contamination
- Aseptic technique usage

In survey question 7, participants were asked if they see the complete separation of people and product during aseptic processing applications as an advantage. Figure 24 shows that 95% (19) of the participants indicated that they felt complete separation of people and drug product was an advantage for aseptic processing, while 5% (1) indicated they did not see this as an advantage.

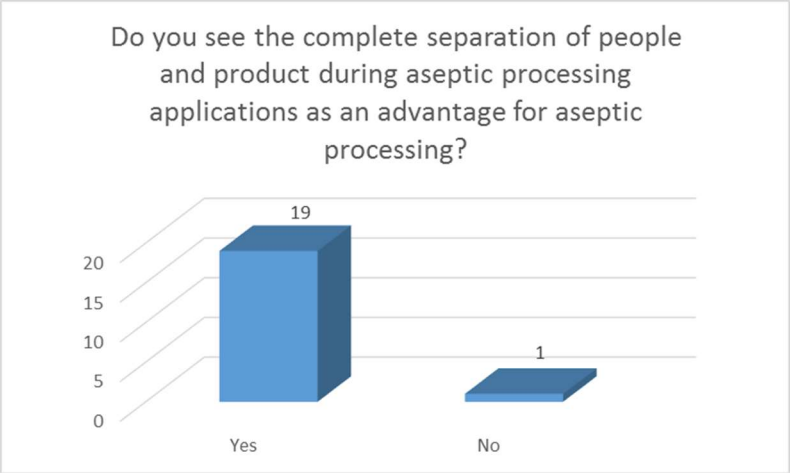

Figure 24. Participants' Opinions of Complete Separation of People and Product Being Advantageous

As noted in chapter 1 of this thesis, personnel are the main source of contamination in aseptic processing. Isolators provide the complete separation of personnel from drug product. The participants' opinions further support that the complete separation of personnel and drug product that an isolator provides is advantageous for aseptic processing.

Survey question 8 asked the participants if they felt isolators had increased sterility assurance when compared to cleanrooms. Figure 25 shows that 95% (19) of the participants indicated that they felt isolators had increased sterility assurance, while 5% (1) indicated they did not.

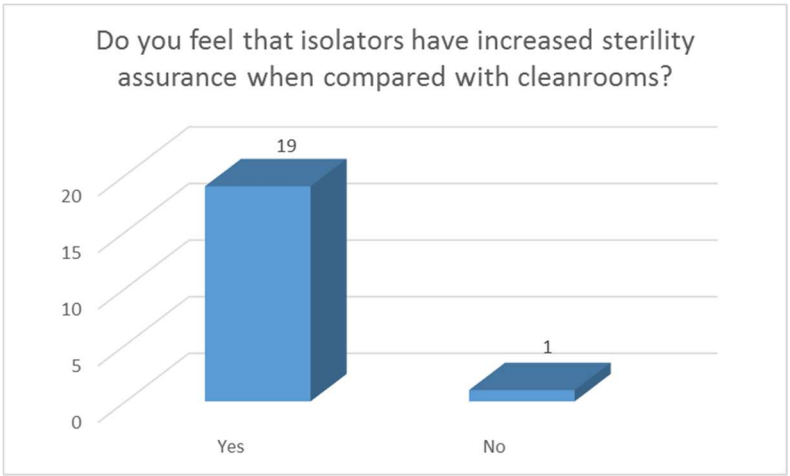

Figure 25. Participants' Opinions of Increased Sterility Assurance in Isolators vs. Cleanrooms

The participants' opinions are aligned with the findings in the literature review which indicated that isolators had an increased sterility assurance level of 10^{-6} as compared to cleanrooms with 10^{-3}. This increase in sterility assurance is further supported by questions 17 and 18 below.

Survey questions 17 and 18 asked the participants about their opinions regarding the detection of microbial contamination in cleanrooms and isolators and if it indicated a failure of the system. When asked if detection of microbial contamination in the cleanroom indicated a failure of the system, 20% (4) of the participants indicated contamination in a cleanroom was indicative of a failure of the cleanroom and its controls, while 80% (16) indicated it was not. When asked the same question, but applied to isolators, 75% (15) of the participants indicated that contamination in an isolator was indicative of a failure in the isolators and its controls, while 25% (5) indicated it was not. Figure 26 summarizes the survey results for questions 17 and 18.

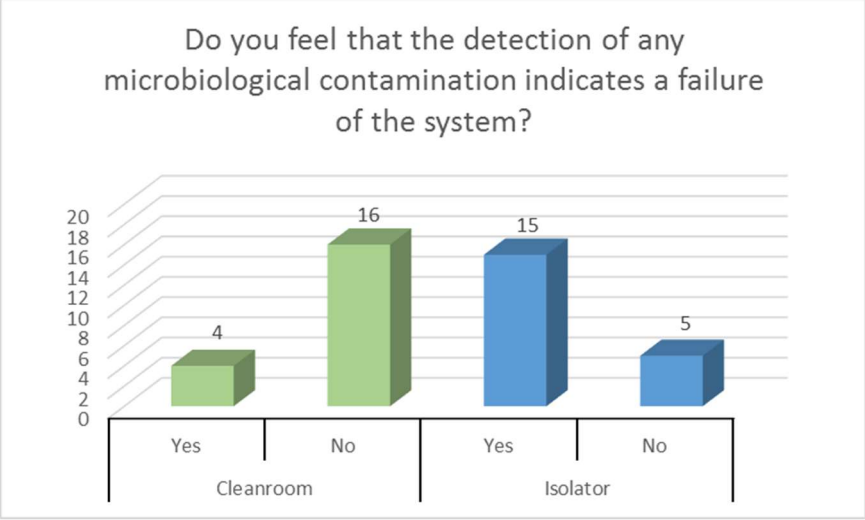

Figure 26. Participants' Opinions of Detection of Microbial Contamination Being Indicative of a Failure of the System

The responses indicate that, given the design and operation of the isolator, it is expected to have better microbial contamination control when compared to the cleanroom. This is due to the presence of people (the primary source of contamination) in a cleanroom versus the isolator,

where people are now completely separated from the process. This is further supported by USP General Chapter <1116> Microbiological Control and Monitoring of Aseptic Processing Environments, where the rates for microbial contamination in environmental monitoring samples are <0.1% for isolators and <1.0% for Cleanrooms (Class 100/ISO 5).[21]

Survey questions 20 and 21 asked the participants about their opinions regarding aseptic technique and its use when performing interventions in cleanrooms versus isolators. When asked if aseptic technique must be used when performing interventions in a cleanroom, 100% (20) of the participants indicated yes. When asked the same question, but applied to isolators, 95% (19) of the participants indicated yes, while 5% (1) indicated no. The results of the survey for questions 20 and 21 are shown in Figure 27.

