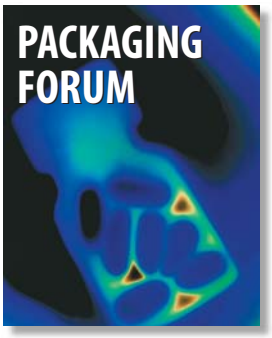

PDA Task Force Issues Guidelines to Aid Isolator Users

Hallie Forcinio

Ten years ago the idea of aseptic filling in an isolator rather than a cleanroom environment was only a concept. Today it's a reality, and standard production equipment is available for aseptic filling and product containment applications. A handful of isolator lines in the United States and Europe have received clearance from FDA and are successful components of the pharmaceutical production process. Several other isolator lines are in the process of being validated.

When FDA reviewed PDA's Technical Report No. 34 about isolator systems, significant differences of opinion between the organizations came to light.

Despite the rapid growth of isolator technology and the existence of successful lines, pharmaceutical manufacturers who are adopting this method still are feeling their way through the process. Considerable confusion surrounds the terms *isolator* and *barrier,* which have different meanings in some parts of the world.

To provide implementation and validation guidance for pharmaceutical manufacturers who are investing in this modification, The Isolation Technology Task Force of the Parenteral Drug Association (PDA) has published Technical Report No. 34 (TR 34), "Design and Validation of Isolator Systems for the Manufacturing and Testing of Health Care Products." This international task force includes cochairmen James Agalloco of Agalloco & Associates (Belle Mead, NJ) and James Akers, PhD, of Akers, Kennedy & Associates (Kansas City, MO) as well as members Uwe-Peter Dammann of ASTA Medica AG (Halle, Germany); Thomas Freund of Mallinckrodt Inc. (Raleigh, NC); William Frieben, PhD, of Pharmacia Corp. (Kalamazoo, MI); Richard Johnson and George Phariss of Abbott Laboratories, Inc. (Abbott Park, IL); Kunio Kawamura, PhD, of Otsuka Pharmaceutical Co., Ltd. (Tokyo, Japan); Jean-Michel Khoury of Aventis Pharma (Le Trait, France); Bengt Ljungqvist, PhD, and Berit Reinmuller of the Royal Institute of Technology (Stockholm, Sweden); Jack Lysfjord of TL Systems Corp. (now Bosch Packaging Technology, Minneapolis, MN); Didier Meyer of la Calhène (Velizy Cedex, France); Scott Pool of B. Braun Medical, Inc. (Irvine, CA); Scott Sutton, PhD, of Alcon Laboratories, Inc. (Fort Worth, TX); Carmen Wagner, PhD, of Merix Bioscience, Inc. (Durham, NC); and Russell Madsen, Jr., of PDA.

Although the TR 34 task force did not intend for the report to establish mandatory or implied standards, it does define terms and provide advice about the use of isolator technology for the preparation and packaging of sterile products and the containment of hazardous materials.

FDA reviewed a draft of the report. Joseph C. Famulare and John A. Eltermann, respective directors of divisions of manufacturing and product quality at the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research, commented about the text in a letter dated 27 July 2001 that was published in the December 2001 issue of *PDA Letter*. In several cases, TR 34 reflects FDA's thinking, but significant differences of opinion arose about the issues of whether the environment surrounding the isolator should be classified and whether the fraction-negative approach to calculate the effectiveness of gaseous decontaminating agents should be used.

FDA is comfortable with the idea of placing sterility-test isolators in an unclassified environment per *USP* ⟨1208⟩, but it believes aseptic manufacturing isolators have more stringent requirements. Considering the isolators' potentially open design, large size, and different usage, FDA believes placing them in an unclassified environment allows a greater risk of contamination; therefore, it recommends a classified environment ("at least Class 100,000," according to the Famulare–Eltermann letter). Contamination could occur if an isolator's air filtration system develops a leak or becomes overburdened or the system is exposed to ambient air during manual cleaning operations. "The choice of an unclassified room in this application would be tantamount to operation on the edge of failure," Famulare and Eltermann noted.

