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PART 1 OF 2

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GOVERNMENT NOTICE

DEPARTMENT OF HEALTH

No. R. 609 **2 May 2003**

MEDICINES CONTROL COUNCIL

MEDICINES AND RELATED SUBSTANCES ACT (ACT 101 OF 1965)

GUIDELINES WITH RESPECT TO THE MEDICINES AND RELATED SUBSTANCES ACT (ACT 101 OF 1965), AS AMENDED

Guidelines for medicines regulation in South Africa as determined by the Medicines Control Council with reference to regulation as published in regulation gazette number 7470 (1230).

Ms M. P. MATSOSO

Registrar of Medicines

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

ADVERSE DRUG REACTIONS REPORTING FORM

Version: MCC2003/1

ADVERSE DRUG REACTION

SPONTANEOUS REPORTING of ADVERSE DRUG REACTIONS

The Medicines Control Council has a system for spontaneous reporting of suspected adverse drug reactions (ADRs) mainly through the National Adverse Drug Event Monitoring Centre (NADEMC). When an ADR report form is received by the NADEMC, the data is entered into the Centre's Adverse Drug Reaction Information (ADRI) database and given a unique identification number. The reporter will receive an acknowledgement letter, which will quote the unique identification number of the report. ADR reports are evaluated by the NADEMC to assess the causal relationship between the medicine and the reported reaction. The data, together with data from other sources, are used to assist in the evaluation and monitoring of the post-marketing safety of medicines.

HOW TO REPORT

The **Adverse Drug Reaction and Product Quality Problem Report Form** is available on this website and can be downloaded for printing. The form is also available from the Medicines Control Council pharmacovigilance units listed below.

The offices of the MCC for the monitoring of suspected adverse drug reactions are:

- The Medicines Regulatory Affairs in Pretoria for all products

Registrar of Medicines
Medicines Control Council
Private Bag X828
PRETORIA
0001

- The NADEMC in Cape Town for all products

  Tel. #: 021 447 1618
  Fax #: 021 448 6181

- The Pharmacovigilance Unit (PVU) for Focused Monitoring of Anti-retroviral medicines, unregistered medicines, and complementary and alternative medicines

  Fax #: 012 521 4335

NOTE:
Any of the units may be contacted for information on any area of safety of medicines.

The completed forms can be returned by fax to the relevant fax number, or by post to the following address:

BUSINESS REPLY SERVICE
Free Mail Number: BNT 178

Department of Health
Registrar of Medicines
Private Bag X828
PRETORIA
0001

BESIGHEIDSANTWOORDDIENS
Vryposnommer: BNT 178

Departement van Gesondheid
Registrateur van Medisyne
Privaatsak X828
PRETORIA
0001

WHO SHOULD REPORT?

The MCC invites all health care professionals (e.g. medical practitioners, dentists, pharmacists, nurses) to report all suspected ADRs.

Reports are not usually accepted directly from patients as a medical opinion on any adverse reaction is important. Patients who experience a suspected adverse reaction are advised to report this to a medical practitioner, dentist, pharmacist, nurse or other health professional who should then report to the MCC, NADEMC, or PVU.

WHAT TO REPORT?

Report suspected adverse experiences

- with all medicines, including vaccines
- with medical devices
- with complementary medicines
- with traditional and herbal medicines
- with homeopathic medicines

Report suspected product quality problems such as

- possible contamination
- questionable stability
- defective components
- poor packaging or labelling

Report especially

- adverse reactions to recently marketed products
- serious reactions with all products
- adverse reactions which are not clearly reflected in the product package insert
- therapeutic failure

REPORT EVEN IF YOU ARE NOT CERTAIN THE PRODUCT CAUSED THE EVENT

PATIENT CONFIDENTIALITY

Patient confidentiality is strictly maintained. It is, however, important to provide some patient identification for ongoing communication between the reporter and the MCC, NADEMC, and PVU. Patient initials and age are sufficient as an identifier. A practice or hospital number may also be provided.

REPORTER CONFIDENTIALITY

Reporter confidentiality is strictly maintained. It is, however, important to provide the name, address and qualification of the reporter to allow for further communication, and to identify the source of the report.

Department of Health Logo Here

AND PRODUCT QUALITY PROBLEM REPORT FORM

(Identities of reporter and patient will remain strictly confidential)

NATIONAL ADVERSE DRUG EVENT MONITORING CENTRE

Medicines Control Council,
The Registrar of Medicines ,
Department of Health
Tel : (021) 447-1618
Fax: (021) 448-6181

In collaboration with the WHO International Drug Monitoring Programme

PATIENT INFORMATION

Name (or initials): ..... **Age:**..... **Weight (kg) :**.....
Sex:: M F **DOB :**..... / ..... / ..... **Height (cm) :**.....

ADVERSE REACTION/PRODUCT QUALITY PROBLEM

Adverse reaction[1] ☐ **and/or Product Quality problem**[2] ☐ **Date of onset of reaction: :**...../...../.....
Time of onset of reaction: .....h.....min

Description of reaction or problem (Include relevant tests/lab data, including dates):

1. MEDICINES/VACCINES/DEVICES (include all concomitant medicines)

Trade Name & Batch No. (Asterisk Suspected Product)	Daily Dosage	Route	Date Started	Date Stopped	Reasons for use

ADVERSE REACTION OUTCOME (Check all that apply)

☐ death
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment damage

☐ life-threatening
☐ hospitalisation
☐ Other.....
.....
.....
.....

Event reappeared on rechallenge:
Y N Rechallenge not done
Treatment (of reaction).....
.....
.....
.....

Recovered: Y N
Sequelae: Y N
Describe Sequelae:.....
.....
.....
.....

COMMENTS: (e.g. Relevant history. Allergies. Previous exposure. Baseline test results lab data)

2. PRODUCT QUALITY PROBLEM:

Trade Name	Batch No	Registration No	Dosage form & strength	Expiry Date	Size/Type of container

Product available for evaluation?: Y N

REPORTING DOCTOR/PHARMACIST Etc:

NAME: ..... QUALIFICATIONS:.....

ADDRESS: .....

....
Signature Date

TEL: (.....).....

This report does not constitute an admission that medical personnel or the product caused or contributed to the event.

ADVICE ABOUT VOLUNTARY REPORTING

Report adverse experiences with:

- medications (drugs, vaccines and biologicals)
- medical devices (including in-vitro diagnostics)
- traditional and herbal remedies
- **For Adverse Events Following Immunisation (AEFI), please follow the reporting procedure recommended by the Expanded Programme in Immunisation (EPI)**

Please report:

- adverse drug reactions to recently marketed products
- serious reactions and interactions with all products
- adverse drug reactions which are not clearly reflected in the package insert.

Report even if:

- you're not certain the product caused the event
- you don't have all the details

Report Product Quality Problems such as:

- suspected contamination
- questionable stability
- defective components
- poor packaging or labelling
- therapeutic failures

Important numbers:

Investigational Products and Product Quality Problems:

- (012) 326-4344 to fax a report
- (012) 312-0000 to report by phone

Registered Medicines and Traditional and Herbal remedies:

- (021) 448-6181 to fax a report
- (021) 447-1618 to report by phone

Adverse Events Following Immunisation:

- (012) 312 0110 to phone for information
- (012) 321 9882 to fax a report

Confidentiality: Identities of the reporter and patient will remain strictly confidential.

Your support of the Medicine Control Council's adverse drug reaction monitoring programme is much appreciated. Information supplied by you will contribute to the improvement of drug safety and therapy in South Africa.

