4.0 WHERE TO SEND APPLICATIONS

Applications should be delivered to Room 204, Hallmark Building, 237 Proes Street, Pretoria or send to:

The Registrar of Medicines
Department of Health
Private Bag X 828
PRETORIA
0001

DEPARTMENT OF HEALTH
Republic of South Africa

IMPORTATION AND EXPORTATION

GW 12/10

APPLICATION FOR A PERMIT IMPORT DRUGS AND/OR PSYCOTROPIC SUBSTANCES IN TERMS OF THE MEDICINES AND RELATED SUBSTANCES CONTROL ACT, 1965 (ACT 101 OF 1965), THE SINGLE CONVENTION ON NARCOTIC DRUGS, 1961, AND THE CONVENTION ON PSYCOTROPIC SUBSTANCES, 1971; REGULATION 20(4) AND 20(7)(S)

The Registrar of Medicines
Private Bag X868
Pretoria 0001

From .....
Postal Address .....
.....
.....
Telephone .....

I,.....
(Name of applicant and, where the application is made on behalf of a body corporate, the name of such body corporate)

Being a registered .....

Practising /conducting .....

.....
(Street address)

hereby apply for a permit authorising me to import a substance/ preparation in respect of which the following details are given:

(a) In the case of the importation of a substance (raw material)
(i) the name and quantity of such substance .....

(ii) The quantity of such substance calculated as a base .....

(b) In the case of the importation of a preparation (finished product)-

(i) the registered name and dosage form of the preparation (in RSA) .....

.....

(ii) the name and quantity of the controlled substances in the preparation (per unit)

(iii) the total quantity of such preparation .....

(iv) the total quantity of the controlled substance calculated as a base .....

.....

I declare that these quantities are reasonable required by me for purposed authorised by law, I estimate that these quantities will meet my requirements for a period ..... Months form the present date. I shall comply with all requirements that the permit is subject to, and will return the tripilosts copy of the permit to the Director – General WITHIN 10 DAYS after importing the substance.

The consignment to be imported from .....

.....
(name and street address of firm in exporting country from whom the substance is to be obtained).

IMPORTATION AND EXPORTATION

(name and street address of firm in exporting country from whom the substance is to be obtained).

The consignment to be imported through

.....

(post of entry or post office)

Date .....

.....
Signature of applicant

GW 12/44

APPLICATION FOR A PERMIT TO EXPORT NARCOTIC AND/OR PSYCHOTROPIC SUBSTANCES IN TERMS OF THE MEDICINES AND RELATED SUBSTANCES CONTROL ACT, 1965 (ACT 101 OF 1965), THE SINGLE CONVENTION ON NARCOTIC DRUGS, 1961, AND THE CONVENTION ON PSYCHOTROPIC SUBSTANCES, 1971: REGULATION 20(4) AND 20(7)(a)

The Registrar of Medicines
Private Bag X868
Pretoria 0001

From .....
Postal Address .....
.....
.....
Telephone .....

I,.....
(Name of applicant and, where the application is made on behalf of a body corporate, the name of such body corporate)

Being a registered .....

Practising /conducting .....

.....
(Street address)

hereby apply for a permit authorising me to **export to** .....
.....

(name & street address of the firm or person in the importing country to which or to whom the substances are to be supplied) substances/preparation in respect of which the following details are given:

(a) In the case of the exportation of a substance (raw material)-

(i) the name and quantity of such substance.....

(ii) the quantity of such substance calculated as a base .....

(b) In the case of the exportation of a preparation (finished product) containing such substance-

(i) the registered name and dosage form of the preparation (in RSA).....
.....

(ii) the name and quantity of the controlled substance in the preparation (per unit).....
.....

(iii) the total quantity of such preparation .....

(iv) the total quantity of the controlled substance calculated as a base.....
.....

I declare that the quantities applied for are appropriate. I shall comply with all requirements that the permit is subject to, and will return the triplicate copy of the permit to the Director-General within 10 days after exporting the substance.

