Points to Consider for the Aseptic Processing of Sterile Pharmaceutical Products in Isolators

Together one step ahead

We at SKAN support you not only during the development process of your product but also provide you with a comprehensive life cycle support. Together with our experts and our unmatched isolator technology you will be able to optimize your processes. You will experience a carefree cooperation thanks to our longstanding experience with documentation and profound knowledge of the current FDA, EMA requirements.

You will find further information at **www.skan.ch**

Points to Consider for the Aseptic Processing of Sterile Pharmaceutical Products in Isolators

ISBN: 978-1-945584-14-5

PDA Points to Consider for the Aseptic Processing of Sterile Pharmaceutical Products in Isolators Task Force

Authors

Guenther Gapp, Gapp Quality GmbH (Chair)

Shelley Preslar, Azzur Group (Chair)

Marcia Cristina Baroni, Eli Lily and Company

Harold Baseman, Valsource, Inc.

Jette Christensen, Novo Nordisk

Richard Denk, SKAN

Phil DeSantis, DeSantis Consulting Associates

Dawn Downey, PhD, Eli Lilly and Company

Sabina Lancaster, Novartis

Jahanvi Miller, Parenteral Drug Association

Alexandra Staerk, Novartis

Stephen C. Yang, PhD, Merck & Co., Inc.

Table of Contents

1. INTRODUCTION AND SCOPE 1

2. GLOSSARY 2

TOPIC 1: ISOLATOR DESIGN 4

Q1-1: What should the pressure differential be between the isolator interior and the surrounding area? 5

Q1-2: What are the design considerations for isolator gloves? 6

Q1-3: How should the isolator be designed to minimize risk posed by interventions? 7

TOPIC 2: PHYSICAL ENVIRONMENT 8

Q2-1: What should the classification of the room surrounding the isolator be? 9

Q2-2: Should the isolator fill zone have unidirectional flow? 10

Q2-3: Should airflow pattern visualization/ demonstration be performed in an isolator? 11

Q2-4: Should the isolator environment qualification runs (at rest and in operation) include the sample sites established according to ISO 14644-1 or can a reduced sampling plan be followed based on a risk assessment? 12

Q2-5: What techniques should be used to identify, track, and evaluate air flow during qualification and maintenance of the isolator? 13

TOPIC 3: PERSONNEL 15

Q3-1: How should personnel be gowned when working in the isolator or the background environment area during aseptic processing? 16

Q3-2: Should operator gloves be disinfected prior to entering isolators gloves? 17

TOPIC 4: INTEGRITY TESTING OF ISOLATOR AND GLOVES 18

Q4-1: What methods should be used for integrity testing of isolators and gloves? 19

Q4-2: What should the maintenance program be for gloves? 20

Q4-3: What is the response to a glove integrity failure? 21

TOPIC 5: ENVIRONMENTAL MONITORING 22

Q5-1: What should the environmental monitoring frequency be in an isolator? 23

Q5-2: Which surfaces should be monitored in an isolator? 25

Q5-3: Should environmental monitoring excursions in isolators be treated differently compared to excursions in conventional filling lines? 26

Q5-4: Should each satellite/transfer isolator be monitored with a full environmental monitoring program similar to the main isolator? 27

Q5-5: What factors should be taken into consideration when transferring environmental monitoring plates into and out of an isolator? 29

TOPIC 6: MATERIAL TRANSPORT AND LOADING OF ISOLATORS 30

Q6-1: How should indirect product contact surfaces be sterilized or decontaminated? 31

Q6-2: Should a test for packaging material integrity of load items be carried out with respect to potential for VHP ingress? 35

Q6-3: What approaches are recommended for transferring stoppers from outside Grade C or D to inside Grade A/ISO 5 — manual or automated rapid transfer system? 36

Q6-4: How should tubs of sterilized syringes or vials be decontaminated and transferred into the isolator? 38

TOPIC 7: CLEANING, DISINFECTION, DECONTAMINATION: CYCLE DEVELOPMENT AND VALIDATION 39

Q7-1: What are the special considerations for cleaning and disinfecting isolator interiors (nonproduct contact surfaces) prior to decontamination? 40

Q7-2: What are the current options for isolator interior decontamination? 43

Q7-3: Should empty isolator mapping of temperature and humidity be performed as part of decontamination qualification studies? 45

Q7-4: What conditions and configurations should be considered during decontamination cycle development and validation? 46

Q7-5: What are the key differences between cycle development and cycle qualification? 47

Q7-6: Which BI should be used for cycle development and cycle qualification? What are the requirements for such a BI (e.g., spore count, D-value)? 49

Q7-7: How should multiple BIs be used and evaluated during VHP decontamination cycle development and validation? 51

Q7-8: What effect could oil-based HEPA-filter integrity agents have on the isolator decontamination cycle? 53

Q7-9: Should each load be qualified during the decontamination cycle qualification? 54

TOPIC 8: ASEPTIC PROCESS SIMULATIONS (APS)..... 55

Q8-1: What are the special considerations for media fills in isolators? 56

Q8-2: What are the special considerations for isolator APS study acceptance criteria? 57