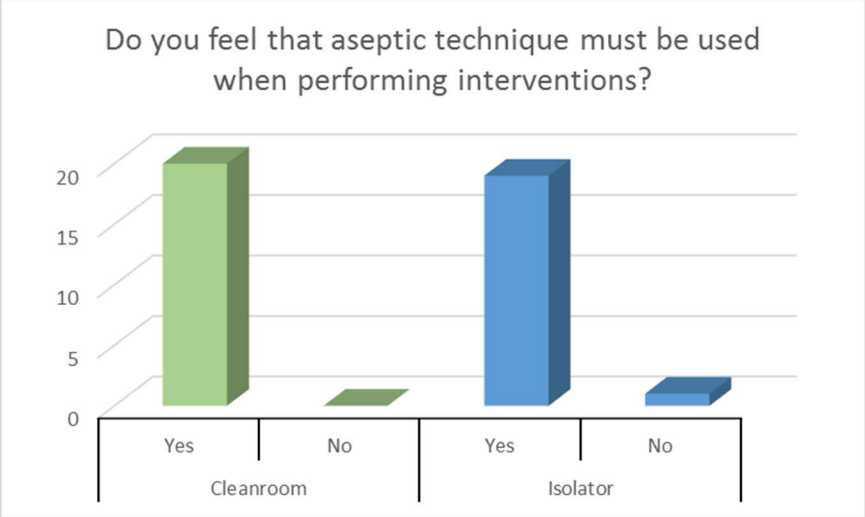

Figure 27. Participants' Opinions of Use of Aseptic Technique when Performing Interventions

Of note is that no matter which technology is utilized, it is recognized that aseptic technique is critical to aseptic processing and must be utilized whether using cleanroom or isolator technology. Even when complete separation of personnel from product is achieved, it is a best practice to utilize aseptic techniques to minimize the potential for manipulations done within the isolator to impact the process.

The opinions of those surveyed were higher when considering the sterility assurance of the aseptic processing in isolators. The industry opinions support sterility assurance advantages with isolator technology through the following:

- Complete separation of personnel from the process,
- Increased sterility assurance levels,
- Detection of microbial contamination, and
- Aseptic technique usage

This supports the hypothesis that the isolator is advantageous when compared to cleanrooms when sterility assurance is being considered.

Ease of Use

Survey questions 14, 15, 22, 23, 24, and 26 were designed to obtain the participants' opinions on the ease of use of cleanrooms versus isolators. These aspects consisted of the following:

- Cleaning and sanitization
- Multi-lot campaigning of product
- Decontamination cycle and isolator validation
- Maintenance

Survey question 14 asked the participants if they felt the sanitization/disinfection practices in cleanrooms are able to be validated. The responses were equally split with 50% of the participants indicating yes, and 50% indicating no. The results are shown in Figure 28.

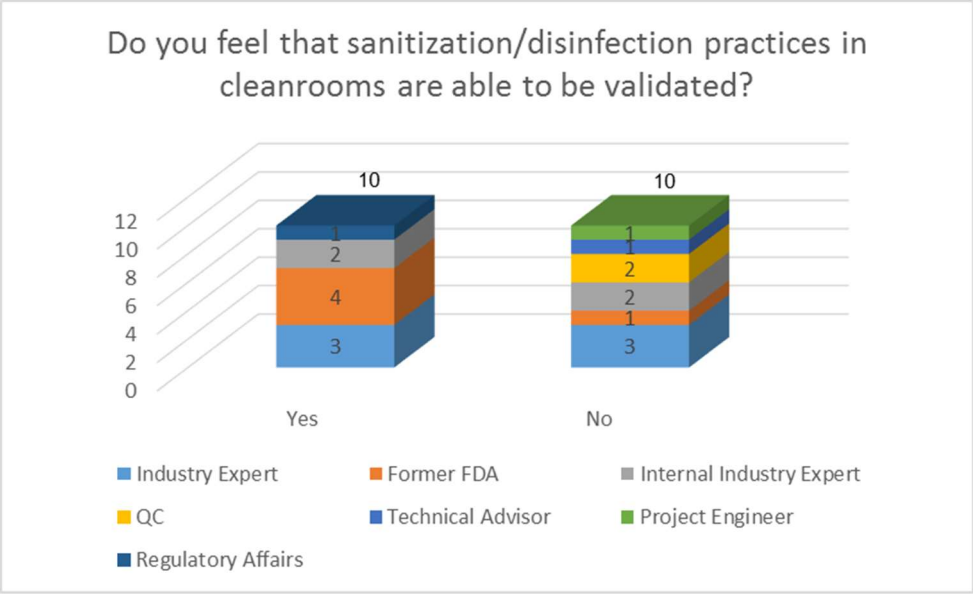

Figure 28. Participants' Opinions and Demographic Breakdown on Validation of Sanitization/ Disinfection Practices in Cleanrooms.

The data indicated that the results of those surveyed were equally split as to whether the manual sanitization/disinfection performed in a cleanroom can able to be validated. The sanitization is performed by gowned personnel which can lead to issues with reproducibility. As mentioned in the literature review, the cleanroom sterility assurance level achieved in a cleanroom is approximately 10^{-3}. This is determined via the qualification of disinfectants used in the area and the acceptance criteria of a 3 log reduction for successful results. For isolators, the decontamination is validated and reproducible with a sterility assurance level of 10^{-6} through the use of biological indicators. In addition, the requirements for the decontamination of isolators are well defined.

Survey question 15 asked the participants if they felt that manual sanitization/ disinfection practices are required for isolators prior to sporicidal (i.e. VHP) decontamination. Figure 29 shows that 65% (13) of the participants indicated yes, while 35% (7) indicated no.

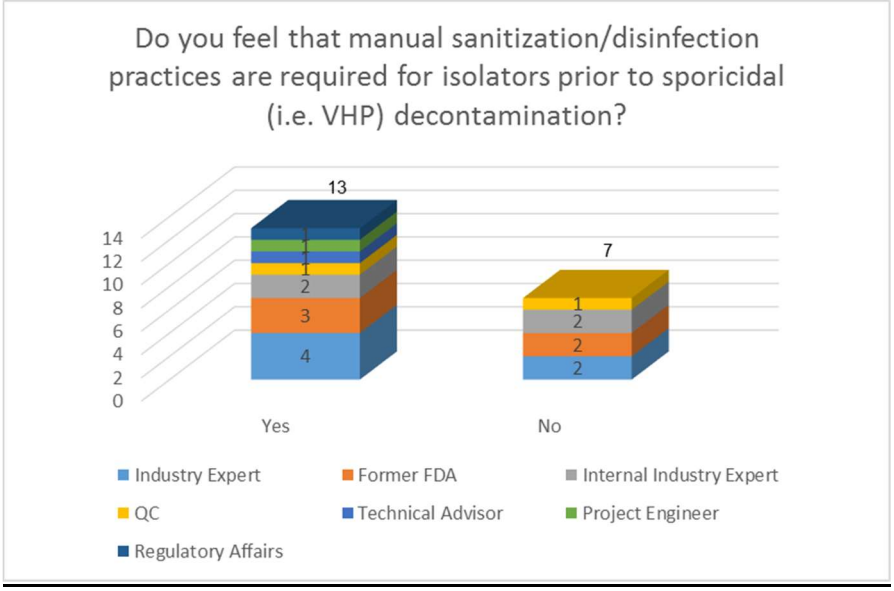

Figure 29. Participants' Opinions and Demographic Breakdown on Manual Sanitization / Disinfection Practices prior to Sporicidal Decontamination.

