SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

ISOLATOR TECHNOLOGY

This document has been prepared to serve as a recommendation for work on isolator technology. It represents the South African Health Products Regulatory Authority's current thinking on this subject. These guidelines should be read in conjunction with the SA Guidelines for Good Manufacturing Practices.

CHIEF EXECUTIVE OFFICER (CEO)

TABLE OF CONTENTS

1 PRINCIPLES

1.1 Isolator technology is now widely used and accepted for the aseptic processing of pharmaceuticals. The use of barrier systems offers improvements in the handling of pharmaceutical products in circumstances where product protection and the maintenance of asepsis, and/or operator protection and the control of hazardous substances are critical requirements. Isolators have several advantages over conventional clean rooms and laminar flow cabinets for aseptic preparation and dispensing of injections. Isolators provide an acceptable level of sterility assurance for aseptic operations. Isolators cannot be regarded as totally sealed units since access to the controlled workspace must be open when materials are transferred into and out of this area and the workspace is continuously supplied with HEPA filtered air. Other than this air supply, the controlled workspace of the isolator will, when in use, be sealed from its background environment.

1.2 Critical SOP's include those detailing sanitisation, introduction of material, withdrawal of material, and training of personnel.

2 DEFINITION OF TERMS

2.1 Isolator

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

2.2 Type 1 Isolator

An isolator primarily designed to protect the product from process-generated and external factors that would compromise its quality.

2.3 Type 2 Isolator

An isolator designed to protect the product from process-generated and external factors that would compromise its quality and to protect the operator from hazards associated with the product during operation and in the event of failure.

2.4 Air Iock

An enclosed space with two or more doors and which is interposed between the controlled workspace and the background environment of the isolator, for the purpose of controlling air flow between them and to facilitate the transfer of materials between them.

2.5 Alarm

An audible and/or visible signaling system which warns of a fault condition. It must incorporate a device to ensure that it cannot be cancelled until corrective action is taken.

2.6 Background Environment

The environment in which the isolator is sited. Background environments are categorised in table 3.

2.7 Controlled Work Space

An enclosed space constructed and operated in such a manner and equipped with appropriate air handling and filtration systems to reduce to a pre-defined level the introduction, generation and retention of contaminants within it.

2 Definition of terms continued

2.8 Critical Zone

That part of the controlled workspace where containers are opened and product is exposed. Particulate and microbiological contamination should be reduced to levels appropriate to the intended use.

2.9 Decontamination

A process which reduces contaminating substances to a redefined acceptance level.

2.9.1 Sanitisation

That part of decontamination which reduces viable micro-organisms.

2.9.2 Particulate Decontamination

That part of decontamination which reduces visible and sub-visible levels to a defined acceptable level.

2.9.3 Chemical Decontamination

That part of decontamination which reduces chemical contamination to a defined acceptance level.

2.10 Docking Device

A sealable chamber which can be (completely removed from or locked onto an isolator and then opened without contamination passing into, or out of, the controlled workspace or the chamber.

2.11 Exhaust Filter

A filter through which the exit stream of air from an isolator

2.12 HEPA (High Efficiency Particulate Air) Filter

Filters with no greater than 0,003 % penetration of 0,5 um particles when tested according to BS 3928.

2.13 Laminar Flow

Airflow in which the entire body of air within a confined area moves with uniform velocity along parallel flow lines.
Note: Mayalso be referred to as "unidirectional flow'.

2.14 Sterilisation

The process applied to a specified field which inactivates viable micro-organisms and thereby transforms the non-sterile field into a sterile one.

2.15 Transfer Chamber
A device which facilitates the transfer of goods into or out of the controlled workspace whilst minimising the transfer of contaminants.

2.16 Transfer Hatch

See Transfer Chamber.

2 Definition of terms continued

2.17 Transfer Isolator

A separate isolator which can be fixed or removable and which is attached to the main operational unit, acting as a complete transfer device.