DEPARTMENT OF HEALTH
Republic of South Africa

IMPORTATION AND EXPORTATION

THE NECESSARY GOVERNMENT AUTHORISATION ISSUED IN TERMS OF THE SAID CONVENTIONS IN RESPECT OF THE IMPORTATION BY THE ABOVE-MENTIONED IMPORTER IS ATTACHED FOR YOUR RECORDS.

The consignment will be exported by ..... through .....
(airfreight / road transport) *(Port / border gate or post office)*

Date .....

.....
Signature of applicant

MBR 20
GW 12/11

IMPORTATION OF ANY MEDICINES AND / OR SPECIFIED SCHEDULE 5, SCHEDULE 6, SCHEDULE 7 OR SCHEDULE 8 SUBSTANCES INTO THE REPUBLIC OF SOUTH AFRICA IN TERMS OF THE PROVISIONS OF THE MEDICINES AND RELATED SUBSTANCES CONTROL ACT, 1965 (ACT 101 OF 1965)

1. The importer shall complete the MBR 20 document in duplicate and attach the following documentation:
(a) Copy of invoice for the medicines and / or Scheduled substances; and
(b) Copy of licence to import medicines as contemplated in section 22C(1)(b) of the Act; and
(c) Copy of permit to import specified Schedule 5, Schedule 6, Schedule 7 or Schedule 8 substances as contemplated in section 22(11)(a) of the Act; or
(d) Copy of authorization to import samples for registration purposes as contemplated in section 15(2)(a) of the Act; or
(e) Copy of authorization to import unregistered medicines as contemplated in section 21 of the Act.
3. The importer shall retain a copy of the MBR 20 document and the attachments at his or her business address.
4. The importer shall submit a copy of the MBR 20 document and the attachments to the Port Health Officer at the authorized port of entry
5. The importer shall fax a copy of the MBR 20 document and the attachments to:

The Law Enforcement Unit
Directorate: Inspectorate and Law Enforcement
Department of Health
Private Bag X 828
PRETORIA
0001

Fax: (012) 312-3114 / 3106

Name of Importer:..... Licence / Authorisation number:.....

Business (physical) address: Postal address:

Telephone number: ..... Fax number:.....

Names, quantities and registration numbers of medicines (finished products):

1.....
2.....
3.....
4.....

Names and quantities of raw materials:
1.....
2.....
3.....

IMPORTATION AND EXPORTATION

4.....

I,.....,hereby certify that I have imported the abovementioned medicines / Scheduled substances through the authorised port of entry indicated below with an "X"

☐ Port Elizabeth Airport ☐ Port Elizabeth Harbour ☐ Johannesburg International Airport
☐ Cape Town Airport ☐ Cape Town Harbour ☐ Durban Airport ☐ Durban Harbour

Signature: Licensed Importer: Date:

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

AEROSOL MANUFACTURING

This document has been prepared to serve as a recommendation to manufacture aerosol-based medicines. It represents the Medicines Control Council's current thinking on the manufacture of aerosol-based medicines.
These guidelines should be read in conjunction with the SA Guidelines for Good Manufacturing Practices.

REGISTRAR OF MEDICINES
MS M. P. MATSOSO
DATE: 30-05-2003

AEROSOL MANUFACTURING

INDEX

1. INTRODUCTION

The manufacture of pressurized aerosol products for inhalation with metering valves requires special consideration because of the particular nature of this form of product. It should be done under conditions which minimise microbial and particulate contamination. Assurance of the quality of the valve components and, in the case of suspensions, of uniformity is also of particular importance.

2. GENERAL

2.1 There are presently two common manufacturing and filling methods as follows:

2.1.1 Two-shot system (pressure filling). The active ingredient is suspended in a high boiling point propellant, the dose is put into the container, the valve crimped on and the lower boiling point propellant is injected through the valve stem to make up the finished product. The suspension of active ingredient in propellant is kept cool to reduce evaporation loss.

2.1.2 One-shot process (cold filling). The active ingredient is suspended in a mixture of propellants and held either under high pressure or at a low temperature, or both. The suspension is then filled directly into the container in one shot.