While 65% (13) of the participants agreed that manual sanitization/disinfection practices are required for isolators prior to decontamination, the percentage was lower than expected. The researcher felt this could indicate that the remaining participants felt that since the product contact parts are typically cleaned out of place (i.e. autoclaved), that there is no need for manual cleaning in an isolator. Non-product contact surfaces within the isolator still require manual cleaning prior to the decontamination cycle.

Survey questions 22 and 23 asked the participants' opinions on campaigning (multi-lot production of the same product) using cleanrooms versus isolators. When asked if participants felt that cleanrooms can be validated for campaigning (multi-lot production of same material) of products, 85% (17) of the participants indicated yes, while 15% (3) indicated no. When asked the same question, but applied to isolators, 100% of the participants indicated yes. The results indicate that both technologies are suitable for campaigning of products. Survey results for questions 22 and 23 are shown in figure 30.

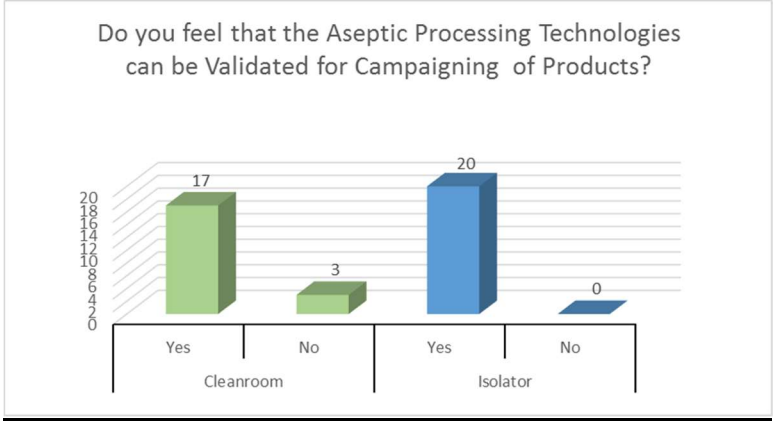

Figure 30. Participants' Opinions on Aseptic Processing Technologies Being Validated for Campaigning

There was not a strong difference in campaigning of products in cleanrooms vs. isolators. The researcher felt this could indicate that the participants felt that the use of isolators was more favorable for campaigning due to the complete separation of personnel from the process, whereas in the cleanroom, personnel are present resulting in a higher contamination risk which could impact multiple lots of product.

Survey question 24 asked participants if they felt that system maintenance can be more readily performed during a production run in an isolator. The responses were equally split with 50% of the participants indicating yes, and 50% indicating no. The results are shown in Figure 31.

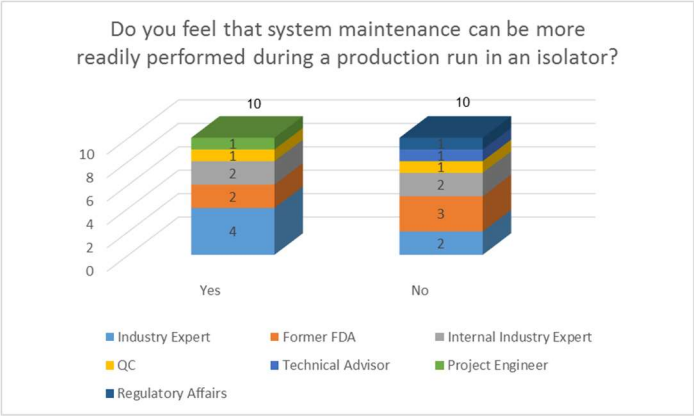

Figure 31. Participants' Opinions and Demographic Breakdown on System Maintenance Performed during a Production Run in an Isolator

The data indicated that of those surveyed, the results were equally split as to whether system maintenance can be readily performed during production runs in an isolator.

Survey question 26 asked participants if they feel that isolator technology is easily validated. Figure 32 shows that 75% (15) of the participants responded yes, while 25% (5) responded no. While the majority of participants agree that isolators are easily validated, the complexity of the technology can result in new issues not previously encountered in the validation of cleanrooms.

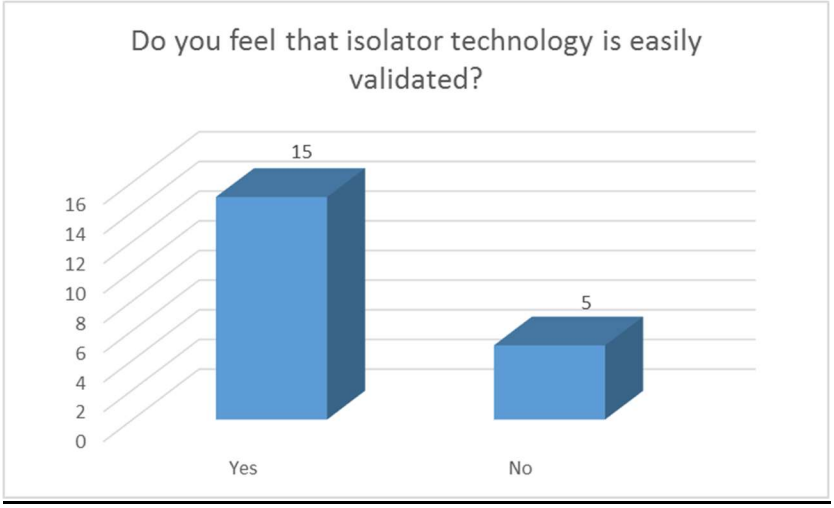

Figure 32. Participants' Opinions on Isolator Technology Being Easily Validated

The opinions of those surveyed were higher when considering the ease of use of isolators when applied to the following:

- the need for manual sanitization,
- campaigning of products, and
- ease of isolator validation.

The results for validation of cleaning/sanitization in the cleanrooms and performance of system maintenance in isolators were equally split, therefore no conclusions could be drawn. This further supports the hypothesis that the isolator is advantageous when compared to cleanrooms when ease of use relative to the need for manual sanitization, campaigning of products and ease of isolator validation is considered.

Application of Guidance Documents

Survey questions 5, 6, 16, 16b, and 19 were designed to obtain the participants' opinions on the application of guidance documents and requirements for cleanrooms versus isolators. These aspects consisted of the following:

- Sufficient FDA guidance for cleanrooms and isolators
- Sporicidal decontamination requirements
- Process simulation requirements

When asked about their thoughts on the whether there was sufficient FDA guidance for the cleanrooms and isolators used in aseptic processing, the results were similar. For survey question 5, the participants were asked if they felt that there is sufficient FDA guidance for cleanrooms in aseptic processing. Seventy percent (14) of the participants indicated yes, while 30% (6) indicated no. When asked the same question, but applied to isolators, 65% (13) of the participants indicated yes, while 35% (7) indicated no. Survey results for questions 5 and 6 are shown in Figure 33.

