Preface to Second Edition

It is now some five years since the first edition of this book appeared. There have been some technological advances in this time, but perhaps the most significant changes have been in the acceptance and the understanding of isolation technology. This acceptance may best be demonstrated by the series of monographs, guidelines, and standards produced by various bodies, designed to describe best practice in the design and operation of isolators. These include:

- Isolators Used for Aseptic Processing and Sterility Testing, Pharmaceutical Inspection Cooperation Scheme (Europe)
- Design and Validation of Isolator Systems for the Manufacturing and Testing of Healthcare Products, Parenteral Drug Association (USA)
- Sterile Drug Products Produced by Aseptic Processing, Food and Drug Administration (USA)
- ISO EN 14644 Part 7, Separative Devices
- Isolators for Pharmaceutical Applications, 3rd Edition, UK Pharmaceutical Isolator Group
- Handling Cytotoxic Drugs in Isolators in NHS Pharmacies, HSE and MHRA (UK)
- Recommendations for the Production, Control and Use of Biological Indicators for Sporicidal Gassing of Surfaces within Separative Enclosures, PDA Committee (USA and UK)

This second edition includes descriptions of and comments on these new documents. Recent technology — such as the new breed of sanitising gas generators — has been brought into the appropriate chapters, and the text has been updated throughout to reflect more recent thinking. Finally, minor errors in the previous edition have been corrected.

The second edition draws heavily on the content of the guideline booklet, Isolator for Pharmaceutical Applications — 3rd Edition, for both information and inspiration. I was closely involved in the assembly and editing of this recent work and make no apology for trawling its content. I am, however, grateful to my co-editors and to the UK Pharmaceutical Isolator Group for allowing me this privilege.
Thanks are also due to GRC Consultants; Malcolm Hughes, Dabur Oncology; Ray Collyer, Dabur Oncology; James Drinkwater, BioQuell Ltd.; and Brian Midcalf, UK Pharmaceutical Isolator Group.

Tim Coles
Cambridge
The Author

Tim Coles holds B.Sc. and M.Phil. degrees in environmental sciences and has been active in the field of pharmaceutical isolation technology for the last 20 years. He has worked with La Calhène SA, Cambridge Isolation Technology, and MDH (now BioQuell Ltd.), and is currently employed as an isolator specialist by GRC Consultants, part of the Mott-MacDonald group. Coles has been active in the UK Pharmaceutical Isolator Group and is on the editorial committee responsible for producing comprehensive new guidelines on isolation technology. He is also a member the PDA Biological Indicator Group and is a frequent speaker at conferences and seminars in the UK and Europe.
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Introduction

The background to isolation technology

The concept of the glovebox, used to protect a process from the operator, or to protect the operator from a process, is hardly new. Gloveboxes were first developed with the atomic weapons programme during World War II; development continued within the nuclear power industry, up to the present day. Gloveboxes were also used almost from the beginning of sterile product manufacture, because operators were quickly recognised to be the major source of contamination. The use of gloveboxes declined when reliable panel high efficiency particulate air (HEPA) filters (see Chapter 2) became available (Agalloco 1995). These filters led to the development of cleanrooms, which have dominated sterile production until recently. Gloveboxes have also been developed for nonnuclear containment purposes, particularly where pathogenic organisms are involved, and clear standards exist for such containments. The Class III Biological Safety Cabinet defined in BS 5295, and latterly in EN 12469, is, of course, a glovebox.

It is not easy to establish dates, but around 20 years ago, some subtle changes began to take place in the commercial climate and especially in the pharmaceutical industry. Consumers began to demand improved product quality whilst, at the same time, better standards of safety for those handling potentially hazardous materials became the norm. At about this time, the French company La Calhène SA recognised that some of the products that it had developed, specifically for the nuclear industry, might well have application in other areas, especially pharmaceuticals. In particular, the well-engineered Double Porte de Transfert Etanche (DPTE), or Double-Door Transfer Port, also known as the Rapid Transfer Port (RTP™) (see Chapter 3), which moved highly toxic plutonium oxide powder from one glovebox to another, was seen as a device with a future in pharmaceuticals. A further factor was the work of Professor Philip Trexler in the 1950s, who produced sealed enclosures from the clear polyvinyl chloride (PVC) films that were then newly introduced. These, combined with glass-fibre “candle” air filters, provided simple and cheap contamination-free environments for research
animals. Indeed, the success of these enclosures was so great that truly specific pathogen-free (SPF) animals could be reared and maintained for long periods; their use continues widely today.

It has been suggested that specific technical developments have led to the recent expansion of isolation. For instance, Carmen Wagner states:

The DPTE (RTP) is, in the author’s opinion, a milestone in the evolution of advanced aseptic processing isolators. (Wagner 1995)

This is not entirely true, because the La Calhène SA port was freely available 25 years ago, yet the real expansion of isolation has only been in the last ten years. The RTP is a very useful device for use in isolation, but, in truth, it has been a blend of various issues — commercial, social, and technical — which has led to a reevaluation of gloveboxes and specialised enclosures, and to the emergence of a new philosophy called isolation technology.