3. PREMISES AND EQUIPMENT

3.1 Manufacture and filling should be carried out as far as possible in a closed system.

3.2 Where products or clean components are exposed, the area should be fed with treated filtered air, and should be entered through airlocks.

3.3 Suitable systems should exist to determine required environment conditions and to monitor and control these conditions, e.g. temperature controls and propellant loss.

4. PRODUCTION AND QUALITY CONTROL

4.1 Metering valves for aerosols are more complex pieces of engineering than most items used in pharmaceutical production. Their specifications, sampling and testing should recognise this. Auditing the Quality Assurance system of the valve manufacturer is of particular importance.

4.2 All fluids (e.g. liquid or gaseous propellants) should be filtered to remove particles greater than 0.2 micron. An additional filtration where possible immediately before filling is desirable.
4.3 Containers and valves should be cleaned using a validated procedure appropriate to the use of the product to ensure the absence of any contaminants such as fabrication aids (e.g. lubricants) or undue microbiological contaminants. Containers should be fed to the filling line in a clean condition or cleaned on line immediately before filling.

4.4 Precautions should be taken to ensure uniformity of suspensions at the point of fill throughout

the filling process.

4.5 When a two-shot filling process is used, it is necessary to ensure that both shots are of the correct weight in order to achieve the correct composition.

4.6 Controls after filling should ensure the absence of undue leakage. Any leakage test should be performed in a way which avoids microbial contamination or residual moisture.

5.CONTACT DETAILS

The Registrar of Medicines
Private bag X828
PRETORIA
0001

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

CEPHALOSPORIN MANUFACTURING

This guideline has been prepared to serve as a recommendation to manufacturers of cephalosporins. This guideline must be read together with the SA Guide to Good Manufacturing Practices.

REGISTRAR OF MEDICINES
MS M. P. MATSOSO
DATE: 30-05-2003

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CEPHALOSPORIN MANUFACTURING

1. INTRODUCTION

These standards do not have direct statutory force , but will be used by the inspectors of the MEDICINES CONTROL COUNCIL, in order to evaluate the suitability of a pharmaceutical plant to manufacture cephalosporin products and to evaluate whether non-cephalosporin products are free and likely to remain free from cephalosporin contamination

These standards will therefore be one of the criteria used by the Council, to decide on the registration and the continued registration of pharmaceutical products

These standards do not replace any of the generally accepted G.M.P. standards, but must be seen as an addition to them, the main focus being on the specific problem of cross-

contamination

2. GLOSSARY

For the purpose of these standards, cephalosporins include cephalosporin P, cephalosporin N, cephalosporin C, semithynthetic compounds derived from 7 aminocephalosporanic acid as well as the cephamycins. This definition includes both Category A and B substances of Act 101 of 1965

3. PREMISES

3.1 Cephalosporin products should only be manufactured in separate, dedicated self contained areas with separate air handling facilities dedicated to these products and on a different site to that of the manufacture of non-cephalosporin products

This means complete separation of:

3.1.1 Active raw material storage

3.1.2 weighing

3.1.3 mixing

3.1.4 processing

3.1.5 filling
3.1.6 packaging

3.1.7 any other associated processes

3.2 Entry into and exit from the cephalosporin area should only be through a properly constructed air-lock

3.3 Change rooms should be provided for the personnel to shed their street clothes and put on their protective clothing for the cephalosporin area

3.4 Adequate shower facilities should be available for the personnel to shower when they leave the cephalosporin area

4. SECONDARY PACKAGING

Secondary packaging i.e. labelling and cartoning of the finished cephalosporin products may be done in a general packaging area, provided that the operation is separated from the general area in such a way as to contain any spillage of
cephalosporin

5. AIR HANDLING SYSTEMS

5.1 Separation

Completely separate air supply systems must be provided for cephalosporin and non-cephalosporin products

5.2 Air pressure Differentials

5.2.1 Air pressure differentials must be adjusted to provide a NEGATIVE PRESSURE in relation to the outside air in the cephalosporin area. The air must enter the area and be vented from the area in such a way as to ensure that no cephalosporin contaminated air enters the atmosphere