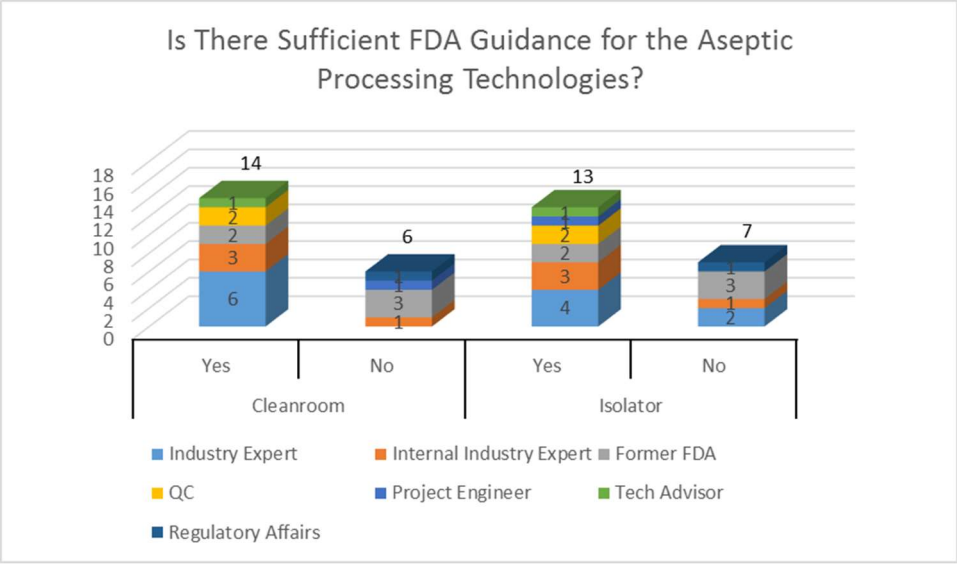

Figure 33. Participants' Opinions and Demographic Breakdown of FDA Guidance for Aseptic Processing Technologies

The opinions of those surveyed indicated participants felt that there is sufficient guidance for both technologies. A demographic breakdown of the participants' opinions on guidance for isolators revealed that 85% of the participants are active in the industry and the remaining 15% are former FDA employees. In the researchers' opinion this represents the industry's ability to adapt existing guidance documents with a cleanroom focus to isolator technology.

Survey question 16 asked participants if they felt that the sporicidal decontamination requirements for an isolator were well defined within the FDA regulations. Figure 34 shows that 65% (13) of participants indicated they did not feel the sporicidal decontamination requirements were well defined within the regulations, whereas 35% (7) participants indicated they did.

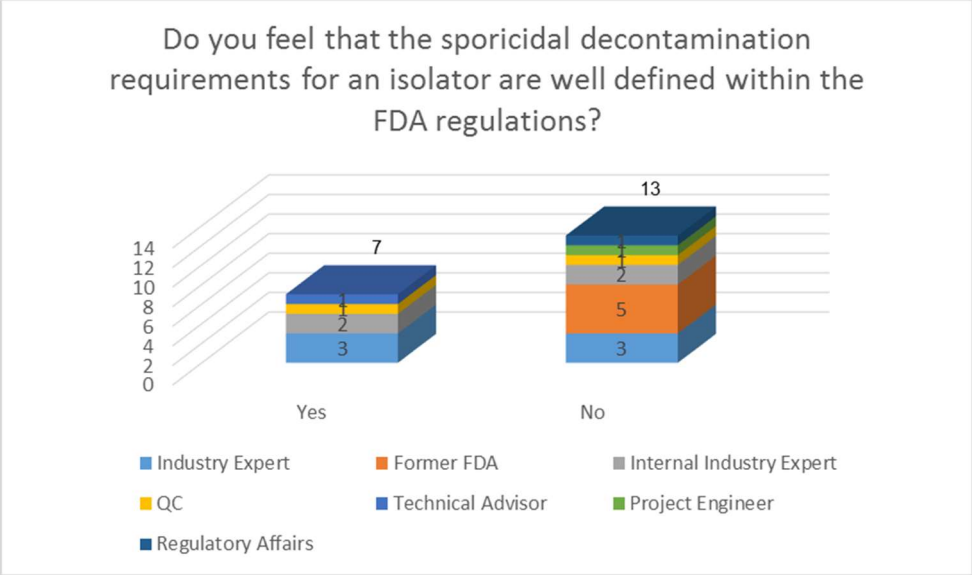

Figure 34. Participants' Opinions and Demographic Breakdown of Sporicidal Decontamination Requirements for Isolators Being Well Defined within the FDA Regulations

Survey question 16 was designed as a two-part question and the seven participants who responded yes to the previous question would proceed to survey question 16b regarding the validation of the sporicidal decontamination cycles. When the participants were asked if they felt that the decontamination cycles were easily validated to achieve a sterility assurance level of 10^{-6}, 86% (6) indicated yes, while 14% (1) indicated no as shown in Figure 35.

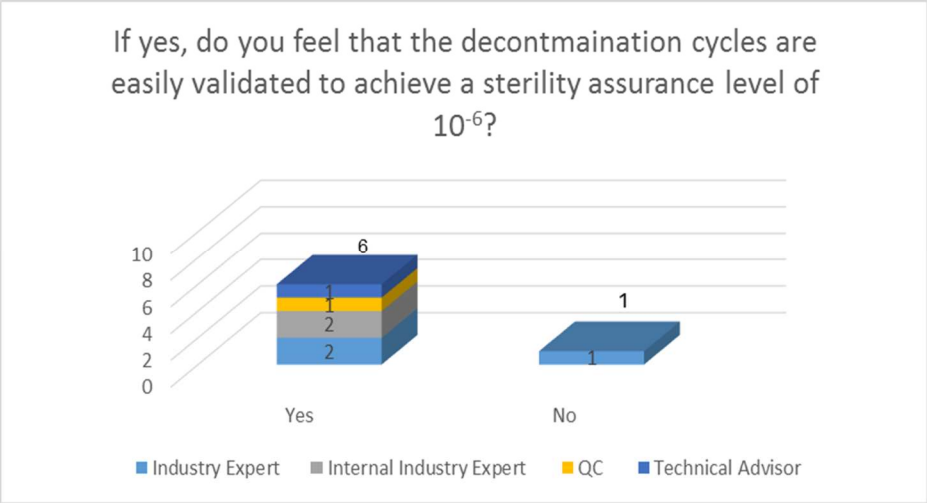

Figure 35. Participants' Opinions and Demographic Breakdown of if Sporicidal Decontamination Cycles are easily Validated to Achieve a SAL 10^{-6}

While thirteen of the participants indicated that they did not feel the sporicidal decontamination requirements were well defined in the regulations, those that did felt that the decontamination cycles were easily validated to achieve a sterility assurance level of 10^{-6}.