PLEASE USE ADDRESS PROVIDED BELOW- JUST FOLD IN THIRDS, TAPE and MAIL

Postage will be paid by Addressee
Posgeld sal deur die geadreseerde betaal word

No postage stamp necessary if posted in the Republic of South Africa
Geen posseël nodig nie indien in die Republiek van Suid-Afrika gepos

BUSINESS REPLY SERVICE
BESIGHEIDSANTWOORDDIENS
Free Mail Number:
Vryposnommer: **BNT 178**

DEPARTMENT OF HEALTH
DEPARTEMENT VAN GESONDHEID
REGISTRAR OF MEDICINES
REGISTRATEUR VAN MEDISYNE
PRIVATE BAG/ *PRIVAATSAK* X828
PRETORIA
0001

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

REPORTING ADVERSE DRUG REACTIONS IN SOUTH AFRICA

This document has been prepared to serve as a guideline to those reporting adverse drug reactions. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request for any additional information to establish the safety, quality and efficacy of a medicine and may make amendments in keeping with the knowledge which is current at the time of consideration of safety data.

REGISTRAR OF MEDICINES
MS. M.P. MATSOSO
DATE: 29/4/2003

Version: MCC2003/1

TABLE OF CONTENTS

1 INTRODUCTION

The following guidelines pertain to Regulations 34 and 37 of Act 90 of 1997 [the Medicines and Related Substances Control Act (Act 101, 1965).]. These guidelines are intended to assist applicants in the reporting of adverse drug reactions (ADRs) associated with medicines and in the management of safety data, which arise during clinical trials.

For the purposes of these guidelines, "**Authority**" refers to the Medicines Control Council and the **NADEMC** refers to the National Adverse Drug Event Monitoring Centre of the Medicines Control Council.

2 DEFINITIONS AND TERMINOLOGY

2.1 ADVERSE EVENT

"Adverse event/experience" is any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment.

An adverse event can be any unfavourable and unintended sign, symptom or disease temporally associated with the use of a medicinal product, whether considered related to the medicinal product, or not.

2.2 ADVERSE DRUG REACTION (ADR) or ADVERSE REACTION

"Adverse drug reaction" or "adverse reaction" means a response to a medicine in humans or animals, which is noxious and unintended, including lack of efficacy, and which occurs at any dosage and can also result from overdose, misuse or abuse of a medicine.

The definition of an adverse drug reaction or adverse reaction applies to registered medicines, medicines for which the applicant holds an application for registration, as well as unregistered medicines being used under Section 21 of Act 101 (1965). This definition includes any significant hazards to patients.

A reaction, contrary to an event, is characterised by the occurrence of a suspected causal relationship between the drug and the reaction, as determined by the reporter or a reviewing health care professional. The fact that the health care professional is making a report to an applicant, serves as an indication that the observed event may be caused by the medicine. All spontaneous reports are, therefore, suspected adverse drug reactions.

In the case of pre- and post-marketing studies, adverse "events" are usually systematically solicited. In cases where there is uncertainty as to whether or not an event is a reaction, it is better to treat the event as a reaction. For the purpose of clinical trials conducted under Regulation 34, an adverse drug reaction includes any adverse event where the contribution of the study medication, concomitant medication or other medicinal intervention of the clinical trial, cannot be ruled out.

2.3 SERIOUS ADVERSE DRUG EVENT OR ADVERSE DRUG REACTION

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- **results in death,**
- **is life-threatening,**
- **requires patient hospitalisation or prolongation of existing hospitalisation,**
- **results in persistent or significant disability/incapacity, or**
- **is a congenital anomaly/birth defect.**

The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death, if it were more severe.

Medical and scientific judgement should be exercised when deciding if other situations are serious. Such instances could include medical events that may not be immediately life-threatening or result in death or hospitalisation, but which may jeopardise the patient or may require intervention to prevent one of the outcomes listed in the definition above. Examples include blood dyscrasias or convulsions not resulting in hospitalisation, or development of drug dependency or drug abuse.

In the case of medicines used in animals, a serious adverse event/reaction includes any such event, which may occur, even in a single animal, within a herd or flock of animals.

2.4 UNEXPECTED ADVERSE REACTION

For the purposes of this regulation, an "unexpected" adverse reaction is one in which the nature, specificity, severity and outcome is not consistent with the applicable product information (i.e., with the approved package inserts for registered medicines, or the investigator's brochure or other product information for unregistered medicines, being used under section 21 of Act 101, 1965).

2.5 HEALTH CARE PROFESSIONAL

For the purposes of reporting suspected adverse reactions, "health care professionals" are medical practitioners, pathologists, dentists, pharmacists, nurses, veterinarians and paraveterinary professionals including veterinary nurses and animal health technicians.

When reports originate from pharmacists or nurses, further information about the case should, where possible, be sought from a medical practitioner responsible for the patient. Furthermore, if there is more than one reporter, the health care professional directly involved with the patient's care and who provides the most complete and clinically relevant information, will be considered the primary reporter.

2.6 ADVERSE DRUG REACTION REPORT

An adverse drug reaction report is a detailed record of all relevant data associated with the use of a medicine in a subject or patient.

2.7 SPONTANEOUS REPORT OR SPONTANEOUS NOTIFICATION

A spontaneous report is a communication to a company, regulatory authority or other organisation that describes a suspected adverse drug reaction in a patient given one or more medicines, and which does not derive from a study.

2.8 REPORTABLE ADVERSE REACTION – MINIMUM INFORMATION

A reportable ADR requires the following minimum information:

- **An identifiable source (reporter) of the information. This should include the name or initials and address of the reporter and the reporter's qualification (for e.g., doctor, dentist, pharmacist, nurse or veterinarian).**
- **An identifiable patient. A patient may be identified by surname and forename(s) or initials of surname and forenames, or by a reference number. For Veterinary Medicines an identifiable patient requires a description of the animal (particularly species).**
- **Suspected product(s).**
- **Suspected reaction(s).**

Information, additional to the minimum, should be actively sought and submitted as soon as it becomes available.

2.9 PERIODIC SAFETY UPDATE REPORTS

A periodic safety update report (PSUR) is an update of the world-wide safety experience of a medicine at defined times post-registration, as determined from the international birth date. Each safety update report should cover the period of time since the last update report. The PSUR should be compiled in accordance with the requirements of the ICH E2C (CPMP/ICH/288/95) Expert Group on Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs.

2.10 LINE LISTINGS

A line listing provides key information but not necessarily all the details customarily collected on individual cases. Reactions are classified by body system for the most serious-presenting sign or symptom. The headings usually included are:

- **Country**
- **Source (physician, literature, etc.)**
- **Age**
- **Sex**
- **Dose of drug**
- **Duration of treatment (prior to event); time to onset**
- **Description of reaction (as reported)**
- **Patient outcome (for e.g., fatal, resolved, etc.)**
- **Comment**
- **Company Reference Number**

In some instances, depending on the type or source, ADR reports should be presented as line listings. A line listing serves to help the Authority to identify cases that it might wish to examine more completely by requesting full case reports.

(iv) Additional information, not available at the time of the initial report, should be provided in the form of follow-up reports.

(v) The applicant is required to submit the name or initials, address and telephone number and qualification of the initial reporter on the adverse drug reaction case report form. In the case of a report from a clinical trial, the trial site at which the reaction occurred, needs to be submitted in addition to other information requested.

3.1.6 Overdose:

Reports of overdose should be submitted only when the overdose was associated with an adverse reaction. Suspected adverse reactions, associated with an overdose, should be reported, as well as other reactions. This should include reports which indicate that taking of the suspect medicine led to suicidal intention and subsequent overdose of the suspect medicine, or other medication.