PDA countered that comment with a statement from task-force member Madsen: "The environment surrounding aseptic manufacturing isolators should be controlled, but it does not require

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formal classification." Madsen, the association's senior vice-president of Science and Technology, made the statement in a written response to the FDA letter on 26 October 2001, which also was published in the December 2001 issue of *PDA Letter*. The final version of TR 34 explains that "properly designed isolators do not allow the exchange of contaminants with the surrounding environment. Therefore, the quality of the surrounding room is a very minor consideration relative to the quality of the internal environment of the isolator or isolator network. The surrounding room should have limited access and should be clean and well organized." However, the report includes a caveat stating that "the reader should be advised that some regulatory authorities may not agree with this perspective and will require aseptic production isolators to be placed in Class 100,000 (ISO Class 8) environments."

FDA's other major point of contention with TR 34 relates to the use of fraction-negative studies to determine the resistance of biological indicators to decontaminating agents. FDA prefers the total-kill analysis method, which also is noted in TR 34 as acceptable. The agency views fraction-negative studies as less accurate because the volume of space and air flow within an isolator may cause variable chemical exposure of biological indicators, depending on their position inside the unit. PDA countered that, because such variations are reflected in the test results, the fraction-negative approach is particularly useful. "The survival of microorganisms at some locations allows the estimation of the D-value [the time in which the population of the challenge organism can be reduced by 90%] at the prevailing conditions within the unit, which results in a higher D-value and consequently a longer decontamination process," explained Madsen in PDA's response to FDA. "While a uniform concentration is always desired, deviations from the uniformity are incorporated into the D-value determination using the fraction-negative method," he continued.

The aforementioned points of disagreement aside, the 24-page report's remaining content covers a range of informative topics. TR 34 begins with an introduction and description of the two basic isolator types, open and closed, and their usage for aseptic and containment applications. Following the introduction is a discussion of isolator design and general construction, which includes a section about operator

Isolator system or barrier system?

ISOLATOR SYSTEM: "An isolator is sealed or is supplied with air through a microbially retentive filtration system (HEPA minimum) and may be reproducibly decontaminated. When closed, it uses only decontaminated (where necessary) interfaces or Rapid Transfer Ports 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." –PDA TR 34

BARRIER SYSTEM: "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." – PDA TR 34

interface and the use of gloves and sleeves, suits or half-suits, and air handling.

One of the longest sections provides guidelines about functional specifications of air-flow, particulate, temperature, and humidity control as well as leak testing. The report notes that "it should be recognized that every system leaks; the objective is to minimize the leak rate so that its effect on the process/operator is minimal." In addition, this section discusses ergonomics and rapid-transfer ports and is followed by guidance related to facility requirements.

Considerable space also is devoted to general user-requirement specifications that are organized according to whether the isolator is used for aseptic manufacturing or containment. These general user-requirement specifications, along with some that are project specific, serve as the basis for developing test functions and qualification testing.

User-requirement specifications related to aseptic manufacturing include sterility assurance; sterilization of production materials, components, containers, and equipment; sterilization of product-delivery piping; decontamination of the isolator and equipment not in contact with a product; surface decontamination of wrapped goods or containers with sterile contents; decontamination methods; and cleaning and cleaning validation. In the containment section, subjects include aseptic processing and containment, isolator cleaning, pressure differentials, sterile cytotoxic materials, and double-wall isolators. Sections about user-requirement specifications related to environmental control, leak testing, monitoring systems, microbiological monitoring of the environment, and process simulation conclude this portion of the report.

TR 34 concludes with a section about requalification testing. The document also includes appendices explaining terminology, some referenced test methods, and a discussion of isolators and sterility assurance.

PDA published TR 34 as a supplement to the September–October 2001 issue of *PDA Journal of Pharmaceutical Science and Technology*. Member copies may be purchased from the association for $75. Nonmember copies are available for $125 each.

For those seeking the most up-to-date information about isolation technology, PDA has scheduled the Isolation Technology Conference, Courses, and Tabletop Exhibit, 29 April–3 May 2002 at the Hilton Hotel in East Brunswick, New Jersey. Highlights of the agenda include the presentation of case studies describing isolator installations, updates about international regulatory issues, and roundtable discussions regarding isolator operation, decontamination, cleaning, and environmental monitoring. Registration information and additional details are available in the calendar section on the PDA Web site at www.pda.org.

For more barrier isolator discussion, see the International Society for Pharmaceutical Engineering's Web site (www.ispe.org) for information about its 11th Annual Barrier Isolation Technology Forum in June 2002. **PT**