Survey question 19 asked participants if they felt that process simulations performed in isolators had the same requirements as those performed in cleanrooms. Figure 36 shows that 80% (16) of participants indicated yes, while 20% (4) indicated no.

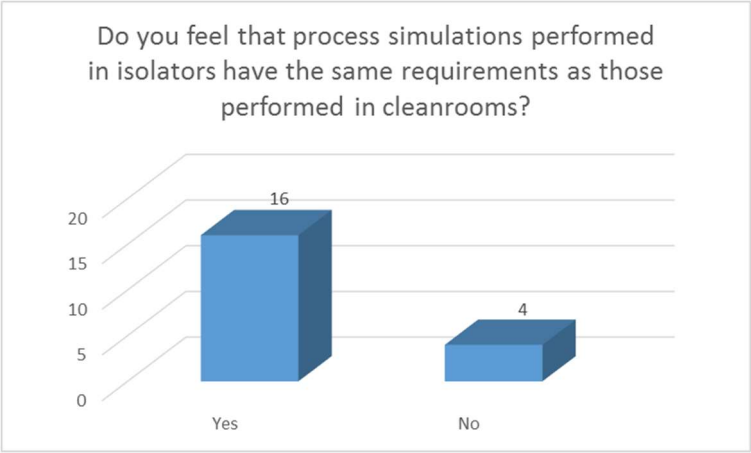

Figure 36. Participants' Opinions of If Process Simulations Performed in Isolators Had the Same Requirements as Those Performed in Cleanrooms

The results indicate that, whether performed in cleanrooms or isolators, the process simulation (media fill) requirements are the same to ensure that the facility design, working environment, and process are suitable for their intended use.

The opinions of those surveyed were consistent when considering the application of the FDA guidance to the aseptic processing technologies. The industry opinions clearly support the following:

- There is sufficient FDA guidance for both cleanroom and isolator technology,
- While sporicidal decontamination requirements could use improvement, the technology is easily validated to achieve a sterility assurance level of 10^{-6}, and
- The process simulation requirements are the same for both cleanroom and isolator technology.

This supports the hypothesis that the isolator is advantageous when compared to cleanrooms when application of the FDA guidance is being considered.

Question 25 was designed to obtain the participants' overall opinion of the superiority of isolators based on the design and ease of use. When participants were asked if they felt that when considering air pressure differentials, smaller facility footprint and ease of decontamination relative to cleanrooms that isolators are the superior technology, Figure 37 shows that 90% (18) of the participants indicated yes, that isolators were the superior technology, while 10% (2) indicated no.

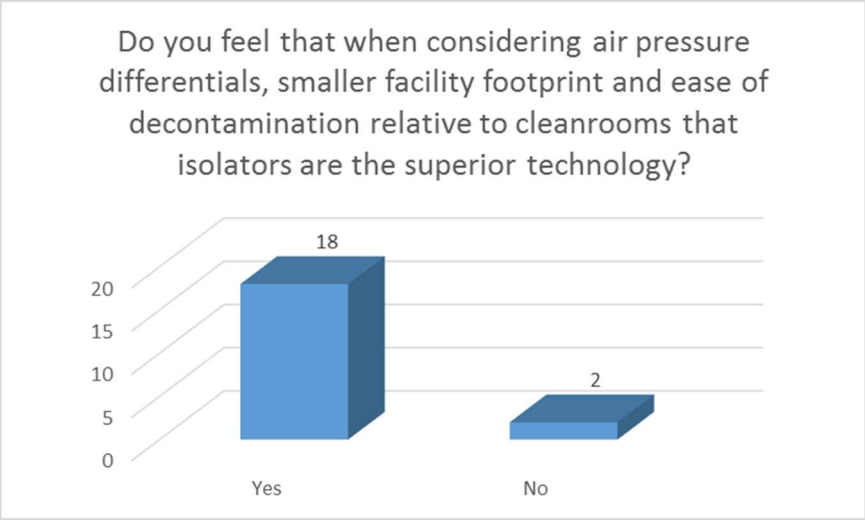

Figure 37. Participants' Opinions of Isolators Being the Superior Technology

This provides further support for the hypothesis that the isolators are the superior technology.

CHAPTER 6

CONCLUSIONS

The choice of an aseptic processing technology for a small, start-up parenteral facility can be considered a daunting task. The technology chosen to perform aseptic processing, whether a cleanroom or an isolator, must ensure the production of safe, effective, and sterile drug products. In addition, a start-up facility must consider the costs associated with implementing the technologies. While both technologies provide acceptable methods for aseptic processing of drug products, this thesis demonstrates that isolator technology is more cost effective and advantageous for a small, start-up facility and is therefore, the superior technology.

From the research presented in this thesis, it can be concluded that two primary documents govern the aseptic processing of drug products. These documents were the FDA regulations, 21 CFR 210 Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General and 21 CFR 211 Current Good Manufacturing Practice for Finished Pharmaceuticals. Both documents define the requirements for a drug manufacturer intending to manufacture drugs for human use. The FDA document 21 CFR 210 addresses the general requirements for manufacturing, facilities, and controls for the manufacturing, processing, packaging, and holding of drug product. FDA document 21 CFR 211 covers all aspects of operations. These documents are viewed as the primary documents for the manufacturing of drug products.

To aid manufacturers in interpreting the regulations in 21 CFR 210 and 21 CFR 211, several guidance documents and standards have been developed with the purpose of assisting

manufacturers with the design and implementation of the technologies. The key guidance and standard documents utilized in this paper consisted of the following:

- FDA Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing
- ISO 14644 Cleanrooms and Associated Controlled Environments
- ISPE Baseline Pharmaceutical Guide – Sterile Manufacturing Facilities

The review of the literature indicates that when comparing isolators to cleanroom technology, the isolators have the following significant advantages when compared to cleanrooms:

- Significantly increased sterility assurance levels due to validated decontamination cycles versus manual disinfection in cleanrooms,
- Complete separation of personnel from drug product thus eliminating the main source of contamination,
- Decreased facility footprint and less stringent background classifications,
- Decreased levels of personnel gowning, and
- Lower operating costs.

While the literature review showed significant advantages with isolators relating to sterility assurance, the costs associated with the technology must also be considered. The cost analysis review for the two technologies was based on a study conducted by Ferreira, et al.[22] The study took into consideration the equipment and facility design, validation, and operating costs. The cost analysis showed that while the initial costs for isolators are significantly higher than those of cleanrooms, when overall operating costs are added to the analysis, the isolator moved from the most costly technology to the least costly. The most cost effective elements of implementing isolator technology are as follows:

- Initial Facility costs (excluding isolator) saves approximately $170K,

- No Class A gowning required so therefore gowning saves approximately $300K annually,
- Utility costs save approximately $660K annually, and
- Reduction in environmental monitoring and personnel monitoring saves approximately $1.3 million annually.