2.18 Transfer Device

A device, which can be fixed or removable, which allows materials to be transferred into or out of the controlled

2 19 Transfer Port

See transfer chamber.

2.20 Transfer System

The process of transfer of materials into and out of the isolator through a transfer device.

2.21 Turbulent Flow

A flow of air which is non-laminar.

3 ISOLATOR DESIGN PRINCIPLES

Although the specifications should not be restrictive, there are basic design parameters to which isolators should conform.

3.1 Air input may be laminar flow, turbulent flow, or a combination of the two.

3.2 The critical zone of the controlled workspace should be equivalent to the EC Grade A, but the airflow in the critical zone need not be laminar flow (see 23.3.3).

3.3 If the isolator is not supplied with a laminar air flow system, tests should be performed so as to confirm that only air complying with the requirements of EC Grade A is applied to the critical zone. Air should be effectively swept from the controlled workspace and startling vortices. Stagnant areas should not exist.

3.4 Type 2 isolators should operate under negative pressure.

3.5 Type 2 isolators for use with radiopharmaceuticals should incorporate an appropriate radiation protective system against ionising radiations.

3.6 For operator protection, in the event of a breach in type 2 isolators a minimum breach velocity of O,7 msec should be maintained.

3.7 The transfer of materials into and out of the controlled workspace is a critical factor of the isolator's operation. The transfer device separates the background environment from the Grade A controlled workspace. It should be designed such that it does not compromise the Grade A controlled environment. To this end an interlocked device will provide greater security. The size of the transfer device should be sufficient to allow all necessary materials and equipment to be passed through.

Note: Commissioning studies should include tests to confirm that contaminants will not pass from the transfer device into the controlled work area. A fully validated transfer procedure should be in place.

3 Isolator design principles continued

3.8 All internal surfaces (including seals, holes, screws) should be accessible to the operator for cleaning and disinfection purposes without compromising the isolator's integrity. They should be resistance to corrosion by cleansing and disinfecting agents and should be capable of withstanding gaseous disinfection or sterilisation.

3.9 The pressure differential between the Grade A controlled workspace and the background environment should be continuously monitored.

3.10 All filters in isolators in which hazardous substances are handled must have a safe change facility. Both the manufacturer and the user should be made aware of the risks associated with changing filters.

3.11 All exhaust (or re-circulated) air should pass through one or more HEPA filters. Extract air from type 2 isolators should normally be ducted to the outside through one or more HEPA filters and another necessary absorption media (eg. carbon). Where isolators are used infrequently or low levels of hazardous materials are handled, then the exhaust air may be re-circulated into the background environment through two HEPA filters in series provided the risk has been assessed and has been shown to be low risk. (For further details of exhaust filters see also appendix 5.)

3.12 When designing isolators, consideration should be given to optical clarity, lighting, noise levels, humidity, electrical safety, temperature, vibration, ergonomics and the comfort of the operator (s).

3.13 Pressure differentials and the direction of air flow should be such that when the access between the transfer system and the controlled workspace is open, contaminants will not pass into the controlled workspace and, additionally in type 2 isolators, operator protection is also maintained.

3.14 If a fixed transfer device has its own air supply it should be HEPA filtered.

3.15 The air change rates in all parts of the isolator system should be sufficient to maintain the defined grade of environment.

Note: The air change rate will be such that any unfiltered air that enters the isolator or transfer device will be purged from the system within 5 minutes.

3.16 The fan should not be capable of damaging the filters in their maximum loaded state.

3.17 Isolators should have the facility to enable routine leak testing and particle counts to be carried out in the isolator itself and in its transfer devices. Where access points are provided for test equipment they should be labelled.