5.2.2 Air pressure differentials should be adjusted to be the greatest in the areas where the most dust is generated and cascade down to those areas where the least dust is generated

5.2.3 For sterile products positive air pressure differentials are required initially: however, the air pressure differentials in the area immediately adjacent to the non-cephalosporin area must be negative The same precautions for the contamination of the atmosphere are applicable

5.2.4 The air handling system must be validated at regular intervals

6. EQUIPMENT

6.1 Equipment should be dedicated to the cephalosporin manufacturing area only

6.2 Any maintenance of the equipment should be done in the cephalosporin area. If the equipment needs removal from the cephalosporin area proper validated decontamination procedures should be available and should be followed

7. PERSONNEL

7.1 Clothing

7.1.1 Overalls, shoe covers, head gear, mask and gloves to be used for cephalosporin manufacture only, must be provided

7.1.2 All clothing used in the cephalosporin manufacturing area must be properly decontaminated according to a validated procedure before being removed from the area for laundering

7.2 Procedures

Written procedures with respect to dress, movement into and out of the area and all other special precautions must be compiled and available at the point of implementation

7.3 Training

Training with respect to the special problems of cephalosporin manufacture must be provided in addition to normal G.M.P. training

7.4 Health Checks

Health checks must be done on a regular basis

8. MONITORING

Air quality outside the cephalosporin area must be monitored on a regular basis to detect any cephalosporin contamination

9. DECONTAMINATION

Validated decontamination procedures must be compile and implemented where necessary

10. CONTAMINATION LIMITS

Contamination limits of non-cephalosporin products have to be determined on the basis of accumulated validation data and the sensitivity of the analytical methods

11. VALIDATION

All methods and processes should be validated and re-validated at regular intervals Equipment should be qualified at regular intervals.

12. CONTACT DETAILS

The Registrar of Medicines
Private Bag X828
PRETORIA
0001

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

ISOLATOR TECHNOLOGY

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

REGISTRAR OF MEDICINES
MS M. P. MATSOSO
DATE: 30-05-2003

ISOLATOR

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ISOLATOR TECHNOLOGY

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[n hazards associated with the product during operation and in the event of failure.

2.4 Air lock

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.

2.8 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 de-defined 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: May also 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.

2.17 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,7m sec- 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.

3.8 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 l/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.

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.

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

2 3.9 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

9.6 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 aspectically 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 achieveable. 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 sterilent, uniform distribution of sterilent, contact times, temperature aeration post sterilisation, condensate remonvals 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.

11.6 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

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13. TABLE 3

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

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

PENICILLIN MANUFACTURING

This document has been prepared to serve as a recommendation for penicillin manufacturing. It represents the Medicines Control Council's current thinking on this subject.
This guideline should be read in conjunction with the SA Guidelines for Good Manufacturing Practices.

REGISTRAR OF MEDICINES
MS M. P. MATSOSO
DATE: 30-05-2003

PENICILLIN MANUFACTURING

INDEX

PENICILLIN MANUFACTURING

1. INTRODUCTION

These standards do not have direct statutory force, but will be used by the inspectors of the MEDICINES CONTROL COUNCIL, in order to evaluate the suitability of a pharmaceutical plant to manufacture penicillin products and to evaluate whether non-penicillin products are free and likely to remain free from penicillin contamination.

These standards will therefor one of the criteria used by the Council ,to decide on the registration and the continued registration of pharmaceutical products.

These standards do not replace any of the generally accepted G.M.P. standards, but must be seen as an addition to them , the main focus being on the specific problem of cross-

contamination

2. GLOSSARY

For the purpose of these standards , penicillin includes all forms of penicillin i.e. all naturally produced penicillin, all synthetic and semi-synthetic preparations as compounds derived from 6-amino-penicillanic acid. This definition includes both Category A and B substances in terms of Act 101 of 1965

3. PREMISES

3.1 Penicillin products should only be manufactured in separate, dedicated self contained areas with separate air handling facilities dedicated to these products and on a different site to that of the manufacture of non-penicillin products.