These elements alone indicate approximately $3 million in savings annually, and further support the hypothesis that the isolator is more cost effective when compared to cleanrooms.

To further support the cost effectiveness of isolator technology, the Internet survey also utilized a series of questions to obtain industry experts opinions on the costs associated with each technology. Cost effectiveness was determined based on facility and equipment design and construction, qualification and validation activities, and general operating costs such as utilities, personnel gowning, testing and revalidation, and maintenance. The survey results support the cost effectiveness of isolators through the following:

- The square footage required for the filling and support areas for isolators was less than required for cleanrooms (Figure 19),
- The Class 100,000/ISO 8 background is sufficient for the surrounding environment for isolators (Figure 20),
- The qualification duration of cleanroom and isolator is similar (Figure 21), and
- The operating costs for isolators are lower than those for cleanrooms (Figure 22).

The survey data regarding cost effectiveness supports the findings of the literature review and demonstrate that the isolator is the more cost effective option for aseptic processing technology.

The remaining survey questions were designed to obtain the industry opinions on the advantages of isolators when compared with cleanrooms relating to the following:

- Sterility assurance,

- Ease of use, and
- Application of the guidance's.

The opinions of those surveyed were higher when considering the sterility assurance of the aseptic processing technologies. The survey results support sterility assurance advantages with isolator technology through the following:

- The complete separation of personnel from the process (Figure 24),
- Increased sterility assurance levels (Figure 25),
- Detection of microbial contamination as an indicator of system failure (Figure 26), and
- Aseptic technique usage (Figure 27).

These opinions further support the literature review and the hypothesis that the isolator is advantageous when compared to cleanrooms when sterility assurance is being considered.

When considering the ease of use as an advantage for isolators, the survey results support ease of use as an advantage for isolators through the following:

- The need for manual sanitization (Figure 29),
- Campaigning of products (Figure 30), and
- Ease of isolator validation (Figure 32).

When considering validation of cleaning/sanitization in the cleanrooms (Figure 28) and performance of system maintenance (Figure 31) in isolators, the results were inconclusive. This survey results support the hypothesis that the isolator is advantageous when compared to cleanrooms when ease of use parameters such as the need for manual sanitization, campaigning of products, and ease of validation are considered.

When considering application of the guidance documents as an advantage, the opinions of those surveyed were consistent when considering the application of the FDA guidance to the aseptic processing technologies. The survey results support the application of guidance documents as an advantage through the following:

- There is sufficient FDA guidance for both cleanroom and isolator technology (Figure 33),
- While sporicidal decontamination requirements could use improvement (Figure 34), the technology is easily validated to achieve a sterility assurance level of 10^{-6} (Figure 35), and
- The process simulation requirements are the same for both cleanroom and isolator technology (Figure 36).

This supports the hypothesis that the isolator is advantageous when compared to cleanrooms when application of FDA guidance is being considered.

In summary, the literature review, cost analysis, and survey analysis support the hypothesis that the isolator is the superior technology for a small, start-up parenteral facility when cost effectiveness and advantages of the technology are considered.

6.1 Recommendations

Based on the research and survey responses, it can be determined that isolator technology has advantages over cleanroom technology when applied to higher sterility assurance levels and reduced operating costs. However, these aseptic processing technologies are very complex operations and are continuously changing. In order to further research the technology that would be appropriate for individual facilities, all aspects of the technology must be considered. Some recommendations for future research are:

- Develop research so that the study design uses multiple choice and/or personal interviews in order to provide detailed information for analysis of responses,
- Narrow the scope of the research so that interpretation of data focuses on fewer elements of aseptic processing. For example, only cost analysis.

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APPENDIX 1

THESIS RESEARCH VALIDATION SURVEY

COMPARISON OF CLEANROOM AND ISOLATOR ASEPTIC PROCESSING TECHNOLOGY FOR SMALL START-UP PARENTERAL FACILITIES

The objective of this survey is to validate survey questions that will be utilized to collect data regarding cleanroom and isolator aseptic processing technology for a small start-up parenteral facility. By participating in this validation, you are part of a pilot group, with knowledge and experience with aseptic processing, who will answer the validation questions. These questions have been designed to ensure that the survey questions are not leading or biased.

Q1 For the following survey question: How would you describe your current position?

Former FDA

Industry Expert

Internal Industry Expert responsible for sterilization/aseptic processing

QC responsible for environmental monitoring, bioburden, etc.

Other Describe: _____

Is it clear that I am asking for the current position of the person responding to the survey?

- ❍ Yes
- ❍ No

Q2 For the following survey question: How many years of experience (education and working experience) do you have with Aseptic Processing?

0-5

6-10

11-15

20-25

26 or more

Is it clear that I am asking for the survey respondents' years of experience (education and working) with aseptic processing? Aseptic processing being defined as subjecting the drug product, container and closure to separate validated sterilization processes and then combining all in their final form using aseptic techniques in a highly controlled quality environment (i.e. cleanroom, isolator).

- ❍ Yes
- ❍ No

Q3a For the following survey question: Would you consider yourself knowledgeable about cleanroom technology and requirements?
If no, please stop the survey here.

Is it clear that I am asking the survey respondent if they consider themselves knowledgeable about cleanroom requirements and aspects such as sterilization processes, equipment/facility design, aseptic technique, personnel gowning, etc.?

- ❍ Yes
- ❍ No

Q3b For the following survey question: Would you consider yourself knowledgeable about cleanroom technology and requirements?
If no, please stop the survey here.

Is it clear that I am asking the survey respondents to stop the survey if they have no knowledge about cleanroom technology and requirements?

- ❍ Yes
- ❍ No

Q4a For the following survey question: Would you consider yourself knowledgeable about isolator technology and requirements?
If no, please stop the survey here.

Is it clear that I am asking the survey respondent if they consider themselves knowledgeable about isolator requirements such as design, classification, decontamination, aseptic technique, personnel training, etc.?

- ❍ Yes
- ❍ No

Q4b For the following survey question: Would you consider yourself knowledgeable about isolator technology and requirements?
If no, please stop the survey here

Is it clear that I am asking the survey respondents to stop the survey if they have no knowledge about isolator technology and requirements?

- ❍ Yes
- ❍ No

Q5a For the following survey question: Do you feel that there is sufficient FDA guidance for cleanrooms used in aseptic processing?

Is it clear that I am asking the survey respondent about current FDAguidance such as the FDA Guidance for Industry - Sterile Drug Products Producedby Aseptic Processing, 2004?

- ❍ Yes
- ❍ No

Q5b For the following survey question: Do you feel that there is sufficient FDA guidance for cleanrooms used in aseptic processing?

Is it clear that I am asking the survey respondent if they consider the FDA guidance for cleanrooms to be sufficient?

- ❍ Yes
- ❍ No

Q6a For the following survey question: Do you feel that there is sufficient FDA guidance for isolators used in aseptic processing?

Is it clear that I am asking the survey respondent about FDA current guidance such as the Guidance for Industry - Sterile Drug Products Produced by Aseptic Processing?