3.1.7 Teratogenicity and congenital anomalies:

For reports on congenital anomalies or teratogenicity:

- Give age and sex of the infant.
- Follow-up reports for the infant should be considered as follow-up to the initial report.
- The birth date or the date on which pregnancy was terminated should be the event onset date.
- Include date and/or duration of *in utero* exposure where possible.
- Any adverse reaction experienced by the mother must be considered a new initial case report on a separate report form.

3.1.8 Product defects:

If an adverse event is suspected to be related to a product defect, it should be reported in the same manner as a suspected adverse reaction. The lot number of the suspected medicine should be included in the report. Applicants should inform the Authority whether the implicated products have been tested for quality and what, if any, corrective actions are being or have been taken.

3.1.9 Drug Interactions:

Any drug interaction, which results in an adverse reaction, should be reported as an adverse reaction in the prescribed manner.

3.1.10 Another Applicant's Product:

(i) **Spontaneous reports:** If a pharmaceutical company receives a report of a suspected adverse reaction to a medicine marketed by another applicant, the report should promptly be forwarded to the applicant of that medicine. The applicant to whom the event was originally reported should not forward such reports to the Authority. An applicant, who receives such a report about its medicine from another applicant, is required to submit the report to the Authority with the same time constraints applicable to other reports.

(ii) **Clinical trials:** When serious, unexpected reactions are found for another applicant's medicine that is being used concomitantly with that of the applicant conducting the clinical trial, a report about the event should be submitted directly to the Authority by the applicant responsible for the study.

3.1.11 Confidentiality:

Strict confidentiality will be maintained by the NADEMC regarding the identities of the patient and the reporter. Other details relating to the adverse drug reactions, however, are in the public domain.

3.1.12 Lack of Efficacy reports:

"Lack of efficacy" is defined as failure to produce the expected pharmacological action. Lack of efficacy applies to registered medicines only. The lot number of the suspected medicine should be included in the report. If the report of "lack of efficacy" is for an unapproved indication, the event is still reportable.

4 POST-REGISTRATION ADVERSE DRUG REACTION REPORTS

4.1 Reactions occurring in South Africa:

(i) All serious, suspected adverse drug reactions, occurring in South Africa with any medicine, must be reported by the applicant within 15 calendar days after first notification.

(ii) All non-serious, unexpected, suspected adverse drug reactions, occurring in South Africa with any medicine, must be reported by the applicant within 15 calendar days after first notification. Do not report non-serious, expected adverse reactions.

4.2 Reactions occurring outside South Africa:

(i) Foreign individual case reports should not be forwarded to the Authority on a routine basis, but should be reported in the context of a specific safety issue or on specific request by the Authority.

(ii) The applicant should advise the Authority of any action relating to safety that has been taken by a foreign agency, including the basis for such action, within three days of first knowledge.

(iii) These guidelines [i.e. 2.2(i) and (ii)] also apply to medicines for which the applicant holds an application for registration.

4.3 Periodic Safety Update Reports:

(i) PSURs should **only** be submitted in the following situations:

- Whenever requested by the Authority.
- When the submission of PSURs is a **condition of registration** for a new medicinal product or range of medicinal products. The applicant must submit these PSURs within **30 calendar days** of initial receipt from the parent company.
- As part of a submission to amend the conditions of registration when the PSUR contains information supporting the amendment.
- When a new medicinal product is **submitted to Council for registration** and where the product has already been marketed elsewhere, PSURs should be sent to the Authority during the evaluation period prior to registration. The applicant must submit

these PSURs within **30 calendar days** of initial receipt from the parent company.

- When a clinical trial under section 21 of Act 101 (1965) is being carried out with a product which is already registered in other countries.

(ii) The applicant should inform the Authority of any steps, which are taken, or to be taken, with regard to safety concerns raised in the periodic safety update report at the time of the submission.

(iii) PSURs for unregistered medicines, or medicines for which no submission for registration has been made, must not be submitted routinely.

4.4 Case reports from published scientific literature:

(i) Applicants should report published suspected adverse drug reactions related to the active substance(s) of their medicinal products, as relevant to the categories identified in 4.1 and 4.2 above. A copy of the relevant published article should be provided.

(ii) An adverse drug reaction report should be completed for each identifiable patient (with an identifiable adverse drug reaction). For instance, if an article describes six identifiable patients with a given adverse experience, six adverse drug reaction reports should be submitted to the Authority.

(iii) If more than one medicine is mentioned in the literature report, only the applicant whose medicine is suspected of being the cause is required to submit a report. The suspect medicine is usually the one stated as such in the body or title of the article by the author(s).

4.5 Reports from post-registration studies:

(i) All suspected adverse reactions from post-registration studies taking place in South Africa must be reported according to 4.1 above. This applies to reports from any type of clinical or epidemiological investigation, regardless of design or purpose, involving a medicinal product.

(ii) Investigators involved in post-registration studies, should be aware of the definition of what constitutes a serious adverse drug reaction, as well as the distinction between 'reactions' and 'events'.

(iii) In the case of post-registration studies, adverse "events" are usually systematically solicited. In cases where there is uncertainty as to whether or not an event is a reaction, the case should be reported as an adverse reaction. Events that are clearly unrelated to the medicine should not be reported.

(iv) If the manufacturer receives a report of a serious adverse drug reaction from the investigator who is blinded to individual patient treatment, the guidelines outlined in section 5.3 below should be adhered to.

4.6 On-going Pharmacovigilance evaluation:

(i) Applicants must inform the Authority, within three calendar days of first knowledge, whenever new evidence becomes available (nationally and internationally) that could significantly impact on the benefit/risk assessment of a medicine or which would be sufficient to consider changes to the conditions of registration of the medicine.

(ii) Applicants must report any change in the nature, severity or frequency of expected adverse drug reactions or any new risk factors identified within 15 calendar days. The basis on which these assessments are made should be included.

(iii) Additional pharmacovigilance data, such as actual case reports, drug usage figures, the regulatory status of the product in other countries, independent pharmacoepidemiology studies, pre-clinical studies or significant product quality data may be requested by the Authority as the situation warrants. This will be requested for submission within a time period specified by the Authority.

4.7 Consumer Reports:

If an applicant receives an adverse drug reaction report from a consumer, the applicant should advise the consumer to report this reaction through his/her medical practitioner, pharmacist, nurse, dentist or veterinarian. If this approach fails, the applicant should attempt to obtain as much information as possible from the consumer. If the minimum information for reporting has been met, and the report is deemed to be relevant by a health care professional within the company, the case is considered reportable.

4.8 Reports Relating to Pregnancy and Breast-Feeding:

The applicant must report suspected adverse drug reactions related to pregnancy or breast-feeding as specified in 4.1.and 4.2 above, regardless of whether the drug is contra-indicated in pregnancy and/or lactation. Reports on pregnancy should not be forwarded before the outcome is known, unless unintended pregnancy is suspected as an adverse drug reaction. Reports on pregnancy should not be submitted if there is no adverse effect to the foetus/infant.

5 PRE-REGISTRATION ADVERSE DRUG REACTION/EVENT REPORTS

This applies to reports from any type of clinical or epidemiological trial, regardless of design or purpose, conducted under Section 21 of Act 101 (1965).

5.1 Adverse Drug Reaction reporting for Clinical Trials:

(i) **All fatal and life-threatening, unexpected** adverse drug reactions occurring in clinical trials in South Africa conducted under Section 21 of Act 101 (1965), should be reported within 7 calendar days after first knowledge by the applicant. The initial notification must be followed by as complete a report as possible, within an additional 8 calendar days. This report must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicines.