This means complete separation of:
3.1.1 Active raw material storage

3.1.2 weighing

3.1.3 mixing

3.1.4 processing

3.1.5 filling

3.1.6 packaging

3.1.7 any other associated processes.

3.2 Entry into and exit from the penicillin area should only be through a properly constructed

air-lock

3.3 Change rooms should be provided for the personnel to shed their street clothes and put on their protective clothing for the penicillin area

3.4 Adequate shower facilities should be available for the personnel to shower when they leave the penicillin area.

4. SECONDARY PACKAGING

Secondary packaging i.e. labelling and cartoning of the finished penicillin products may be done in a general packaging area, provided that the operation is separated from the general area in such a way as to contain any spillage of penicillin

5. AIR HANDLING SYSTEMS

5.1 Separation

Completely separate air supply systems must be provided for penicillin and non-penicillin products

5.2 Air pressure Differentials

5.2.1 Air pressure differentials must be adjusted to provide a NEGATIVE PRESSURE in relation to the outside air in the penicillin area. The air must enter the area and be vented from the area in such a way as to ensure that no penicillin contaminated air enters the atmosphere.

5.2.2 Air pressure differentials should be adjusted to be the greatest in the areas where the most dust is generated and cascade down from this area to those areas where the least dust is generated.

5.3 For sterile products positive air pressure differentials are required initially: however the area immediately adjacent to the non-penicillin area must be

negative.
The same precautions for the contamination of the atmosphere is applicable

5.4 The air handling system must be validated and re-validated at suitable intervals

6. EQUIPMENT

6.1 Equipment should be dedicated to the penicillin manufacturing area only.

6.2 Any maintenance of the equipment should be done in the penicillin area. If the equipment needs removal from the penicillin area proper validated decontamination procedures should

be available and should be followed

7. PERSONNEL

7.1 Clothing

7.1.1 Overalls, shoe covers, head gear, mask and gloves to be used for penicillin manufacture only, must be provided.

7.1.2 All clothing used in the penicillin manufacturing area must be properly decontaminated according to a validated procedure before being removed from the area for laundering

7.2 Procedures

Written procedures with respect to dress, movement into and out of the area and all other special precautions must be compiled and available at the point of implementation

7.3 Training
Training with respect to the special problems of penicillin manufacture must be provided in addition to normal G.M.P. training

7.4 Health checks

Health checks with respect to penicillin sensitivity must be done on a regular basis

8. MONITORING

Air quality outside the penicillin area must be monitored on a regular basis to detect any penicillin contamination

9. DECONTAMINATION

Validated decontamination procedures must be compiled and implemented where necessary

10. TESTING OF NON-PENICILLIN PRODUCTS

No detectable levels of contamination should be allowed, employing a test method acceptable to Council

The accuracy of the method should be such as to detect quantities of not less than 0,05 units of penicillin

11. VALIDATION

All methods and processes should be validated and re-validated at suitable intervals.

Equipment should be qualified at regular intervals.

12. CONTACT DETAILS

The Registrar of Medicines
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MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

RADIOPHARMACEUTICAL MANUFACTURING

This document has been prepared to serve as a recommendation for manufacture of radiopharmaceuticals. It represents the Medicines Control Council's current thinking on the subject.
This guideline should be read in conjunction with the SA Guidelines for Good Manufacturing Practices..

REGISTRAR OF MEDICINES
MS M. P. MATSOSO
DATE: 30-05-2003

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RADIOPHARMACEUTICALS

1. Introduction:

Radio pharmaceutical products should be manufactured in accordance with the Good Manufacturing Practices, described in the current South African Guide to Good Manufacturing Practices, this guidance document and the supplementary guidelines such as those for sterile preparations where appropriate. Some points are nevertheless specific to the handling of radioactive products and are modified by or detailed in these supplementary guidelines.

2. General:

2.1 Radio pharmaceutical preparations are preparations containing one or more radionuclides. They may be formulated in any of the pharmaceutical formulations covered in this guide and the general and specific guidance should be followed at all times, but considerations must be given to the special requirements of radiation work.