3.18 The isolator should be designed so that the HEPA filters can be integrity tested in situ.

4 THE SITING OF ISOLATORS

4.1 Isolator(s) should be sited in a dedicated rooms(s) used only for the isolator and its ancillary equipment and related activities. The interior surfaces of the rooms (walls, floots, ceiling) should be smooth, free from cracks and open joints. They should not shed particulate matter and should allow easy and effective cleaning and sanitisation.

4.2 The classification of the background environment in which the isolator is located will depend upon the design and, operational characteristics of the isolator, but should be at least grade D. When deciding on the siting of isolators, consideration should be given to the following:
The type of isolator - type 1/type 2.
The transfer system - see appendix 1.
The level and frequency of use i.e. dispensing/ preparation/manufacture.

In order to address these variables, isolators have been classified according to the transfer system.

4 The siting of isolators continued

Details of the different transfer systems and the corresponding transfer devices are shown in appendix 1. The background environment for the isolator can then be categorised as I, II, III, IV, V or EC Grade A-D depending upon the transfer system and the use to which the isolator will be put (tables 1 and 2).

4.3 The definitions of air quality categories I-V are given in table 3. The categories have been defined according to their permitted levels of viable and non viable particles. For comparative purposes, the requirements of the different environmental classifications from commonly quoted standards documents are also included in the table.

It should be noted that the levels of viable micro-organisms for categories II-IV of the background environment are more stringent than then nearest grade of air quality specified in the EC GMP.

4.4 For pharmaceutical applications the major criterion upon which the background environment is categorised should be the risk of microbiological contamination of the product. For this reason the environment has been classified in this document according to the number of viable organisms that can be detected.

It is recognised however that environmental testing is not a guarantee that environmental quality is maintained.
Procedures and quality systems should be used to provide the necessary level of quality assurance.

5 FACTORY ACCEPTANCE TEST (FAT)

5.1 A factory acceptance test (FAT) should be performed. The report should cover at least a check against Customer Order for completeness, visual check for appearance and identification, the record of serial numbers of filters, dimensional check, electrical installation and safety check, functional check, including operation of interlocks and alarms and documentation dossier.

6 INSTALLATION QUALIFICATION (IQ)

6.1 Qualification data (records) of the isolator should at least cover installation qualification (IQ), i.e. integrity and leakage test, filter integrity test, filter mounting integrity test, instrument check and calibration as well as functional check of all operating systems.

7 OPERATIONAL QUALIFICATION (OQ)

7.1 Operational qualification (OQ) should be performed.

7.2 Records should cover checks on air flow rates, pressures controlled within specified limits, air flow patterns, temperature and humidity patterns, particle counts as well as noise and light levels.

7.3 Testing of filters and filter housings should be done at regular intervals.

7.4 The vibration effects of HVAC fans and filling equipment on joints and particularly on hepa filter clamping systems should be tested. Maximum limits for vibration should be set, monitored and controlled.

7.5 The ventilation/filtration system should be appropriate for functions performed in the isolator and should be validated.

7.6 Leak tests of the Isolator should be performed on a regular basis, including the glove/sleeve system.

8 PERFORMANCE QUALIFICATION (PQ)

8.1 Performance qualification (PQ) should be performed.

8.2 Sterilisation cycles with standard loadings should be developed and validated.

8.3 There should be relevant SOP's with respect to operations being performed.

9 MICROBIOLOGICAL MONITORING

9.1 General

Viable particle monitoring for micro-organisms and non-visible particle monitors should be performed at regular intervals.

A plan of the isolator should be prepared with coded positions for settle plate, swabbing and air sampling sites. The following methods may be employed:

9.2 Settle Plates

Coded and dated, sterile, tryptone soya agar plates should be exposed for two hours at all test sites within the isolator.

These should be incubated in accordance with a written SOP at the appropriate temperature for up to five days, or as otherwise chosen by the microbiologist.

9.3 Surface Samples

Surface samples at coded sites using sterile contact plates or sterile moistened swabs should be taken.

Note: Each sample site should be sanitized to remove any material transferred to it during the sampling process.