- ❍ Yes
- ❍ No

Q6b For the following survey question: Do you feel that there is sufficient FDA guidance for isolators used in aseptic processing?

Is it clear that I am asking the survey respondent if they consider the FDA guidance for isolators to be sufficient?

- ❍ Yes
- ❍ No

Q7 For the following survey question: Do you see the complete separation of people and product during aseptic processing applications as an advantage for sterility assurance?

Is it clear that I am asking if the survey respondent sees the complete separation of people and product during aseptic processing as an advantage when applied to sterility assurance?

- ❍ Yes
- ❍ No

Q8 For the following survey question: Do you feel that isolators have increased sterility assurance when compared with cleanrooms?

Is it clear that I am asking if isolators have a greater probability or perception of ensuring sterility assurance when compared with cleanrooms?

- ❍ Yes
- ❍ No

Q9 For the following survey question: Do you feel that isolators have lower operating costs when compared to cleanrooms?

Is it clear that I am asking about operating costs and not initial installation costs?

- ❍ Yes
- ❍ No

Q10 For the following survey question: Do you feel that isolators reduce the facilities footprint (amount of space within the facility) when compared to a cleanroom?

Is it clear that I am asking about the footprint (square footage or space taken in the print of a building) of an isolator when compared to a cleanroom?

- ❍ Yes
- ❍ No

Q11a For the following survey question: Do you feel that the qualification (IQ/OQ/PQ) duration of isolators is similar to that of cleanrooms?

Is it clear that by qualification duration I am asking about installation qualification, operational qualification and performance qualification & the amount of days/man hours it takes to conduct them?

- ❍ Yes
- ❍ No

Q11b For the following survey question: Do you feel that the qualification (IQ/OQ/PQ) duration of isolators is similar to that of cleanrooms?

Is it clear that I am asking about the duration of qualification activities being similar for isolators and cleanrooms?

- ❍ Yes
- ❍ No

Q12 For the following survey question: Do you feel that a Class 100,000 (ISO 8) classification background is sufficient for the area surrounding an isolator?

Is it clear that I am asking if a Class 100,000 (ISO 8) background is sufficient for isolators?

- ❍ Yes
- ❍ No

Q13 For the following survey question: Do you feel that isolator operations take longer due to access restraints by operators?

Is it clear that by access restraints I am referring to the limited access to the inside of the isolator due to the closed nature of the process?

- ❍ Yes
- ❍ No

Q14a For the following survey question: Do you feel that sanitization/disinfection practices in cleanrooms are able to be validated?

Is it clear that I am asking about manual sanitization/disinfection practices used for cleanrooms?

- ❍ Yes
- ❍ No

Q14b For the following survey question: Do you feel that sanitization/disinfection practices in cleanrooms are able to be validated?

Is it clear that I am asking if the respondent feels these practices are able to be validated for cleanrooms?

- ❍ Yes
- ❍ No

Q15 For the following survey question: Do you feel that manual sanitization/ disinfection practices are required for isolators prior to sporicidal (i.e. VHP) decontamination?

Is it clear that I am asking if the survey respondent feels that manual sanitization/disinfection should be required prior to VHP decontamination?

- ❍ Yes
- ❍ No

Q16a For the following survey question: Do you feel that the sporicidal decontamination requirements for an isolator are well defined within FDA regulations?

If yes, do feel that the decontamination cycles are easily validated to achieve a sterility assurance level of 10-6?

Is it clear that I am asking about sporicidal decontamination for an isolator?

- ❍ Yes
- ❍ No

Q16b For the following survey question: Do you feel that the sporicidal decontamination requirements for an isolator are well defined within FDA regulations?

If yes, do feel that the decontamination cycles are easily validated to achieve a sterility assurance level of 10-6?

Is it clear that I am asking about how decontamination requirements are defined in the FDA regulations?

- ❍ Yes
- ❍ No

Q16c For the following survey question: Do you feel that the sporicidal decontamination requirements for an isolator are well defined within FDA regulations?

If yes, do feel that the decontamination cycles are easily validated to achieve a sterility assurance level of 10-6?

Is it clear that I am asking if the survey respondents feel that the decontamination cycles are easily validated?

- ❍ Yes
- ❍ No

Q16d For the following survey question: Do you feel that the sporicidal decontamination requirements for an isolator are well defined within FDA regulations?

If yes, do feel that the decontamination cycles are easily validated to achieve a sterility assurance level of 10-6?

Is it clear that by validated I am asking about a 10-6 log reduction?

- ❍ Yes
- ❍ No

Q17 For the following survey question: Do you feel that the detection of any microbiological contamination in a cleanroom indicates a failure of the system?

Is it clear that I am asking if any microbiological contamination (viable samples) indicates a system failure in the cleanroom?

- ❍ Yes
- ❍ No

Q18 For the following survey question: Do you feel that the detection of any microbiological contamination in an isolator indicates a failure of the system?

Is it clear that I am asking if any microbiological contamination (viable samples) indicates a system failure in the isolator?

- ❍ Yes
- ❍ No

Q19 For the following survey question: Do you feel that process simulations performed in isolators have the same requirements as those performed in cleanrooms?

Is it clear that I am asking about the requirements for process simulations performed in isolators?

- ❍ Yes
- ❍ No

Q20 For the following survey question: Do you feel that aseptic technique must be used when performing interventions in a cleanroom?

Is it clear that I am asking about aseptic technique for interventions such as equipment set-up, aseptic connections, sampling, maintenance, etc. performed in a cleanroom?

- ❍ Yes
- ❍ No

Q21 For the following survey question: Do you feel that aseptic technique must be used when performing interventions in an isolator?

Is it clear that I am asking about aseptic technique for interventions such as equipment set-up, aseptic connections, sampling, maintenance, etc. performed in an isolator?

- ❍ Yes
- ❍ No

Q22a For the following survey question: Do you feel that cleanrooms can be validated for campaigning (multi-lot production of same material) of products?

Is it clear that I am asking about multiple lots of the same product being produced in one activity with no cleaning / disinfection in between each lot?

- ❍ Yes
- ❍ No

Q22b For the following survey question: Do you feel that cleanrooms can be validated for campaigning (multi-lot production of same material) of products?

Is it clear that I am asking about whether or not this multi-lot process can be validated for cleanrooms with no cleaning/disinfection in between each lot?

- ❍ Yes
- ❍ No

Q23a For the following survey question: Do you feel that isolators can be validated for campaigning (multi-lot production of same material) of products?

Is it clear that I am asking about multiple lots of the same product being produced in one activity with no cleaning/decontamination in between each lot?

- ❍ Yes
- ❍ No

Q23b For the following survey question: Do you feel that isolators can be validated for campaigning (multi-lot production of same material) of products?

Is it clear that I am asking about whether or not this multi-lot process can be validated for isolators with no leaning/decontamination in between each lot?

- ❍ Yes
- ❍ No

Q24 For the following survey question: Do you feel that system maintenance can be more readily performed during a production run in an isolator?