2.2 The manufacturing and handling of RADIO PHARMACEUTICALS is potentially hazardous. The level of risk depends in particular on the types of radiation emitted and the half-lives of the radioactive isotopes. Particular attention must be paid to the prevention of cross-contamination, to the retention of radionuclide contaminants and to waste disposal. Special consideration may be necessary with reference to small batch sizes made frequently for many RADIO PHARMACEUTICALS. Due to their short half-life, some RADIO PHARMACEUTICALS are released before completion of certain Quality Control tests. In this case, the continuous assessment of the effectiveness of the Quality Assurance system becomes very important.

3. Registration Requirements:

3.1 Care should be taken to comply with national and local regulations concerning production, supply, storage, use and disposal of radioactive products.

3.2 Premises in which radioactive work is conducted must be licensed by the Department of Health.

3.3 RADIO PHARMACEUTICALS, produced by a nuclear reactor or cyclotron, may only be used by physicians who are qualified by specific training in the safe use and handling of radioisotopes, and whose experience and training have been approved by an appropriate governmental agency authorised to licence the use of radionuclides.

3.4 All people engaged in radioactive work are required by law to be registered as radiation workers. Maximum permitted radiation doses for radiation workers are prescribed by the International Atomic Energy Agency and are monitored by film badges and pocket dosimeters or TLD. At all times the ALARA principle (i.e. as low as reasonably attainable dose) applies to any person working with radioactivity.

4. Personnel:

4.1 All personnel (including those concerned with cleaning and maintenance) employed in areas where radioactive products are manufactured should receive additional training specific to this class of products. In particular, they should be given detailed information and appropriate training on radiation protection.

5. Premises and Equipment:

5.1 Radioactive products should be stored, processed, packaged and controlled in dedicated and self-contained facilities. The equipment used for manufacturing operations should be reserved exclusively for RADIO PHARMACEUTICALS.

5.2 In order to contain the radioactive particles, it may be necessary for the air pressure to be lower where products are exposed than in the surrounding areas. However, it is still necessary to protect the product from environmental contamination.

5.3 For sterile products, the working zone where products or containers may be exposed should comply with the environmental requirements described for Sterile Products. This may be achieved by the provision within the work station of a laminar flow of HEPA-filtered air and by fitting air-locks to entry ports. Total containment work stations may provide these requirements. They should be in an environment conforming to at least a grade D.

5.4 Air extracted from areas where radioactive products are handled should not be recirculated; air outlets should be designed to avoid possible environmental contamination by radioactive particles and gases.

5.5 There should be a system to prevent air entering the clean area through extraction ducts e.g. when the extraction fan is operating.

6. Production and Handling of Radioactive preparations:

6.1 Each isotope should be worked in a separate specially shielded, contained work station to prevent cross-contamination of the radionuclide. Production of different radioactive producers in the same workstations and at the same should be avoided in order to minimize the risk of cross-contamination or mix-up. The operator must be shielded from the radiation which must be contained in the work station.

6.2 Radioactive materials should be handled in a contained work station operated at an air-pressure below that of the room in which it is sited. Air admitted to the work station should still have passed through terminal filters of appropriate porosity so that the required class conditions are maintained at the point of greatest risk, where

products are exposed.

6.3 All operations should be carried out in such a manner as to minimize the risk of microbial or particulate contamination.

6.4 All sterile products are terminally sterilised before despatch either by autoclave or filtration.

NOTE: The radiation in the Radio pharmaceutical is not sufficient to effect sterilisation.

6.5 Process validation, in-process controls and monitoring or process parameters and environment assume particular importance in cases where it is necessary to take the decision to release or reject a batch or a product before all the tests are completed.

7. Quality Control:

7.1 When products have to be dispatched before all the tests are completed, this does not obviate the need for a formal recorded decision to be taken by the Qualified Person on the conformity of the batch. In this case there should be a written procedure detailing all production and Quality Control data which would be considered before the batch is dispatched. A procedure should also describe the measures to be taken by the Qualified Person if unsatisfactory test results are obtained after dispatch.