9.4 Active Air Sampling

Samples should be taken at the coded sites.

Where the test utilises standard plates or strips, these should be incubated at the appropriate temperature for up to five days.

The point during the production process that finger dabs should be carried out should be defined eg. at a break time or end of a day's work, in accordance with a written SOP

9.5 Broth, or Media Fills (Media Process Simulation)

The broth fill is a validation procedure that challenges both operator and facilities. The purpose of broth fills is to simulate routine aseptic operations in such a way as to produce broth filled units that can be tested for microbiological contamination.

The number of units filled should represent a normal batch size.

Incubate at the designated temperature for up to 14 days. If the final container is part filled to ensure all surfaces are in contact with broth at some stage during incubation.

A procedure should define actions following positive results and should focus initially on whether the facility/equipment or operator practices are failing.

Note: The type of broth used is often sterile tryptone soya broth that may be presented in double strength to allow for dilution with buffer, saline, or water to simulate the process.

Any suitable liquid culture medium may however be used but the ability of the broth to support growth should be demonstrated.

10 SANITISATION OF MATERIALS

This section addresses disinfection procedures using chemical agents during which fluids are applied to surfaces with the intention of' reducing the count of micro-organisms inside the controlled workspace of an isolator.

10.1 Introduction

Most isolator systems will require two different procedures:

- A procedure for treatment of the impervious internal surfaces of the isolator and external surfaces of the resident equipment.

- A second procedure for treating surfaces of transient components which will be present in the isolator for a particular procedure.

The cleaning down of equipment and related treatments can employ a wide range of agents. Components and other aids to production should usually be treated with alcohol-based preparations, which enable rapid evaporation of the solvent of such disinfectant agents and therefore facilitates a smooth, responsive work flow during production.

10.2 Methods for Treating Resident Surfaces

Transient material should be removed from the controlled workspace. Internal surfaces should be cleaned with a non-corrosive and low residue detergent. There should be no evidence of corrosion due to incompatibility with disinfection regimes.

10.3 Methods for Treating Transient Surfaces

The surfaces of components and aids to preparation (syringes etc.) should be treated by using rapid drying agents, such as aseptically filtered alcohol (70% w/v ethanol or isopropanol).

10.4 Disinfectants should not penetrate outer packaging and thus contaminate the contents.

11 GAS STERILISATION OF ISOLATOR SYSTEMS

11.1 Introduction

Alcohol-based solutions are routinely used to sanitise equipment and component surfaces during aseptic processing. The major disadvantage of this technique is that alcoholic agents process negligible activity against bacterial endospores. Control measures can minimise the incidence of spores on the surfaces of vials, syringe wraps etc; but their absence is not assured. A properly designed and validated gas treatment of isolator systems can reduce the probability of spores surviving and increase the sterility assurance of the product.

Gaseous agents may be introduced into the controlled workspace of the isolator system to sterilise the entire space, integral surfaces and transient or resident components inside. It reduces the numbers of viable micro-organisms to a predetermined and acceptable level.

11.2 Objectives of Gas Sterilization

Various gaseous agents can be used within suitably-designed isolators to achieve sterilisation of working and component surfaces, thereby significantly reducing the overall probability of sterility failure in the final product.

Note: This process does not guarantee product sterility, but merely eliminates one of the factors which can result in product contamination during aseptic processing.

11.3 Choice of Agent

The ideal sterilant would have the following properties:

rapidly lethal against all micro-organisms, highly penetrative, non-aggressive to metals or polymers, rapid elimination of residues and harmless to humans.

A sterility assurance level of 10^6 of better should be achievable. A variety of methods are available and include the use of ethylene oxide, formaldehyde, paracetic acid, hydrogen peroxide or chlorine dioxide.

The agent of choice will be determined by a number of and equipment-related factors. For pharmaceutical applications in isolators the sterilants in most general use are peracetic acid and hydrogen peroxide.