(iii) **Serious, unexpected adverse drug reactions that are not fatal or life-threatening**, which occur in clinical trials in South Africa registered under section 21 of Act 101 (1965), must be reported as soon as possible, and not later than 15 calendar days after first knowledge by the applicant.

(iv) All suspected **serious, unexpected** adverse drug reaction reports originating from world-wide clinical sites **outside South Africa** for clinical trials conducted with the same medicine under section 21 of Act 101 (1965), should be reported as part of the 6-monthly progress reports in a line listing format.

(v) The Authority must be notified, within 15 calendar days after first knowledge by the applicant, when there is a suggestion of a change in the nature, severity or frequency of **expected** adverse drug reactions or when new risk factors are identified. The basis on which these assessments are made should be included.

(vi) Any information, which may in any way influence the benefit-risk assessment of a medicine or which would be sufficient to consider changes in the administration of the medicine or in the overall **conduct of a clinical trial,** must be reported to the

Authority. The applicant must submit this information to the Authority within three calendar days of first knowledge thereof. This could include individual case reports or a major safety finding from other sources.

(vii) All serious adverse **events** must be included as part of the 6-monthly progress reports in a line listing format only.

(viii) All non-serious unexpected suspected adverse drug reactions must be included as part of the 6-monthly progress reports in a line listing format only.

(ix) A clinical investigator, who has been approved by the Authority, must sign all reports originating from South Africa. A single copy of the original report should be submitted to the Authority.

(x) If the sponsor of a clinical trial or the applicant for the trial does not agree with the causal association assigned by the initial reporter or the investigator, the reaction should still be reported.

(xi) Expedited (rapid) reporting will be inappropriate for serious events from clinical trials that are considered not related to the study product. All cases judged by the clinical investigator or the sponsor, as having a reasonable suspected causal relationship to the medicine, qualify as adverse drug reactions. (Refer point 2.2.)

5.2 Managing Blinded Therapy Cases:

(i) When a serious, unexpected, suspected adverse drug reaction occurs which results in death or, which is life-threatening, and is, therefore, judged reportable on an expedited (rapid) basis, it is recommended that the blind be broken only for that specific patient by the sponsor, even if the investigator has not broken the blind. It is also recommended that, when possible and appropriate, the blind be maintained for those persons, such as biometrics personnel, responsible for analysis and interpretation of results at the study's conclusion.

(ii) When a fatal or other serious outcome is the primary efficacy endpoint in a clinical trial, the integrity of the clinical trial may be compromised if the blind is broken. Under these and similar circumstances, agreement should be reached in advance with the Authority concerning serious events that would be treated as disease-related and not subject to routine expedited (rapid) reporting. An independent data safety monitoring board should be established prior to commencement of the trial, and its composition and terms of

reference, should be submitted with the clinical trial application documents to the Authority for evaluation.

5.3 Post-study events:

Serious adverse events that occur after the patient has completed a clinical trial (including any post-treatment follow-up required according to the protocol) should be considered for expedited (rapid) reporting purposes as though they were study reports. A causality assessment and determination of expectedness are needed for a decision on whether or not expedited (rapid) reporting is required.

5.4 Medicines used under Section 21 of Act 101 (1965), not within a clinical trial

The prescriber of a medicine approved for use under Section 21of Act 101 (1965) for patients not enrolled in a clinical trial (for e.g., compassionate use, named-patient use, etc.), must report any serious suspected adverse drug reaction that occurred with the use of the medicine in the specified patient(s) within 15 calendar days of first knowledge by the prescriber.

5.5. Protocol design details:

(i) Each clinical trial protocol submitted to Council, should include a risk management procedure, including unblinding procedures, for dealing with serious, unexpected events or reactions which may arise during the conduct of the trial and which could significantly impact on the safety of the study subjects.

(ii) There may be differences in the clinical safety profile for different presentations, for e.g., dosage form, formulation or delivery system of the pharmacologically active compound(s) or different indications/uses of a given product. All adverse reactions which qualify for reporting should be cross-referenced with all other dosage forms and uses for that product. The Investigator's Brochure must, therefore, cover adverse drug reaction information that applies to all product presentations and uses.

6 REFERENCES

1. European Agency for the Evaluation of Medicinal Products: Human Medicines Evaluation Unit. Notice to Marketing Authorisation Holders: Pharmacovigilance Guidelines: 29 January 1999: CPMP/PhVWP/108/99 corr.

2. International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: ICH Harmonised Tripartite Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting and recommended for adoption at Step 4 of the ICH process on 27 October 1994.

3. International Reporting of Periodic Drug-Safety Update Summaries. Final report of CIOMS Working Group II. Geneva 1992.

4. International reporting of Adverse Drug Reactions: Final report of the CIOMS working group. Geneva 1990.

5. Adverse Drug Reaction Reporting by Manufacturers for Marketed Drugs. Bureau of drug Surveillance, Drugs Directorate, Health Canada.

6. U.S. Food and Drug Administration. Guideline for post-marketing reporting of adverse drug experiences. Docket No. 85D-0249, March 1992.

7. Guidelines on the reporting of Adverse Drug Reactions by Drug Sponsors. Therapeutic Goods Administration: Australia. July 1994.

ADRguid6.rtf

7 APPENDICES

7.1 APPENDIX 1: ADDRESSES

Reportable Safety Information as reflected in the Guidelines associated with **registered human medicines** must be sent to:

National Adverse Drug Event Monitoring Centre
Medicines Control Council
C/o Department of Pharmacology
University of Cape Town
Observatory
7925

Tel.: (021) 4471 618
Fax: (021) 448 6181

Reportable Safety Information as reflected in the Guidelines associated with **medicines** used under section 21 of Act 101 (1965) and in clinical trials involving **unregistered medicines** must be sent to:

Office of the Registrar of Medicines
Clinical Trials Business Unit
Private Bag X828
Pretoria
0001

Tel: (012) 312 0279/ 6
Fax: (012) 326 4344

All Adverse Drug Reactions associated with **registered and unregistered veterinary medicines** must be sent to:

Veterinary Pharmacovigilance Centre
C/o Department of Paraclinical Sciences
Section of Pharmacology
Faculty of Veterinary Science

University of Pretoria
Private Bag x 04
Onderstepoort
0110

Tel.: (012) 529-8353
Fax: (012) 529-8304

All safety information associated with medicines (**human and veterinary**) for which an application for registration has been submitted must be sent to:

Office of the Registrar of Medicines
The Clinical Business Unit
Private Bag X828
Pretoria
0001
Tel: (012) 312 0321
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7.2 APPENDIX 2: TABULATED SUMMARY OF REPORTING REQUIREMENTS

Post-Registration ADR Reports (registered medicinal products)

Type of ADR report	Time frame for reporting	Format
Local Reports (spontaneous/published/study):		
• Serious (expected and unexpected)	15 days	ADR form #
• Non serious (unexpected)	15 days	ADR form #
• Non serious (expected)	No report	Not required
Foreign Reports (spontaneous/published/ study):	On request or relating to specific safety issue	As appropriate
• Serious		
Notification of Change in Nature, Severity or Frequency or Risk factors	15 days	Detailed report (including publications)
New information impacting on benefit-risk profile of product including international regulatory decisions	3 days	Detailed report (including publications)

Applicant's in-house ADR report form or NADEMC ADR report form.

