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Table of Contents

1.0 INTRODUCTION	
1.1 Preface	1
1.2 Scope	1
1.3 Key Definitions	1
1.4 Purpose	2
2.0 TYPES OF ISOLATORS	
2.1 Closed Isolators	2
2.1.1 Closed Isolators Intended for Aseptic Applications	2
2.1.2 Closed Isolators Intended for Containment Applications.	2
2.1.3 Closed Isolators Intended for Asepsis and Containment	2
2.2 Open Isolators	3
2.2.1 Open Isolators Intended for Aseptic Applications	3
2.2.2 Open Isolators Intended for Asepsis and Containment	3
3.0 ISOLATOR DESIGN AND GENERAL CONSTRUCTION	
3.1 Materials of Construction	3
3.1.1 Polyvinyl Chloride (PVC)	3
3.1.2 Stainless Steel	4
3.1.3 Glazing Materials	4
3.1.4 Other Materials	4
3.2 Operator Interface	4
3.2.1 Gloves/Sleeves	5
3.2.2 Suits or Half-Suits	5
3.2.3 Air Handling System	6
4.0 FUNCTIONAL SPECIFICATIONS FOR ISOLATORS	
4.1 Air Supply Specifications	6
4.1.1 Air Change Rate	7
4.1.2 Air Velocity	7
4.1.3 Particulate Air Specification	7
4.1.4 Recirculation Rate	8
4.1.5 Temperature and Humidity	8
4.1.6 Aeration of the Decontaminating Agent	8
4.2 Leak Testing	8
4.2.1 Pressure Decay Test	9
4.2.2 Tracer Gas Detection Test	9
4.3 Ergonomics	10
4.4 Rapid Transfer Ports (RTPs)	10

5.0 FACILITY REQUIREMENTS	
5.1 Classification of the Isolator Room	11
5.2 Temperature and Humidity Control	11
5.3 Process Utilities	11
6.0 USER REQUIREMENT SPECIFICATIONS (URS)	
6.1 General User Requirement Specifications	11
6.1.1 Sterility Assurance	11
6.1.2 Cleaning and Cleaning Validation	14
6.1.3 Containment	14
6.1.4 Environmental Control	16
6.1.5 Leak Testing	17
6.1.6 Monitoring Systems	17
6.1.7 Microbiological Monitoring of the Environment	17
6.1.8 Process Simulation	18
7.0 RE-QUALIFICATION TESTING	18
8.0 CONCLUSION	19
APPENDIX A: Glossary	20
APPENDIX B: Ljungqvist/Reinmüller (L-R) Method	20
APPENDIX C: Test Methods, Pressure Drop Test	21
APPENDIX D: Isolators and Sterility Assurance	22
REFERENCES AND TEXT NOTES	23

1.0 INTRODUCTION

1.1 Preface

In recent years, isolation technology has rapidly emerged as an alternative to human-scale classified environments for the production and testing of many different types of health care products. The operational characteristics of isolators make them ideally suited for use in the preparation of sterile materials, as well as in the containment of potent materials. Additional applications can be found in the preparation of clinical supplies, sterile bulk drugs/bio-pharmaceuticals, sterile cytotoxic materials, and in sterility testing.

The absence of authoritative implementation and validation guidance for this technology and the considerable confusion that has emerged between “isolators” and “barriers” were prime motivators for PDA to develop this document. It is the product of an international committee made up of representatives of PDA U.S., PDA’s Japan Chapter, A₃P, The Parenteral Society, and R³-Nordic.

This document should be considered as guidance; it is not intended to establish any mandatory or implied standard.

1.2 Scope

This technical report addresses essential user requirements for the application of isolator technology to a broad range of manufacturing, development, and testing applications in the health care product manufacturing industry. This technical report covers not only product sterility assurance, but also the use of isolators for the containment of hazardous materials.

An important component of this technical report is the glossary (Appendix A). The health care industry has lacked a uniform set of definitions with respect to isolator technology. The committee recognizes that, in order to suggest truly usable technical information, we must ensure that there can be no confusion among readers as to the application of recommendations made within this technical report.

The committee also recognizes that in some regions of the world, processing environments called “isolators”

are widely used in the clinical pharmacy setting. These devices have some general features in common with isolators as defined in this document, however, they are distinctly different from the isolator systems currently in use for sterile product manufacturing and testing in the health care product industry. This technical report does not pertain to devices that do not meet the minimum performance criteria defined and explained in this document.

1.3 Key Definitions

The establishment of a clear distinction between what is and what is not an isolator is essential to understanding this document. PDA suggests the following definition of isolator be adopted by the worldwide health care industry:

An isolator is sealed or is supplied with air through a microbially retentive filtration system (HEPA minimum) and may be reproducibly decontaminated (1). When closed, it uses only decontaminated (where necessary) interfaces or Rapid Transfer Ports (RTPs) for materials transfer. When open, it allows for the ingress and/or egress of materials through defined openings that have been designed and validated to preclude the transfer of contamination. It can be used for aseptic processing activities, for containment of potent compounds, or simultaneously for both asepsis and containment.