7.2 Unless otherwise specified in the marketing authorization, reference samples of each batch should be retained.

8. Packaging of RADIO PHARMACEUTICALS:

8.1 Due to the short half-life of certain RADIO PHARMACEUTICALS it may be necessary to despatch the products before all the tests are completed. This does not reduce the need for a formal recorded decision to be taken by an authorized person as to whether or not the product should be released based on the production and quality control data available at the time. Specifications should define at which stage of testing a decision on release may be taken.

8.2 All containers must be checked by a Health Physicist for radioactive contamination before packaging and the radiation levels emanating from the package monitored by a Health Physicist.

8.3 IAEA transport regulations prescribe the maximum acceptable levels of radiation measured at the surface of the package and one metre from the package permitted on road and air transport. The conditions under which the packages may be transported are also prescribed.

9. Non-Radioactive Kits:

9.1 Non-radioactive chemicals are supplied as kits to be reconstituted with the radioactive eluate from a radionuclide generator such as a Molybdenum-99 / Technetium-99m generator at the hospital. These kits must conform to the requirements of pharmaceuticals as listed in the chapter on guidelines for small volume parenterals.

9.2 The preparation of these RADIO PHARMACEUTICALS at the hospital must be carried out using aseptic technique. It may be acceptable to carry out this work under environmental conditions of a lower grade than those prescribed for aseptic work when the following situation pertains:

- the preparation is done entirely by transference of materials between closed containers, for example by use of syringe and hypodermic needle penetrating a rubber closure (so-called 'closed procedures')
- manipulations are performed within a contained work station which, whilst giving the required degree of operator protection, also maintains the critical working zone at the standard of Class 1
- the product is administered within a few hours of preparation.

10. Distribution and Recalls:

10.1 Detailed distribution records should be maintained and there should be procedures which describe the measures to be taken for stopping the use of defective RADIO PHARMACEUTICALS. Recall procedures should be shown to be operable within a very short time.

11. Contact Details:

The Registrar of Medicines
Private Bag X828
PRETORIA
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MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINE FOR ELECTRONIC SUBMISSION OF APPLICATIONS TO REGISTER MEDICINES

This document has been prepared to serve as a recommendation to applicants wishing to submit applications for registration of medicines in electronic format. Comments on this document will be appreciated before 30 June 2003.

REGISTRAR OF MEDICINES
MS M. P. MATSOSO
DATE: 30-05-2003

ELECTRONIC SUBMISSION PROJECT

GUIDELINES FOR AN E-SUBMISSIONS PILOT OF MEDICINES REGISTRATION APPLICATIONS

1. General

- The applicant is to supply a comprehensively completed hard copy application of the medicine they wish to get registered.
- The applicant must make sure that the electronic submission of the application being submitted is an exact replica of the hard copy version.
- A windows-based notebook to be submitted with the following minimum specifications.
    - Pentium III or higher, 128MB RAM, 20GB HDD and DVDROM drive
    - Adobe Acrobat 5.0 (or later)
    - Microsoft Word 2000 (or later)
- When submitting an electronic version of the dossier, the following recommendations will help the applicant create PDF files that the MRA can evaluate and archive accordingly.

2. Version

The MRA will use version 4.0 (or higher) of Acrobat Reader with the search plug in. This allows for ease of document navigation and access.

3. Fonts

We believe that Times New Roman, 12-point font is adequate in size for reading narrative text. In tables and charts, fonts smaller than 12 points should be avoided whenever possible.

The applicant is to make sure that the font used in the PDF file can be relayed (copied) into the MRA's preferred word processor (MS WORD 2000), for evaluation and report writing purposes.

We recommend the use of a black font colour, with a blue font used for hypertext links. If font colors other than black are used, avoid light coloured fonts.

4. Page Orientation

Pages should be properly oriented. For example, the applicant should set the page orientation of landscape pages to landscape prior to saving the PDF document in final form to ensure correct page presentation.

5. Page Size and Margins

The print area for pages should fit on a sheet of paper that is 21cm X 29.7cm (A4). The applicant should allow a margin of at least 1.6 centimeters on all sides to avoid obscuring information if the pages are subsequently printed and bound.