Pre-Registration ADR/ADE reports (i.e. unregistered medicines being used under section 21 of Act 101, 1965 or Regulation 34 of Act 90, 1997)

TYPE OF ADR REPORT	TIME FRAME FOR REPORTING	FORMAT
Local Reports:		
• Fatal or life-threatening (unexpected)	7+8**	SAE form
• Other serious (unexpected)	15 days	SAE form
All (local & foreign) reports:		
• Serious (unexpected and expected) events	6-monthly##	Line listing
• Non-serious unexpected reactions	6-monthly	Line listing
Notification of Change in Nature, Severity or Frequency of Risk factors	15days and in 6 monthly report##	Detailed report
New information impacting on risk-benefit profile of product or conduct of trial	3 days and in 6-monthly report##	Detailed report

6-monthly progress report which should be submitted to Council during the entire duration of the clinical investigation.

** 7+8 - initial notification to Council as soon as possible but within 7 calendar days followed by a complete report within 8 calendar days of the initial notification.

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDANCE DOCUMENT: GOOD MANUFACTURING PRACTICE FOR MEDICINES IN SOUTH AFRICA

This document has been prepared to serve as a guidance document on the requirements for Good Manufacturing Practice applicable to the manufacturing of medicines. It is not intended as an exclusive approach. Council reserves the right to request for any additional information to establish the safety, quality and efficacy of medicine and may make amendments in keeping with the knowledge which is current at the time of consideration of data accompanying applications for registration of medicines. Alternative approaches may be used but these must be scientifically and technically justified. The MCC is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy.

REGISTRAR OF MEDICINES
MS M.P. MATSOSO
DATE: 29/4/2003

Version MCC1997/1

FOREWORD

Standards set in South Africa for the registration and control of medicines are widely regarded as being comparable with anywhere in the world. This serves our health system well as it ensures to the greatest possible extent the safety, quality and efficacy of the medicines that are available to the public. Without such safeguards in place, a national drug policy is not achievable or sustainable. It is possible for us in South Africa to be confident in the implementation of those aspects of the national health policy that are aimed at bringing essential medicines at affordable cost to everyone who requires them. Our system of drug regulation also makes allowance for rapid introduction of new medicines which may have a vital role in the prevention or cure of illnesses for which presently available treatments are insufficient.

I am honoured to have been invited to write the foreword to this guide which is aimed at the assurance of quality of medicines. It is a joint effort of the pharmaceutical Manufacturers Association and the secretariat of the Medicines Control Council. As such, it is another example of the strong professional relations that characterise the relationship of the Medicines Control Council and the pharmaceutical industry in South Africa. The work is the culmination of the efforts of a number of participants and I think I can speak for many in expressing appreciation of what has been achieved.

Peter I Folb, MD, FRCP
Chairman: South African Medicines Control Council

Members of the working group: P Smith (Chair), C Giltrow, M Kirkman, T Mlati, A van Zyl (MCC), S Struwig, S Johnson, M de Necker, I Rose-Kelly.

SA GUIDE TO GMP

CONTENTS

INTRODUCTION

The purpose of this guide is to set out generally accepted principles relating to the assurance of pharmaceutical product quality. These principles relate to (selective) aspects of the manufacturing process which experience in the pharmaceutical industry has identified as being potential problem areas insofar as product quality is concerned. Many factors which fall outside the scope of GMP principles may also affect product quality, and the principles referred to in this guide should therefore not be interpreted as being a benchmark against which to measure a manufacturer's (total) quality assurance system.

The content of this Guide is addressed to the manufacturers of ethical and proprietary medicines. The Guide has, however, no legal standing. The responsibility for GMP lies with the individual company to comply with Act 101 of 1965 as amended and to satisfy the Medicines Control Council during plant inspections. Nevertheless, companies may impose stricter in-house standards. Alternative measures capable of achieving the requirements are also acceptable.

Chapter one of the Guide outlines the concept of Quality Management as it refers to the production of medicines. Each chapter is headed by a GMP principle and thereafter contains text in sufficient detail to inform manufacturers of the essential matters to be considered when implementing the principle. Where required, additional guidance is given in appendices on specific topics such as penicillin manufacturing. Supplementary guidelines on specialized areas of activity which only apply to some manufacturers, for example Large Volume Parenterals, are available as a separate Guide.

GLOSSARY

Definitions given below apply to the words/terms as used in this guide. They may have different meanings in other contexts.

ADVERSE DRUG REACTION

An adverse drug reaction is defined as one which is noxious and unintended and which occurs at doses normally used in man of the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

ADVERSE DRUG REACTION (SERIOUS)

This is an adverse drug reaction which is fatal, life-threatening, disabling, incapacitating or which results in or prolongs hospitalisation.

ADVERSE DRUG REACTION (UNEXPECTED)

This relates to an adverse reaction which is not mentioned in the summary of product characteristics (SPC) or national data sheet of the country in which the reaction occurs if a SPC does not exist.

ADVERSE EVENT

Any undesirable experience occurring to a patient treated with a pharmaceutical product whether or not considered related to the medicinal product.

AIR-LOCK

An enclosed space with two or more doors, and which is interposed between two or more rooms, e.g. of differing class of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An air-lock is designed for and used by either people or goods.

ANALYTICAL METHOD

A detailed description of the procedures to be followed in performing tests for conformity with a specification.

AUDIT

A planned and systematic examination and check of a system, procedure or operation in order to monitor compliance with and the effectiveness of established standards and to allow for improvement and corrective measures where required.

BATCH (OR LOT)

A defined quantity of starting material, packaging material or bulk, intermediate or finished product that is intended or purported to be homogeneous in character and quality, and which has been produced during a defined cycle of manufacture. To complete certain stages of manufacture it may be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final uniform batch.

A batch is sometimes described as a lot.

BATCH NUMBER (OR LOT NUMBER)

A distinctive combination of numbers and/or letters which specifically identifies a batch or lot and permits its history to be traced.

BATCH MANUFACTURING RECORD

A document stating the materials used and the operations carried out during the processing of a given batch, including details of in-process controls, but normally excluding packaging information. It should be based on the Master Formula and Method and be compiled as the manufacturing operation proceeds.

BATCH PACKAGING RECORD

A document stating the bulk product and packaging materials used, and the processes carried out during the packaging of a given batch, with details of in-process controls. It should be based on the Master Packaging instruction and be compiled during the packaging operation.

BIOLOGICAL

Biological medicines comprise those derived or extracted from living organisms or tissues and those which contain living or inactivated organisms in the end product.

BULK PRODUCT

Any product which has completed all processing stages up to, but not including, final packaging.

CALIBRATION

The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.

CONTRACT MANUFACTURE, ANALYSIS OR SERVICING

Manufacture (or partial manufacture), analysis or service work ordered by one person or organisation (the Contract Giver) and carried out by an independent person or organisation (the Contract Acceptor).

DEDICATED FACILITY

A room or suite of rooms with attendant equipment and services (including air-supply as necessary) used only for the manufacture of one product, or a closely related group of products. (Equipment may be similarly 'dedicated').

DOCUMENTATION

All the written production procedures, instructions and records, quality control procedures, and recorded test results involved in the manufacture of a medicinal product.

FINISHED PRODUCT

A medicinal product which has undergone all stages of production, including packaging in its final container.

GOOD MANUFACTURING PRACTICE

Good Manufacturing Practice (GMP) is that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and legal requirements. GMP is thus concerned with both production and quality control matters.

IN-PROCESS CONTROL

Tests, checks and measurements made during the course of manufacture (including packaging) to ensure that the resultant product will comply with its specification and to provide feedback to production for process adjustment. The control of the environment or equipment may also be regarded as a part of in-process control. In-process control may be a responsibility of either production or quality control.

INTERMEDIATE PRODUCT

A partly processed material which must undergo further processing before it becomes a bulk or finished product.

