Pharmaceutical Isolators

A guide to their application, design and control

Edited by the Pharmaceutical Isolator Working Party

A Working Party of the UK NHS Pharmaceutical Quality Assurance Committee

Principal Editors for the Pharmaceutical Isolator Working Party

Brian Midcalf
BPharm, FRPharmS
Assistant PTQA Course Director
School of Continuing Education, University of Leeds, UK

W Mitchell Phillips
BPharm, MRPharmS
West Midlands Quality Assurance Pharmacist
Birmingham, UK

John S Neiger
MA, CEng, MI MechE, MSEE
Chairman
Envair Limited, Haslingden, UK

Tim J Coles
BSc, MPhil
Isolator Specialist
GRC Consultants, Alton, UK
1 Isolator applications

1 Introduction 1

1.1 Applications 1

1.1.1 Non-pharmaceutical applications 2
1.1.2 Pharmaceutical industry applications 3
1.1.3 Hospital pharmacy applications 5

1.2 Summary 5

2 Design

2 Scope 9

2.1 Definitions and terminology 9
2.2 Characterisation of a pharmaceutical isolator 9

2.3 Design considerations 11

2.3.1 Product protection 11
2.3.2 Operator protection (containment) 11
2.3.3 Operator protection (containment) and product protection 12
2.3.4 Protection against process-generated contamination 12
2.3.5 Radiopharmacy 12

2.4 Construction 13

2.4.1 General 13
2.4.2 Main components 13
2.4.3 Flexible film 14
2.4.4 Stainless steel 14
2.4.5 Coated mild steel 14
2.4.6 Rigid plastics 14
2.4.7 Windows in rigid isolators 15
2.4.8 Pneumatic and other gas services 15
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 Filtration</td>
<td>15</td>
</tr>
<tr>
<td>2.5.1 General</td>
<td>15</td>
</tr>
<tr>
<td>2.5.2 Filter manufacturers' standards</td>
<td>16</td>
</tr>
<tr>
<td>2.5.3 Standards for the in situ leak testing of installed HEPA filters</td>
<td>17</td>
</tr>
<tr>
<td>2.5.4 Specification of HEPA filters</td>
<td>18</td>
</tr>
<tr>
<td>2.5.5 Incorporation of HEPA filters into isolator designs</td>
<td>19</td>
</tr>
<tr>
<td>2.5.6 Carbon filters</td>
<td>21</td>
</tr>
<tr>
<td>2.6 Pressure regimes</td>
<td>22</td>
</tr>
<tr>
<td>2.6.1 Positive pressure isolators</td>
<td>22</td>
</tr>
<tr>
<td>2.6.2 Negative pressure isolators</td>
<td>22</td>
</tr>
<tr>
<td>2.6.3 Containment</td>
<td>22</td>
</tr>
<tr>
<td>2.6.4 Pressure differentials</td>
<td>23</td>
</tr>
<tr>
<td>2.7 Leakage and leaktightness</td>
<td>23</td>
</tr>
<tr>
<td>2.7.1 Summary</td>
<td>23</td>
</tr>
<tr>
<td>2.7.2 Leakage in positive pressure isolators</td>
<td>23</td>
</tr>
<tr>
<td>2.7.3 Leakage in negative pressure isolators</td>
<td>24</td>
</tr>
<tr>
<td>2.7.4 High pressure integrity/low hourly leak rate isolators</td>
<td>24</td>
</tr>
<tr>
<td>2.7.5 Gloves, sleeves and half-suits</td>
<td>24</td>
</tr>
<tr>
<td>2.7.6 Internal leakage</td>
<td>25</td>
</tr>
<tr>
<td>2.7.7 Filter seals</td>
<td>25</td>
</tr>
<tr>
<td>2.7.8 Clean air</td>
<td>25</td>
</tr>
<tr>
<td>2.7.9 Induction leakage</td>
<td>25</td>
</tr>
<tr>
<td>2.7.10 Edge effects</td>
<td>27</td>
</tr>
<tr>
<td>2.7.11 Macro-leakage</td>
<td>27</td>
</tr>
<tr>
<td>2.7.12 Measurement and detection of leaks</td>
<td>27</td>
</tr>
<tr>
<td>2.8 Airflow (flow) regimes</td>
<td>27</td>
</tr>
<tr>
<td>2.8.1 Turbulent airflow (non-unidirectional)</td>
<td>27</td>
</tr>
<tr>
<td>2.8.2 Unidirectional airflow</td>
<td>28</td>
</tr>
<tr>
<td>2.8.3 Zoned airflow</td>
<td>28</td>
</tr>
<tr>
<td>2.8.4 Gassing</td>
<td>29</td>
</tr>
<tr>
<td>2.9 Fan systems</td>
<td>29</td>
</tr>
<tr>
<td>2.10 Controls, instrumentation, alarms and performance monitoring</td>
<td>31</td>
</tr>
<tr>
<td>2.10.1 Controls</td>
<td>31</td>
</tr>
<tr>
<td>2.10.2 Instrumentation</td>
<td>31</td>
</tr>
<tr>
<td>2.10.3 Alarms</td>
<td>31</td>
</tr>
<tr>
<td>2.10.4 Performance monitoring</td>
<td>32</td>
</tr>
<tr>
<td>2.11 Ergonomics, lighting, noise, vibration and electrical safety</td>
<td>32</td>
</tr>
<tr>
<td>2.11.1 Ergonomics</td>
<td>32</td>
</tr>
<tr>
<td>2.11.2 Lighting</td>
<td>32</td>
</tr>
<tr>
<td>2.11.3 Noise levels</td>
<td>33</td>
</tr>
<tr>
<td>2.11.4 Vibration</td>
<td>33</td>
</tr>
<tr>
<td>2.11.5 Electrical safety</td>
<td>33</td>
</tr>
<tr>
<td>2.12 Design for decontamination</td>
<td>34</td>
</tr>
<tr>
<td>2.13 Design for validation</td>
<td>35</td>
</tr>
</tbody>
</table>
3 Transfer devices