Is it clear that I am asking about the ease of performing maintenance during a production run (i.e. product is being filled & capped) in an isolator?

- ❍ Yes
- ❍ No

Q25 For the following survey question: Do you feel that when considering air pressure differentials, smaller facility footprint and ease of decontamination relative to cleanrooms that isolators are the superior technology?

Is it clear that I am asking about the superiority of an isolator due to maintaining air pressure differentials, smaller facility footprint and ease of decontamination when compared to cleanroom technology?

- ❍ Yes
- ❍ No

Q26 For the following survey question: Do you feel that isolator technology is easily validated?

Is it clear that I am asking about the ease of achieving a sterility assurance level of 10-6 when validating isolator technology?

- ❍ Yes
- ❍ No

APPENDIX 2

THESIS RESEARCH SURVEY

COMPARISON OF CLEANROOM AND ISOLATOR ASEPTIC PROCESSING TECHNOLOGY FOR SMALL START-UP PARENTERAL FACILITIES

I am a graduate student under the direction of Dr. David Mullis in the BioPharma Graduate Education Program of Pharmacy at The University of Georgia. I invite you to participate in a research study entitled Comparison of Cleanroom and Isolator Aseptic Processing Technology for Small Start-up Parenteral Facilities. The purpose of this study is to demonstrate through the evaluation of current regulations and guidance documents and cost analysis that isolator technology is more cost effective and advantageous for a small start-up parenteral facility and is therefore the superior technology.

Your participation will involve completing an online survey and should only take about 30-40 minutes of your time. Your involvement in the study is voluntary, and you may choose not to participate or to stop at any time without penalty or loss of benefits to which you are otherwise entitled. If you decide to stop or withdraw from the study, the information/data collected from or about you up to the point of your withdrawal will be kept as part of the study and may continue to be analyzed.

Any/all company information collected for this thesis will be confidential and will not be shared or used for any other purpose. The results of the research study may be published, but your name or any identifying information will not be used. In fact, the published results will be presented in summary form only.

No risks or discomforts are anticipated from taking part in this study. If you feel uncomfortable with a question, you can skip that question or withdraw from the study altogether.

The research may demonstrate a cost and ease of use benefit for isolator technology versus the use of cleanroom technology for testing and manufacturing of pharmaceutical drug products.

If you have any questions about this research project, please feel free to call me Shannon Burton at (706) 951-7671 or send an e-mail to slburton@uga.edu or Dr. David Mullis at dmullis@rx.uga.edu. Questions or concerns about your rights as a research participant should

be directed to The Chairperson, University of Georgia Institutional Review Board, 629 Boyd GSRC, Athens, Georgia 30602; telephone (706) 542-3199; email address irb@uga.edu.

Please print and save a copy of this page for your records.

Statement of Your Consent: I have read the above description of this research study. I have been informed of the risks and benefits involved, and all my questions have been answered to my satisfaction. Furthermore, I have been assured that any future questions I may have will also be answered by a member of the research team. By signing below, I affirm that I am at least 18 years of age and voluntarily agree to take part in this study.

* I have read the above information and agree to participate in this research project.

- ❍ Yes
- ❍ No

Q1 How would you describe your current position?

- ❍ Former FDA
- ❍ Industry Expert
- ❍ Internal Industry Expert responsible for sterilization/aseptic processing
- ❍ QC responsible for environmental monitoring, bioburden, etc
- ❍ Other : Please Describe below _____

Q2 How many years of experience (education and working experience) do you have with Aseptic Processing?

- ❍ 0-5
- ❍ 6-10
- ❍ 11-15
- ❍ 16-20
- ❍ 21 or more

Q3 Would you consider yourself knowledgeable about cleanroom technology and requirements?

- ❍ Yes
- ❍ No, if no, please stop the survey here.

Q4 Would you consider yourself knowledgeable about isolator technology and requirements?

- ❍ Yes
- ❍ No, if no, please stop the survey here.

Q5 Do you feel that there is sufficient FDA guidance for cleanrooms used in aseptic processing?

- ❍ Yes
- ❍ No

Q6 Do you feel that there is sufficient FDA guidance for isolators used in aseptic processing?

- ❍ Yes
- ❍ No

Q7 Do you see the complete separation of people and product during aseptic processing applications as an advantage for sterility assurance?

- ❍ Yes
- ❍ No

Q8 Do you feel that isolators have increased sterility assurance when compared with cleanrooms?

- ❍ Yes
- ❍ No

Q9 Do you feel that isolators have lower operating costs when compared to cleanrooms?

- ❍ Yes
- ❍ No

Q10 Do you feel that isolators reduce the facilities footprint (amount of space within the facility) when compared to a cleanroom?

- ❍ Yes
- ❍ No

Q11 Do you feel that the qualification duration of isolators is similar to that of cleanrooms?

- ❍ Yes
- ❍ No

Q12 Do you feel that a Class 100,000 (ISO 8) classification background is sufficient for the area surrounding an isolator?

- ❍ Yes
- ❍ No

Q13 Do you feel that isolator operations take longer due to access restraints by operators?

- ❍ Yes
- ❍ No

Q14 Do you feel that sanitization/disinfection practices in cleanrooms are able to be validated?

- ❍ Yes
- ❍ No

Q15 Do you feel that manual sanitization/ disinfection practices are required for isolators prior to sporicidal (i.e. VHP) decontamination?

- ❍ Yes
- ❍ No

Q16a Do you feel that the sporicidal decontamination requirements for an isolator are well defined within the FDA regulations?

- ❍ Yes
- ❍ No

Q16b Do you feel that the decontamination cycles are easily validated to achieve a sterility assurance level of 10-6?

- ❍ Yes
- ❍ No

Q17 Do you feel that the detection of any microbiological contamination in a cleanroom indicates a failure of the system?

- ❍ Yes
- ❍ No

Q18 Do you feel that the detection of any microbiological contamination in an isolator indicates a failure of the system?

- ❍ Yes
- ❍ No

Q19 Do you feel that process simulations performed in isolators have the same requirements as those performed in cleanrooms?

- ❍ Yes
- ❍ No

Q20 Do you feel that aseptic technique must be used when performing interventions in a cleanroom?

- ❍ Yes
- ❍ No

Q21 Do you feel that aseptic technique must be used when performing interventions in an isolator?

- ❍ Yes
- ❍ No

Q22 Do you feel that cleanrooms can be validated for campaigning (multi-lot production of same material) of products?

- ❍ Yes
- ❍ No

Q23 Do you feel that isolators can be validated for campaigning (multi-lot production of same material) of products?

- ❍ Yes
- ❍ No

Q24 Do you feel that system maintenance can be more readily performed during a production run in an isolator?

- ❍ Yes
- ❍ No

Q25 Do you feel that when considering air pressure differentials, smaller facility footprint and ease of decontamination relative to cleanrooms that isolators are the superior technology?

- ❍ Yes
- ❍ No

Q26 Do you feel that isolator technology is easily validated?

- ❍ Yes
- ❍ No