LEGALLY AUTHORISED PERSON

A person who has successfully completed the Pharmaceutical Manufacturers' Association's Advanced Technologist Course Part II and subsequently the examination set by the South African Pharmacy Council and is registered by the Pharmacy Council as a Pharmacist's Assistant (Industry).

MANUFACTURE

The cycle of processing of a medicinal product from the acquisition of all materials up to but normally not including, packaging of the finished product.

MASTER DOCUMENT

A master document is a formally authorised source document relating to specifications and/or manufacturing/analytical methods, which is protected from unauthorised access or amendment.

MONITOR

To monitor a process or a situation is to carry out repeated measurements or observations of one or more characteristics of the process or situation to determine whether or not it is continuing as intended. Monitoring may be continuous or intermittent and not necessarily performed on every batch.

PACKAGING

All operations, including filling and labeling, which a bulk product has to undergo in order to become a finished product.

NOTE: Sterile filling would not normally be regarded as part of packaging - the bulk product being the filled. but not finally packaged, primary container.

PACKAGING MATERIAL

Any material employed in the packaging of a medicinal product, excluding any outer packaging used for transportation or shipment
NOTE ·There are various categories of packaging materials e.g.
(a) Packaging materials which come in contact with the product (often called 'Primary Packaging Materials')
(b) Printed packaging materials
(c) Other packaging materials.
Although these categories are not necessarily mutually exclusive, the nature and extent of the control which needs to be applied to them may vary.

PROCEDURES

Description of the operations to be carried out, the precautions to be taken and measures to be applied directly or indirectly to the manufacture of a medicinal product.

PROCESSING STAGES

The separate operations (or groups of related operations) involved in the manufacture of a medicinal product.

PRODUCTION

All operations involved in the preparation of a medicinal product, from receipt of materials. through manufacturing and packaging, to its completion as a finished product.

QUALIFICATION

Qualification is a documented program which provides the assurance that the equipment and installations operate consistently within the pre-determined mechanical, electrical or other operating parameters.

QUALITY ASSURANCE

Is the sum total of all organised arrangements made with the object of ensuring that medicines are of the quality required for their intended use. It is Good Manufacturing Practice plus factors outside the scope of this Guide (such as original product design and development).

QUALITY CONTROL

Is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are, in fact, carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

RADIOPHARMACEUTICALS

A radiopharmaceutical is a preparation of adequately constant composition, radiochemical and radionuclidic purity and uniformity of physiological (pharmacological) action for use in medicine as a diagnostic aid or therapeutic agent.

RECALL

Refers to the removal from the market of a specific batch or batches of the product.

RECONCILIATION

A comparison, making due allowance for normal variation, between the amount of product or materials theoretically and actually produced or used.

RECORDS

Records provide a history of each batch of product, including its distribution, and also all other pertinent information relevant to the quality of the final product.

REPROCESSING

The reworking of all or part of a batch of product of an unacceptable quality from a defined stage of production so that its quality may be rendered acceptable by one or more additional operations; or the introduction of all or part or residues of previous batches of the required quality into another batch at a defined stage of manufacture.

SPECIFICATION

A document giving a description of a starting material, packaging material, intermediate, bulk or finished product in terms of its chemical, physical and (possibly) biological characteristics. A specification normally includes descriptive clauses and numerical clauses. the latter stating standards and permitted tolerances.

STANDARD OPERATING PROCEDURE (S.O.P.)

A written authorised procedure which gives instructions for performing operations not necessarily specific to a given product or material, but of a more general nature the. equipment operation; maintenance and cleaning; recall of products; purchasing; cleaning of premises and environmental control; sampling and inspection; etc.). Certain Standard Operating Procedures may be used to supplement the product-specific Master and Batch production documentation.

STATUS

The classification of any goods, materials, containers or machines in relation to their acceptance (or otherwise) for use, further processing or distribution (e.g. 'Quarantine', 'On Test', 'Released', 'Restricted Use', 'Hold', 'Rejected', 'Clean', 'To be Cleaned').

VALIDATE

To provide documented evidence that an item of equipment, process, system or method is in a state of control (i.e. that all assignable causes of variation have been eliminated) and is able to consistently deliver specified results.

WITHDRAWAL

Implies the total withdrawal of the product from the market.

CHAPTER 1:

QUALITY MANAGEMENT

1.1 PRINCIPLES

1.1.1 Quality is not merely a regulatory requirement; it is also a crucial determinant for business success or failure in modern performance-oriented markets. The **business strategic value** of quality relates **inter alia** to improvement of the enterprise's competitive position, increased productivity, improved risk management and increased profitability.

1.1.2 There should be a comprehensively designed and correctly implemented quality management system which is fully documented, effectively controlled and adequately staffed with competent personnel, suitable and sufficient premises, equipment and facilities, so as to provide the assurance that products have the necessary quality, safety, efficacy and therapeutic availability, comply with the requirements of the regulatory authorities and are fit for their intended use.

1.1.3 This quality management system is the responsibility of senior management and involves them and all those concerned with the design, development, manufacture, packaging, control, purchasing, storage, handling and distribution of medicinal products or their ingredients and components.

1.1.4 Many of the factors which affect product quality lie outside the scope of this guide. All members of the pharmaceutical industry are therefore encouraged to adopt quality management systems that are based on the **total quality** approach, which includes the following principles.

1.1.4.1 Basic quality responsibility rests with top management.

1.1.4.2 Top management should identify and communicate company quality objectives by means of a formal quality policy statement.

1.1.4.3 Quality is affected at every stage of the industrial cycle; i.e. during new design control incoming materials control, production control, and post marketing surveillance activities.

1.1.4.4 Quality knows no functional boundaries; quality is everybody's job and requires carefully planned organisationwide integration.

1.1.5 The basic concepts of Quality Assurance, Good Manufacturing Practice and Quality Control are inter-related. They are of fundamental importance to the production and control of medicinal products.

1.2 QUALITY ASSURANCE

1.2.1 Quality Assurance (QA) is the sum total of all organized arrangements made with the objective of ensuring that medicines are of the quality required for their intended use. It is thus a wide-ranging concept which covers all matters affecting quality. It is the sum total of the organised arrangements made with the object of ensuring that medicinal products are of the quality required for their ultimate use.

1.2.2 The requirements and objectives of Quality Assurance are as follows:

(a) medicines are designed and developed in such a way that they can be produced to comply with the quality requirements and lot to lot conformity to specifications can be maintained
(b) production operations and Good Manufacturing Practices are clearly specified and adhered to
(c) the production environment and services to the production operation are monitored
(d) deviations are adequately recorded, investigated and responded to
(e) the supply and use of adequate starting and packaging materials is assured
(f) all the necessary controls on intermediate and final products and other in-process controls. validations and, if necessary, trend analysis are carried out

(g) no product is sold or supplied until a responsible pharmacist has ensured that each batch has been produced and controlled in accordance with legal and other requirements

(h) medicines are stored, handled and distributed so that quality is maintained throughout their shelf life.

(i) laboratory operations and Good Laboratory Practices are clearly specified and adhered to

(j) the Quality Assurance system is regularly audited by self-inspection for effectiveness and applicability.

1.3 GOOD MANUFACTURING PRACTICE

1.3.1 Good Manufacturing Practice (GMP) is that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate for their intended use and the legal requirements. GMP is thus concerned with both production and quality control matters.