Scope 37

3.1 Function of different transfer devices 37

3.2 Types of transfer device 39

3.2.1 Type A1 transfer device 39
3.2.2 Type A2 transfer device 40
3.2.3 Type B1 transfer device 41
3.2.4 Type B2 transfer device 41
3.2.5 Type C1 transfer device 42
3.2.6 Type C2 transfer devices 43
3.2.7 Type D transfer devices 44
3.2.8 Type E transfer devices 45
3.2.9 Type F transfer devices 46

4 Access devices

Introduction 49

4.1 Gloves 49

4.1.1 General requirements 49
4.1.2 Glove type 51
4.1.3 Glove material 51
4.1.4 Glove sizes 51
4.1.5 Glove manufacture 53
4.1.6 Variable thickness gloves 53
4.1.7 Laminated and loaded gloves 53
4.1.8 Glove properties 54
4.1.9 CE marking and standards 55

4.2 Sleeves 55

4.2.1 General properties 55
4.2.2 Accordion sleeves 56
4.2.3 Cuff rings and glove changes 57
4.2.4 Changing gloves 57
4.2.5 Leak testing 58
4.2.6 Shoulder rings 58
4.2.7 Provision for gassing 58

4.3 Gauntlets 58
4.4 Half-suits 59
4.5 Full suits 60
4.6 Robotics 61
4.7 Training and user maintainence 62

5 Siting of isolators and clothing regimes

Scope 65

5.1 Construction 65
5.2 Access 66
5.3 Isolator room 66
5.4 Support room 67
6 Cleaning, decontamination and disinfection
Scope 73
6.1 Cleaning 73
  6.1.1 General considerations 73
  6.1.2 Cleaning schedule or timing 75
  6.1.3 Cleaning methods 75
  6.1.4 Cleaning agents 76
6.2 Disinfection 77
  6.2.1 General 77
  6.2.2 Disinfectants (liquid sanitising agents) 78
  6.2.3 General guidance 79
6.3 Nebulisation or fogging 79
6.4 Sporidical gassing processes or fumigation 82
  6.4.1 Formaldehyde 82
  6.4.2 Hydrogen peroxide vapour 83
  6.4.3 Peracetic acid vapour 85
  6.4.4 Chlorine dioxide gas 86
  6.4.5 Ozone gas 86
  6.4.6 Ultraviolet and white light 86
6.5 Sterilisation 87
6.6 Biological indicators (BIs) 87
6.7 Chemical contamination 88
6.8 Validation 89
  6.8.1 Cleaning validation 89
  6.8.2 Disinfection validation 89
  6.8.3 Gassing validation 90
6.9 Training 92
6.10 Safety 92