In marked contrast to the “isolator” definition above, PDA suggests the following definition for “barrier systems:”

A barrier system is an open system that can exchange contaminants with the surrounding area, and cannot be decontaminated to the extent possible in an isolator.

Isolators, whether operated in a closed or open manner, offer significant advantages over barrier systems: isolators can be decontaminated using reproducible and validated methods, do not allow the ingress of airborne contamination from the surrounding environment, and prevent the introduction of personnel borne contamination into the isolator. In contrast, a barrier system is an open system which can exchange unfiltered air with the surrounding environment, can only be manually disinfected, and is directly accessed by gownned personnel.

1.4 Purpose

The increased use of isolators in the health care product industry over the last decade and a half has been remarkable. In fact, isolators now clearly represent the most rapidly growing technology for the production of health care products. In spite of the rapid growth this segment of the industry has enjoyed, very little technical guidance exists for those who work in this field.

It was often said at the beginning of the “isolator era” that isolators could be considered nothing more than small clean rooms. Experience has taught scientists and engineers that functional requirements for isolators are, in fact, distinctly different from those for human scale or “conventional” clean rooms. Although human scale clean rooms and isolators have much in common, they have many important differences and this technical report endeavors to focus on and discuss these differences.

2.0 TYPES OF ISOLATORS

2.1 Closed Isolators

Isolators operated as closed systems do not exchange unfiltered air or contaminants with adjacent environments. Their ability to operate without personnel access to the critical zone makes isolators capable of levels of separation between the internal and external environment unattainable with other technologies. Because of the effectiveness of this separation, closed isolators are ideally suited for application in the preparation of sterile and/or toxic material.

There are two types of closed isolators: aseptic and containment. Aseptic isolators are intended to exclude external contamination from the critical zone inside the isolator. Containment isolators are intended to prevent the release of toxic materials processed inside the isolator to the surrounding environment in which personnel are located.

2.1.1 *Closed Isolators Intended for Aseptic Applications*

These units are typically operated under positive pressure and are subject to validatable decontamination procedures prior to use. Isolators intended for the

processing of sterile materials adhere to the following general principles:

- They must not exchange air with the surrounding environment except when that air passes through a microbially retentive filter.
- They must be decontaminated in a reproducible and quantifiable manner.
- All work or handling of materials within the isolator enclosure must be accomplished remotely; no human operator or part thereof can directly enter the isolator during operation.
- All materials that enter the isolator must be decontaminated or sterilized and must enter either directly through a decontaminating or sterilizing system, or via a rapid transfer port.

2.1.2 *Closed Isolators Intended for Containment Applications*

These units generally operate under negative pressure and are cleared of all potentially hazardous materials prior to opening. Isolators intended for containment applications adhere to the following general principles:

- They must not exchange air with the surrounding environment except when that air passes through a filter capable of retaining the materials being processed.
- All work or handling of materials within the isolator enclosure must be accomplished remotely. No human operator or part thereof can directly enter the isolator during operation.
- All materials exiting the isolator must be cleaned or contained in such a way that hazardous materials are not released to the surrounding environment.
- They must be cleanable in a reproducible and quantifiable manner.

2.1.3 *Closed Isolators Intended for Asepsis and Containment*

These units are subject to the constraints of sections 2.1.1 and 2.1.2, above. They are typically operated under positive pressure, with additional safety measures such as negative pressure airlocks. The use of supplementary personal protective equipment by the workers may be considered.

2.2 Open Isolators

Open isolators differ from closed isolators in that they are designed to allow for the continuous or semi-continuous ingress and/or egress of materials during operation, while maintaining a level of protection over the internal environment. Open isolators do not exchange unfiltered air or contaminants with adjacent environments. Open isolators are decontaminated while closed, and then opened during manufacturing. Open isolators typically are used for the aseptic filling of finished pharmaceuticals.

2.2.1 Open Isolators Intended for Aseptic Applications

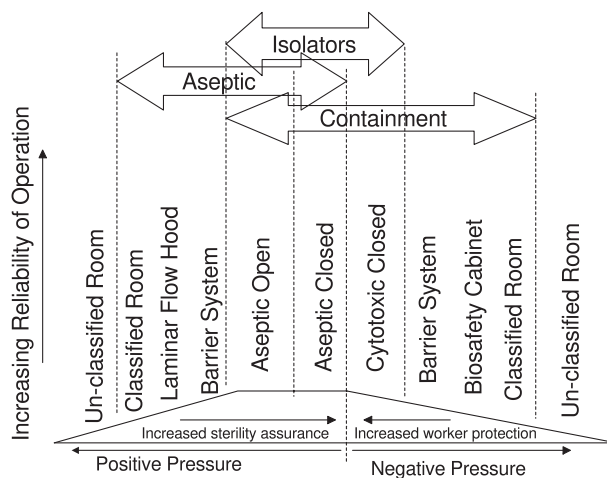
With the exception of the presence of openings during manufacturing, open isolators satisfy the same general principles as noted above for closed isolators. There are numerous designs that can successfully manage the ingress and egress of components of filled containers, while preventing the ingress of contamination from the surrounding environment.