1.3.2 The basic requirements and objectives of Good Manufacturing Practice are as follows:

(a) the production processes are clearly defined, systematically reviewed and validated to ensure products of the required quality

(b) all the necessary facilities are provided, including:

- appropriately qualified and trained personnel
- adequate premises and space
- suitable equipment and services
- correct materials, containers and labels
- approved procedures and instructions
- suitable storage and transport

(c) critical processing steps, key equipment and services are validated

(d) all production operations are conducted in such a way as to produce products of the required quality

(e) instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided

(f) operators are trained to carry out procedures correctly

(g) records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected. Any significant deviations are fully recorded and investigated

(h) in-process and final controls for materials, processes, intermediates and products are adequate to determine suitability

(i) records of production, control and distribution which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form

j) distribution (wholesaling) of the products minimizes any risk to their quality

(k) system is available to recall any batch of product from sale or supply

(l) complaints about marketed products are examined, the causes of quality defects investigated and interpreted and appropriate measures taken in respect of the defective products to prevent recurrence.

1.4 QUALITY CONTROL

1.4.1 Quality Control (QC) is that part of GMP which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

1 4 2 The basic requirements and objectives of Quality Control are as follows:

(a) adequate facilities, trained personnel and approved procedures are available for sampling, inspecting and testing starting materials, packaging materials, intermediates, bulk and finished products, and where appropriate for monitoring environmental conditions for GMP purposes.
(b) samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by personnel and by methods approved by Quality Control.
(c) test methods are validated
(d) adequate standards and reagents are maintained
(e) records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are fully recorded and investigated
(f) the finished product complies with all legal requirements and is enclosed within its specified container and correctly labelled
(g) records are made of the results of inspection and testing of materials, intermediates, bulk and finished products is formally assessed against specification. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures
(h) no batch of product is released for sale or supply prior to certification by a qualified pharmacist that it is in accordance with all legal requirements
(i) sufficient reference samples of starting materials and products are retained to permit future examination of the product if necessary, and the product is retained in its final pack unless exceptionally large packs are produced
j) follow-up stability trials in final packaging are conducted to assess the validity of the shelf-life.

1.5 AUDITS

1.5.1 Audits on all systems, procedures and operations should be regularly conducted in order to monitor compliance with and the effectiveness of Good Manufacturing Practice and Quality Assurance principles in the various operations and to allow for improvement and corrective measures where required.

Audits may be in house or carried out by local regulatory authorities or the regulatory authorities of countries to which companies wish to export.

1.5.2 Audits should follow a pre-arranged programme and include inspection of the following:

(a) organizational matters and responsibilities
(b) qualifications and training programmes
(c) compliance with hygiene requirements and entry restrictions
(d) cleaning and disinfection programmes
(e) medical checks on personnel
(f) production facilities, premises and equipment, including quality control
(g) production operations, procedures and documentation including quality control
(h) storage, handling, distribution and materials management
(i) quality assurance aspects such as complaints, returned goods and validation
t) suppliers of starting and packaging (especially printed) material
(k) third party contractors for manufacturing, packaging, analysis and where required distribution of medicines.

1.5.3 Audits should be detailed and conducted by competent and impartial persons from the company. External auditors may also be useful.

1.5.4 Audit reports should be made and corrective measures agreed upon, recorded and followed up.

1.6 QUALITY EVALUATION AUDITS

1.6.1 Written records as detailed in Chapter 8 should be maintained so that data therein can be used for evaluating the quality standards of each product to determine the need for changes in product specifications or manufacturing and control procedures.

1.6.2 Written procedures should be established and followed for such evaluations and should include provisions for:

- a review of every batch, whether approved or rejected, and where applicable, records associated with the batch

- a review of complaints, recalls, returned or salvaged products, and investigations conducted during normal product record reviews before a batch is released

1.6.3 Procedures should be established to ensure that the responsible official of the firm, if not personally involved in or immediately aware of recalls, salvaged products, complaints etc. be notified in writing of such issues.

1.7 CRITICAL PROCEDURES OR STANDARD OPERATING PROCEDURES

1.7.1 Certain procedures governing critical operations are key to the Quality Assurance system. These procedures should be written and followed. All the relevant requirements in chapter 8 apply to critical procedures as well.

1.7.2 Critical or Standard Operating procedures should include:

(a) self-inspection (audits)
(b) recall of medicines from the market
(c) handling of technical complaints
(d) handling of returned goods
(e) vendor inspection / approval of printed packaging materials
(f) purchasing procedures
(g) procedures for handling and disposal of dangerous, highly toxic or sensitising materials
(h) rodent and pest control.

1.7.3 As and where the scale and nature of an operation demands, there should be written procedures covering other aspects, which could influence the quality of a product, for example:

(a) cleaning and maintenance of buildings and equipment
(b) setting-up and operating manufacturing and packaging equipment
(d) control of the manufacturing environment and monitoring it for potential chemical, physical and biological contamination hazards
(e) training of personnel, particularly with regard to the understanding of relevant procedures and hygiene
(f) the return of unused material to store and the handling of reject material
(g) set procedure to be followed in the case of reworks
(h) dress requirements
(i) sampling
(i) manufacturing and analytical contract agreements

(k) minimum qualifications for key personnel
(l) waste disposal.

1.7.4 Standard operating procedures should be prepared for all systems. procedures and operations which are required to be performed.

1.7.5 The distribution of new and the withdrawal of obsolete procedures should be controlled to ensure the only valid procedures are available.

All procedures should be reviewed on at least a bi-annual basis.

1.7.6 Major or critical equipment should be accompanied by log books recording, as appropriate, any validations, calibrations, maintenance, cleaning or repair operations, including dates and identity of people who carried these operations out.

CHAPTER 2

ORGANISATION AND PERSONNEL

2.1 PRINCIPLES

2.1.1 The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture and control of medicines rely upon people. For this reason, there should be sufficient personnel at all levels with the ability, training, experience and, where necessary, the professional / technical qualifications and managerial skills appropriate to the tasks assigned to them. Their duties and responsibilities should be clearly explained to them and recorded as written job descriptions or by other suitable means. All personnel should be aware of the principles of Good Manufacturing Practice (GMP) that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs.

2.2 RESPONSIBILITIES OF KEY PERSONNEL

2.2.1 The firm must have an organisation chart. People in responsible positions should have specific tasks recorded in written job descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with application of GMP. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

- the organogram should clearly indicate the reporting lines and level of responsibility. The organogram should be authorised and be in accordance with the functional relationships described in the individual job descriptions of the functionaries referred to.

- proper job descriptions should include the responsibilities and document in detail the policy and requirements.

- responsibilities should be delegated and acceptance acknowledged in writing.

2.2.2 Key personnel include the Managing Director, the person responsible for Production and the person responsible for Quality Assurance. The person responsible for Production and the person responsible for Quality Assurance, should be different persons of equal level of authority, neither of whom should be responsible to the other, but who both have a responsibility for achieving the requisite quality.

NOTE - The duties of this person responsible for Quality Assurance are wider than those which may be suggested by such terms as "Chief Analyst", "Laboratory Head", etc.

2.2.3 Persons in responsible positions should have sufficient authority to discharge their responsibilities. In particular, the person responsible for Quality Assurance should be able to carry out his defined functions impartially.

2.2.4 Suitably qualified persons should be designated to take up the duties of key personnel during the absence of the latter.

2.2.5 Key personnel should be provided with adequate supporting staff.

2.2.6 The way in which the various key responsibilities which can influence product quality are allocated may vary with different manufacturers. These responsibilities should be clearly defined and delegated.

2.2.7 Consultants

Only in exceptional circumstances should persons engaged part time or in a consultative capacity be appointed to key positions. Consultants advising on the manufacture, processing, packing, or storage of medicines shall have sufficient education, training and experience, or any combination thereof, to advise on the subject for which they are retained. Records shall be maintained stating the name, address and qualifications of any consultants and the type of service they provide.