The technology has applications in many areas of endeavour, but it is principally with its application in the pharmaceutical industry, as regulated by the Medicines and Health Care Products Regulatory Agency (MHRA), formerly the Medicines Control Agency, in the UK and by the Food and Drug Administration (FDA) in the U.S., that this book is concerned. This scope extends, however, to include hospital pharmacy work and some aspects of biotechnology, research animals, and direct medical uses. Figure 1.1 shows the development pathways of the various types of isolator applications.

**Isolation technology — a definition**

It seems only fair to explain what is meant by isolation technology at an early stage in this account, although this seems to be an area where agreement is still lacking. The definition of the technology is bound up with the definition of the word isolator. In the recent publication *Isolator Technology*, edited by Carmen Wagner and James Akers (1995), the word isolator is given four separate definitions in the glossary section, reflecting the views of several authors. Isolators are then further subdivided into open and closed categories. Meanwhile, in the guideline booklet *Isolators for Pharmaceutical Applications* (Lee and Midcalf 1994), an isolator is defined as follows:

A containment device which utilises barrier technology for the enclosure of a controlled workspace.

Isolators are then subdivided in the booklet into Type 1, positive pressure, used for product protection, and Type 2, negative pressure, used for operator protection. This definition was criticised by James Lyda of the Parenteral Drug Association (PDA) (Lyda 1995) for failing to utilise the words environment and microbiological quality. However, a fully comprehensive definition
would become inordinately lengthy, and these issues are clearly addressed elsewhere in the booklet.

Yet another definition has been given by the working group established by the International Organisation for Standardisation (ISO) on contamination control (ISO/TC209/WG7, reported by Brammah 1995), as follows:

A localised environment created by a sealed enclosure to isolate the product from contamination and/or people.

This committee has more recently produced Part 7 of ISO 14644 (ISO/FDIS 14644–7 2001), in which an isolator is defined as “An industry specific separative enclosure.” In light of such arguments, it seems that, for the purposes of this book, a rigorous definition is probably counterproductive.
Let us say, then, that isolation technology is the placement of a physical barrier between a process and its operators. The purpose of the barrier may be to protect the process and its materials from the effects of the operators, or it may be to protect the operators from the effects of the process; in some cases, it may seek to do both. The barrier may be total, so that the process is always behind either a physical wall or at least behind HEPA filters, or it may be partial, so that the process may be separated only, for instance, by engineered airflow.

Beyond this, we can say that the environment, workspace, or critical area, delineated by the barrier, should have a defined quality that takes account of the intended purpose. This quality may be defined in terms of microbiology, particle burden, humidity, oxygen content, or whatever combination is appropriate.

**Isolation technology versus barrier technology**

The use of the word *barrier* in the preceding section promptly engenders a new argument concerning the differences, be they technical or semantic, between isolation technology and barrier technology. It is probably true to say that the terms were practically synonymous in the early days, but now it seems to be accepted that they do convey quite separate technical meanings.

James Agalloco clearly described the received wisdom in a paper given to a meeting of the Scottish Society for Contamination Control in Birmingham, UK, in 1996 (Agalloco 1996). Put quite simply, isolation technology is absolute and barrier technology is not. In true isolators, a physical wall of perhaps plastic or stainless steel exists at all times between the process and the operators. The inlet and exhaust of air, or other gases, can be only via HEPA filters. This includes any transfer devices in use on the isolator.

By contrast, barrier technology allows for some limited exchange of atmospheres between the workspace and the outside environment. Thus, a rather open form of barrier is the curtaining around a Vertical Laminar Flow unit in a cleanroom, whilst a more closed form would be the mousehole devices frequently used for the exit of vials from enclosed filling lines (see Chapter 3). Carmen Wagner (1995) describes partial barriers and closed barriers, along with open isolators and closed isolators, under the all-embracing title of *Protective Barrier Systems*. The closed isolator has full containment and is probably used only in batch processes, whereas the open isolator may carry a transfer device, like the mousehole, with very restricted atmospheric exchange, inevitable for continuous line processes. The degree to which the defined workspace is closed has implications for the establishment and maintenance of a sterile environment. Clearly, a sealed isolator is more easily sterilised (though note the limitations of the word *sterile*, which are discussed at the start of Chapter 7) than a barrier enclosure that may exchange air with the outside environment. As a rule, this book is concerned only with isolation technology; but under the strict definition, certain aspects of barrier
technology may be invoked, particularly in continuous process applications. Figure 1.2 shows a typical flexible film isolator with many of the features described later in this book.

**The aim of isolation technology**

There are a number of factors that may combine in various ways to lead the user toward isolation technology. The priority of such factors will depend on the nature of the process, but, generally speaking, the aims of the technology are given below.
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