2.2.2 Open Isolators Intended for Asepsis and Containment

These isolators share similarities with the ordinary open isolator (see 2.2.1) and the containment isolator (see 2.1.1). For these systems, the design usually incorporates a cleaning process to allow for removal of any toxic contaminant from the exterior of the sealed container prior to exit from the isolator. The design must also prevent the ingress of air in order to preserve the aseptic nature of the internal environment.

The following diagram provides an overview of isolators, barrier systems, and clean rooms depicting some of their operating characteristics and application. It should be noted that the systems at the edge of the drawing are essentially equivalent, and afford minimal protection to the materials and personnel.

The Isolation Continuum



3.0 ISOLATOR DESIGN AND GENERAL CONSTRUCTION

Isolators may be manufactured of any suitable material provided the isolator satisfies the functional requirements established for it, and the material is sufficiently rugged to resist puncture or damage that could affect system integrity. In general, isolators are termed either “flexible wall” or “rigid wall” depending upon their general construction. Isolators that are used in containment applications are often of rigid wall construction because these systems allow for a more aggressive cleaning of surfaces.

3.1 Materials of Construction

3.1.1 Polyvinyl Chloride (PVC)

PVC sheeting is, by far, the most common material of construction for flexible wall isolators. Flexible wall isolators have been successfully used for both sterility testing and manufacturing isolators. The PVC isolator canopy is generally externally supported by a metal (typically stainless steel) frame. The PVC material should be thick enough to resist puncture. PVC isola-

tors may be damaged by exposure to UV light, or chemicals such as solvents. PVC is most commonly used in isolators which cover a general size range of about 0.5 per cubic meter to about 8 per cubic meter, although other sizes are possible. The generally non-reactive nature of PVC enables the material to withstand repeated exposure to sterilizing/sanitizing agents commonly used with isolators and their contents. If cleanability is an issue, smooth wall floor junctions and seams are essential. The use of a properly sloped smooth stainless steel floor should be considered where superior cleanability is required.

3.1.2 Stainless Steel

Stainless steel is commonly used as a flooring material in both rigid wall and flexible wall isolators. Stainless steel is the most commonly used wall and ceiling material in rigid wall isolators. 300 series stainless steels are generally used, typically either 304 or 316 grade. Where welding is a consideration, or prolonged exposure to halogen salts or other corrosive substances is expected, low carbon (304L, 316L) should be considered. The surface finish is most critical in those applications for which cleanability is an important user requirement. For many aseptic process applications, only a general “buff” finish is required; for cleanability, however, higher levels of polish up to and including electropolish (RA 5-7 micrometers) can be considered.

3.1.3 Glazing Materials

Many isolators have rigid windows to allow easy view of the processes contained within the isolator. The most commonly used materials for these windows are polycarbonate (i.e., Lexan®), acrylic plastics, or tempered glass. The most important consideration in the use of windows is the mounting of the window to the isolator framework. The window mounting assembly or frame may either be permanently or semi-permanently bolted in place, or it may be designed to be easily opened to allow access to the interior of the isolator when the unit is undergoing maintenance or changeover. It is important that the cleanability of the window mount and seal is considered and that the gasket material is chosen with full consideration of its compatibility with cleaning agents and sanitizing/sterilizing chemicals.

Windows should provide a distortion free view of the interior of the isolator and adequate light should be provided for safe and effective working conditions. It may be preferable to have lighting fixtures located outside the isolator in order to avoid exposing them to cleaning and sanitizing agents.

A number of successful small rigid wall isolator designs have utilized a plastic enclosure, typically of acrylic, that is bonded with cement. In this design, the isolator is built completely without a frame. Isolators of this construction may be impractical for large systems with complex air-handling requirements, however, they are very useful for small portable systems and for containment applications. Frameless designs have the advantage of superior visibility of interior operations and relatively lower cost.

3.1.4 Other Materials

Any material that is suitably strong, cleanable, and resistant to cleaning and sanitizing agents could be used to build isolator systems. Isolators are equipped with gloves, half-suits, door gaskets, filter gaskets and other materials, all of which must be compatible with the materials processed within and/or used upon the isolator for cleaning and decontamination. There need be no restriction on the use of materials provided the functional requirements include:

- Chemical compatibility with production materials, decontamination and cleaning agents
- Structural integrity
- Cleanability (to the degree required)

3.2 Operator Interface

Isolators are designed to prevent the exchange of contamination between the enclosed work environment and the surrounding environment in which personnel are located. Therefore, manipulations of materials within the isolator must be made either via gloves or body suits, or auto-manipulators. The design execution of interface devices is critical both to successful integration of equipment into the isolator system, and to the avoidance of process hazards that could affect product qual-