11.4 Gas Contact

To ensure their effectiveness, the sterilant vapours must be in contact with all contaminated surfaces. The following points should be considered:

* Equipment should be raised appreciably above worktops, and efforts made to provide point contact of supports.

* Components should not be laid on worktops or other solid surfaces. Wire baskets or racking can be utilised to approximate point contact support. Wherever possible, containers and components should be suspended farce point contacts (eg. wire hooks), to allow free circulation of sterilant around all items. If necessary components should be rotated or repositioned during processing to ensure all surfaces are exposed to the gaseous sterilant.

* Glove/gauntlet fingers should be fully extended, and supported well clear of the worktop in such a way that the glove/sleeve materials are not unduly folded.

Critical validation issues associated with the sterilisation process should include the concentration of the sterilant, uniform distribution of sterilant, contact times, temperature aeration post sterilisation, condensate removals and residue as well as the frequency of sterilisation.

11.5 Microbiological Validation

Biological indicators (BI) can be used to confirm the effectiveness of the selected conditions and standard patterns. The test organisms should be selected to represent a known challenge to the process. In practice Bacillus subtilis (var niger) is frequently used, at a concentration of 10^6 - 10^7 spores per strip.

Initial tests should concentrate on establishing approximate death curves for the test organism, and/or progressively increasing sterilant contact time until the target lethality is achieved. The process contact time and sterilant vapour concentration should then be selected to include an acceptable safety margin, which makes allowance also for the compatibility of equipment and with the sterilant. Once process conditions have been established, the cycle/loading pattern should be validated by performing replicate cycles, again using BI's in worst case positions. Positive controls should be performed and the recovery conditions verified. When some degree of occlusion is unavoidable such that the diffusion path of gas is greater than 1 or 2 ram, the actual lethality delivered can be investigated by direct inoculation of the surfaces and estimation of survivors. Positive controls should be used for other techniques and recovery conditions verified as being effective.

11 Gas sterilisation of isolator systems continued

11.6 Routine Cycle Monitoring

The correct loading of the isolator prior to gassing should be the subject of properly documented control, and it is good practice for isolator access doors to be locked once correct loading has been checked. The gas generator's airflow and sterilant dispenser flow are often pre-set by the manufacturer, but if this is not the case their correct adjustment should also be formally documented. The generator should ideally allow these parameters, as well as sterilant injection time, to be recorded for each cycle, as happens with steam sterilisers. If the generator does not feature computer or chart recording of data, the parameters should be manually recorded at regular intervals, and documented for each cycle.

12 CONTACT DETAILS

The Chief Executive Officer
CSIR Campus
Meiring Naude Road
Brummeria
Pretoria, 0001

13 TABLE 2

DEFINITION OF AIR QUALITY CATEGORIES 1-V.
COMPARISON WITH EQUIVALENT INTERNATIONAL STANDARDS

CATEGORIES OF BACKGROUND ENVIRONMENT OF ISOLATOR	STANDARDS OF BACKGROUND ENVIRONMENT						NEAREST INTERNATIONAL STANDARDS				
	Particle Count (Particles M^{-3})				Viable Micro-organisms		European GMP	Current British Standard BS5295:1989	Previous British Standard BS5295:1976	US Federal Standard 209E
	0,5uM	5 uM	10 uM	25 uM	Airborne viable count (colonies M^{-3})	Settle plate (colonies per plate)	GRADE	CLASS	CLASS	CLASS
	35	0						C		1
	350	0						D		10
I	3,500	0			5	1 per 2 plates	B	F	1	100
	35,000	200						H		1,000
	350,000	2,000	450				C	J	2	10,000
II	3,500,000	20,000	4,500	500	50	5	D	K	3	100,000
III	NS	200,000	45,000	5,000	100	10		L	4	
IV	NS	NS			500	50				
V		NS			NS	NS				