Q8-3: What are the special considerations and criteria for determining the types and frequency of interventions to be included in isolator APS? 58

Q8-4: Should the connection, use, and unloading of transfer devices, such as RTP containers, DPTE bags, or alpha-beta ports and bags be included in the APS? 60

Q8-5: Should participation in an APS be used to qualify aseptic filling operators working in isolators? 61

Q8-6: Does qualification by participating in an APS on a conventional aseptic processing filling line qualify aseptic processing personnel on a similar isolator filling line? 62

Q8-7: Should the maximum number of operators be considered during the performance of the APS in the isolator? 63

Q8-8: Should the APS be used to validate the isolator loading pattern? 64

Q8-9: What are the special considerations for setting the duration of the APS for multiple shifts and multiple-day campaign production in isolators? 65

Q8-10: What are the special considerations for the inclusion and rejection of units during the isolator APS? 67

Q8-11: Should power failures that result in loss of airflow, loss of differential pressure, or loss of integrity of the isolator be simulated in an APS? 68

Q8-12: What are the special considerations for determining worst-case conditions in an isolator APS? 69

TOPIC 9: BEST PRACTICES IN ASEPTIC OPERATIONS.. 70

Q9-1: Is it necessary to use the same aseptic technique and practices when performing interventions in isolators and conventional fill lines? 71

Q9-2: Should interventions that disrupt unidirectional airflow in the isolator in proximity to or above exposed sterile product, product contact surfaces, and indirect product contact surfaces be permitted? 72

Q9-3: Should contact between decontaminated isolator gloves and direct or indirect product contact surfaces during setup or operations be permitted? 74

Q9-4: Should surfaces or materials that have not been sterilized or decontaminated be exposed in the isolator interior during aseptic operations? 75

Q9-5: Should different precautions or steps be taken when handling decontaminated materials versus sterilized materials in the decontaminated isolator? 76

1. Introduction and Scope

This document is designed to communicate best practices and considerations and to encourage further dialog with industry, health authorities, and suppliers of technology and materials while taking into account the changes and needs of the modern, global, sterile, healthcare product manufacturing industry.

In 2001, PDA issued *Technical Report No. 34: Design and Validation of Isolator Systems for the Manufacturing and Testing of Health Care Products*. Since then, much has been learned by industry, and several important regulatory guidelines, scientific articles, and conference presentations have been published.

In an effort to address the impact of the knowledge gained, this task force was established to focus on important regulatory and technology updates impacting isolator design, validation, and operations for aseptic processing. Two primary types of isolators—open and closed—will be addressed in this Points to Consider (PtC) document (see Glossary). Additional related topics, such as sterility testing isolators and containment isolators, will be discussed in a separate PtC document in the future.

Isolators provide superior environmental control compared with conventional grade A/B aseptic manufacturing operations and restricted access barrier systems (RABS), since isolators increase the sterility assurance of aseptically prepared products.[1] This document is intended to support identification and use of modern technology; it does not represent a standard or regulatory guidance.

Aseptic processing within isolation systems physically separates the external environment from the aseptic processing line, minimizing personnel exposure. By design, isolators are decontaminated while closed, using validated methods (e.g., controlled application of vapor phase hydrogen peroxide). A traditional isolator enclosure consists of a shell, viewing window, glove/sleeve assemblies, supply and exhaust filters, lights, input and output openings (e.g., equipment door airlocks, rapid transfer ports), and various other connection points. Filling isolators are designed to allow continuous or semicontinuous pass-through of materials during operation. A properly designed positive pressure isolator, along with adequate procedures for its maintenance, monitoring, and control, provides great advantages over traditional aseptic processing of sterile dosage forms, offering fewer opportunities for microbial contamination during processing.

Throughout the process of creating this document, two guiding and linked principles for improvement in sterile health care products emerged that were used to develop these points. Science- and risk-based approaches should be used to obtain information needed to make decisions related to the evaluation, design, qualification, operation, monitoring, and interpretation of results from various studies of sterile product manufacturing processes. Science- and risk-based approaches should be used to develop and implement control strategies and acceptance criteria designed to ensure the establishment and maintenance of manufacturing conditions that affect the sterility of products. Sterile drug substance/product manufacturing processes and testing requirements should be based on and relevant to the risk to product quality and patient safety. Quality risk management and assessment methods should be developed to identify risk and allow for the continuous improvement of processes and control strategies. It should be recognized that a properly designed and operated isolator will have a lower contamination risk than a conventional aseptic process design.

Where scientific approaches are similar and agreed upon, global health authority requirements and guidance should be consistent in technical language and definition. Having harmonized technical and regulatory language in place, where possible, consistent with approaches presented in other similar guidance's is an important factor. This practice should provide greater clarity of global regulatory expectations and reduce the risk of misunderstandings and redundant efforts.

This PtC is organized by Topics, followed by relevant Points to Consider. Each Point begins with a problem statement in the form of a question, representing issues or points needing clarification on that specific topic. Recommendations from subject matter experts on the PDA task force are presented in response to each question. The rationale for the recommendation follows, as well as references,

[1] **Note:** This PtC does not specifically address RABS, however, some of the recommendations may be applicable.