7 Physical monitoring
Scope 93
7.1 Leak testing of installed HEPA filters 93
7.2 Particle counts 95
7.3 Airflow testing 95
7.4 Flow visualisation and recovery testing 96
7.5 Pressure testing 97
7.6 Breach testing 98
7.7 Recommendations for physical testing 98

8 Leak testing 101
8.1 Introduction 101
8.2 Leak detection methods 102
  8.2.1 Distributed leak test 102
  8.2.2 Soap solution 103
  8.2.3 Ammonia 103
  8.2.4 Helium 103
  8.2.5 DOP (dispersed oil particulates) 104
  8.2.6 Sonics 104
8.3 Leak rate measurement methods 105
  8.3.1 Introduction 105
  8.3.2 Factors which affect leak rate measurement 105
  8.3.3 Oxygen method 107
  8.3.4 Pressure hold method 107
  8.3.5 Parjo test method 107
  8.3.6 Pressure decay method 108
8.4 Discussion of pressure decay leak rate measurement 109
  8.4.1 Changes in atmospheric pressure 109
  8.4.2 Changes in internal temperature of the isolator 109
  8.4.3 Movement in flexible parts 109
8.5 Guidelines for leak rate measurement by pressure decay 110
  8.5.1 Test method for isolators where a maximum leak rate of 1.0% per hour is specified 110
  8.5.2 Test method for isolators where a maximum leak rate of 0.25% or 0.05% per hour is specified 111
8.6 Expression of pressure decay and pressure hold leak rate results 113
  8.6.1 Hourly leak rate 113
  8.6.2 Percentage volume change per hour 115
  8.6.3 Standard decay time 115
  8.6.4 Volumetric leak rate 116
  8.6.5 Single hole equivalent (SHE) 117
8.7 Summary of expressions 118
8.8 Determination of acceptable leak rates 118
8.9 Tests for gloves, sleeves and half-suits 119
  8.9.1 Gloves 119
  8.9.2 Sleeves 120
  8.9.3 Half-suits 121
8.10 Leak testing schedule 121
9 Microbiological monitoring

Scope 123

9.1 General 123
  9.1.1 Media 123
  9.1.2 Fertility challenge, sterility and records 124
  9.1.3 Sampling 124
  9.1.4 Culture incubation and recording 125
  9.1.5 Reporting 127

9.2 Recommended test protocols 128
  9.2.1 Active air sampling 128
  9.2.2 Settle plates 128
  9.2.3 Surface sampling of isolator surfaces 129
  9.2.4 Finger dabs 130
  9.2.5 Process validation 130
  9.2.6 Microbiological validation of the operator 131

9.3 Hand washing facilities 131
  9.3.1 Hand washing 132

9.4 Sterility testing 132

9.5 Suggested target levels 133

9.6 Transfer devices 133

9.7 Recommended microbiological sampling frequencies 134

10 Validation

Scope 135

10.1 Overview 135

10.2 Documentation 136
  10.2.1 Document types 136
  10.2.2 Document structure 136

10.3 Change control 137

10.4 Summary of validation stages 137
  10.4.1 User requirement specification (URS) 137
  10.4.2 Validation master plan (VMP) 138
  10.4.3 Validation plan (VP) 138
  10.4.4 Functional design specification (FDS) 138
  10.4.5 Design qualification (DQ) 138
  10.4.6 Factory acceptance testing (FAT) 138
  10.4.7 Type qualification testing (TQT) 139
  10.4.8 Factory qualification testing (FQT) 139
  10.4.9 Installation qualification (IQ) 139
  10.4.10 Site acceptance testing (SAT) 139
  10.4.11 Operation qualification (OQ) 139
  10.4.12 Performance qualification (PQ) 140
  10.4.13 Commissioning and validation 140
  10.4.14 Requalification testing 140
## 10.5 User requirement specification (URS)
- 10.5.1 URS bespoke isolators 140
- 10.5.2 URS standard isolators 141
- 10.5.3 URS content 141

## 10.6 Validation master plan
- 10.6.1 VMP structure and content 143

## 10.7 Design qualification (DQ) 144

## 10.8 Installation qualification (IQ) 145

## 10.9 Operational qualification (OQ) 146

## 10.10 Performance qualification (PQ) 148

## 10.11 GAMP – Good automated manufacturing practice 149

## 10.12 Summary 150

### 11 Standards and guidelines

**Introduction** 153

#### 11.1 Designation and terminology 153

#### 11.2 Clean air and isolator standards 155

#### 11.3 Filter standards 155

#### 11.4 Biotechnology standards 156

#### 11.5 Other relevant standards 156

#### 11.6 GMP guidelines 156
- 11.6.1 EC GMP 2002 and Orange Guide 2002 156
- 11.6.2 Quality Assurance of Aseptic Preparation Services 2000 158
- 11.6.3 A Code of Practice for Tissue Banks providing tissues of human origin for therapeutic purposes DoH 2001 158
- 11.6.4 GAMP Guide for Validation of Automated Systems 158
- 11.6.5 PIC/S Recommendation Pl 014-1 24 June 2002: Isolators used for aseptic processing and sterility testing 158
- 11.6.6 PDA Technical Report No. 34: Design and validation of isolator systems for the manufacturing and testing of health care products 159
- 11.6.7 FDA Sterile drug products produced by aseptic processing (Draft) 159

#### 11.7 Biotechnology and safety guidelines: ACDP (Advisory Committee on Dangerous Pathogens] documents 159
- 11.7.1 Categorisation of biological agents according to hazard and categories of containment (Fourth edition, 1995) 159
- 11.7.2 Second supplement to: Categorisation of biological agents according to hazard and categories of containment (Fourth edition, 1995) 159
11.7.3 The management, design and operation of microbiological containment laboratories 160
11.7.4 Biological agents - managing the risks 160
11.7.5 Working with hazard group 4 agents 160

11.8 COSHH 160
11.8.1 EH40 Occupational exposure limits 2002 161

12 Definition of terms 175
Scope 175
Definitions 175

A1 ‘Handling cytotoxic drugs in isolators in NHS pharmacies.’
HSE/MCA January 2003 189
A1.1 Introduction 189
A1.2 Routes of operator exposure 191
   A1.2.1 Factors involved in employee exposure or product contamination 192
   A1.2.2 Factors specific to employee exposure 193
   A1.2.3 Factors specific to product contamination 194
A1.3 Combining risk to operator with risk to product 194
A1.4 Negative and positive pressure: Decision table 196
References 201
Further information 202

A2 Training 203
A2.1 Introduction 203
A2.2 Performance objectives 203
   A2.2.1 Principles of basic theory, design, and siting of isolators 203
   A2.2.2 Procedures for the operation of isolators 204
   A2.2.3 Procedures for materials transfer – non-gassed isolators 204
   A2.2.4 Procedures for loading and sanitisation of gassed isolators 204
   A2.2.5 Procedures for aseptic processing 204
   A2.2.6 Procedures for integrity testing 204
   A2.2.7 Procedures for routine glove changing 205
   A2.2.8 Procedures for decontamination 205
   A2.2.9 Environmental monitoring 205
   A2.2.10 Safety 206
   A2.2.11 Documentation and change control 206
A2.3 Structure and assessment 206
  A2.3.1 Under-pinning knowledge 206
  A2.3.2 Performance 206
  A2.3.2 Assessment 206
A2.4 Ongoing treatment and assessment 206
A2.5 Records 207
A2.6 Other training 207
A2.7 Practical note 207
References 208

A3 Stainless steel for isolators 209
A3.1 Steel alloys 209
A3.2 Corrosion resistance of stainless steel 210
A3.3 Stainless steel finishing 211
A3.4 Finishing methods 211
  A3.4.1 Prefinished 211
  A3.4.2 Hand finish and emery belt finish 211
  A3.4.3 Electropolishing 211
A3.5 Terminology 212
  A3.5.1 Grit size 212
  A3.5.2 Roughness average (Ra) 212
A3.6 Application to pharmaceutical isolators 212
  A3.6.1 Very high corrosion resistant alloys 212
  A3.6.2 Cleaning 213
Suggested reading 213

A4 HEPA filtration mechanisms, MPPS and typical particle sizes 215
A4.1 Introduction 215
A4.2 Mechanisms 215
  A4.2.1 Straining 215
  A4.2.2 Impaction 216
  A4.2.3 Interception 216
  A4.2.4 Diffusion 216
A4.3 MPPS (most penetrating particle size) 216
  A4.3.1 Typical particle sizes 217
  A4.3.2 Common particle sizes 217
A4.4 Viruses 218

A5 Calculations to estimate the size of a leak that can be detected using DOP 219
Scope 219
A5.1 Calculation 219
A5.2 Conclusion 221