2.2.8 Head of Production
The Production Manager, in addition to his responsibilities for production areas, equipment, operations and records; for the management of production personnel; and for the manufacture of products in accordance with the appropriate Master Formulation and Manufacturing instructions, will have other responsibilities bearing on quality which he should share, or exercise jointly, with the person responsible for Quality Control.

2.2.9 Head of Quality Control

The person responsible for Quality Control should have the authority to establish, verify and implement all quality control procedures. He should have the authority, independent of Production, to approve materials and products, and to reject, as he sees fit, starting materials, packaging materials and intermediate, bulk and finished products which do not comply with the relevant specification, or which were not manufactured in accordance with the approved methods and under the prescribed conditions, and to evaluate batch records. (His authority in relation to packaging materials may be limited to those which may influence product quality, identity, and safety in use).

2.2.10 The shared or joint responsibilities of the Head of Production and Head of Quality Control may include authorising written procedures; master documentation, monitoring and control of the manufacturing environment; plant cleanliness; process validation; training of personnel; approval of suppliers of materials and of contract acceptors; protection of products and material against spoilage and deterioration; retention of records; the monitoring of compliance with the requirements of GMP; the inspection, investigation and taking of samples in order to monitor factors which may affect product quality. It is important that both direct and shared responsibilities are understood by those concerned.

2.2.11 In some companies there is appointed a Quality Assurance Manager who oversees all the quality assurance arrangements and reports to senior management. The person responsible for Quality Control may report to the Quality Assurance Manager and share some of the responsibilities with him.

The person responsible for Quality Assurance should be part of the decision-making process in all matters that affect the quality of products including development, production, laboratory, storage, distribution, vendors and third party contractors

2.3 LEGAL ASPECTS

2.3.1 Pharmaceutical Companies

2.3.1.1 South African law lays down certain requirements for pharmaceutical companies, the managing director and pharmacists e.g.:
·the company and the managing director (who must be a pharmacist residing in the Republic) must be registered with the Pharmacy Council

·all directors must confirm that they will abide by the Pharmacy Council's ethical rules

·pharmaceutical operations must be conducted under the constant personal supervision of a pharmacist whose name is displayed over the main entrance

·certain duties and responsibilities must be performed by pharmacists e.g. manipulation, preparation or compounding of medicines, manufacturing, furnishing of advice with regard to medicines, distribution and sale of medicines.

2.3.2 Further Legal Requirements

2.3.2.1 South African law further lays down requirements for the following activities:

·labelling of medicines, including package inserts

·records and registers for scheduled medicines

·sale of medicines only to registered and approved customers

·registration of medicines with the Medicines Control Council

·adherence to standards

·reporting of adverse reactions and technical errors

·advertising of medicines

·carrying and supply of professional samples.

2.3.3 Narcotics/Psychotropics

2.3.3.1 The Medicines and Related Substances Control Act No 101 of 1965 requires returns to be submitted in respect of Schedule 6, Schedule 7, and specified Schedule 5 Substances before 28 February of each year. The Act further requires that wholesalers and manufacturers keep registers of sales and receipts of both Schedule 6 and Schedule 7 Substances, and records of Schedule 5 Substances.

2.3.3.2 The International Narcotics Control Board (I.N.C.B.) has requested the co-operation of the Government of the Republic of South Africa with regard to expanding the requirement of obtaining permits for the importation and exportation of Schedule 6 and Schedule 7 Substances, for all substances under international control. Companies importing or exporting Schedule 5 substances or medicines, which are internationally controlled, are expected to obtain import and/or export permits, although it is not required by law. After the importation or exportation of narcotic drugs or psychotropic substances had been affected, reporting by means of returning the triplicate copy of the permit to the Department of Health, should be done without delay.

2.3.3.3 Any unusual loss or theft of narcotic or psychotropic drugs, should immediately be reported to the South African Police Services and to the Registrar of Medicines.

2.3.3.4 The Department of Health prescribes the procedure to be followed for the destruction of large quantities of Schedule 6 or Schedule 7 drugs, and requires a written statement of quantities of drugs to be destroyed.

2.4 QUALIFICATIONS

2.4.1 Each person engaged in the manufacture, processing, packing or storage of a medicine shall have the education, training and experience or combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in general and specific GMP and written procedures as they relate to the employee's functions. Training in GMP shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to ensure that employees remain familiar with GMP requirements applicable to them.

2.4.2 Each person responsible for supervising the manufacture, processing, packing or storage of a medicine shall have the education, training and experience or combination thereof, to perform assigned functions in such a manner as to provide assurance that the medicine has the quality, safety, efficacy and availability that it purports or is represented to possess.

2.4.3 There shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing or storage of each medicine.

2.5 TRAINING

2.5.1 All Production, Quality Assurance and Stores personnel and all other personnel (eg. maintenance, service and cleaning staff) whose duties take them into manufacturing areas, or which bear upon manufacturing activities, should be trained in the principles of GMP and in the practice (and the relevant theory) of the tasks assigned to them.

2.5.2 Besides the basic training on the theory and practice of GMP, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given and its practical effectiveness should be periodically assessed. Written training programs should be available, approved by either the head of Production or the head of Quality Control, as appropriate. Training records should be kept.

2.5.3 Personnel working in areas where contamination is a hazard e.g. clean areas or areas where highly active, toxic, infectious or sensitizing materials are handled, should be given specific training.

2.5.4 To assess the effectiveness of training, checks should be carried out to confirm that designated procedures are being followed by staff at all levels.

2.5.5 Visitors or untrained personnel should not be taken into the manufacturing areas. However, if deemed necessary, they should be given information in advance, particularly about personal hygiene and prescribed protective clothing which may be required. They should be closely supervised.

2.5.6 The concept of Quality Assurance and all the measures capable of improving its understanding and implementation should be fully discussed during the training sessions.

2.5.7 Pharmacist Intern (Industry)

After formal university education, the Pharmacist Intern must undergo one year internship in Industry, being trained as prescribed by the South African Pharmacy Council.

2.5.8 Pharmacist's Assistant (Industry)

After formal education by the PMA, the Pharmacist's Assistant in Industry is required to pass the Pharmacy Council's examination which enables the assistant to perform certain functions of a Pharmacist as defined by the Pharmacy Council.

2.6 HYGIENE

2.6.1 Personal Hygiene

2.6.1.1 High standards of personal cleanliness should be observed by all those concerned with production processes. (The special requirements for Sterile Products are covered in Chapter 22).

2.6.1.2 Personnel should be instructed to use the handwashing facilities.

2.6.1.3 Detailed hygiene programmes should be established and adapted to the different needs within the factory. They should include instructions relating to the health, hygiene practices and clothing of personnel. These instructions should be understood and followed in a very strict way by every person whose duties take him into the manufacturing and control areas. They should be promoted by management and widely discussed during training sessions.

2.6.1.4 Eating, drinking, chewing and smoking, or the storage of food, drink, smoking materials and personal medication should not be permitted within manufacturing areas or in any other area where they might adversely influence product quality.

2.6.1.5 Direct contact should be avoided between the operators' hands and starting materials, intermediates and products (other than when they are in closed containers), as well as with any part of the equipment that comes into contact with the products.

2.6.2 Area Control

2.6.2.1 Requirements regarding personal hygiene and protective clothing apply to all persons (including visitors, maintenance personnel, senior management and inspectors) entering production areas.

2.6.2.2 All persons entering production areas should wear protective garments appropriate to the processes being carried out. The garments should be regularly and frequently cleaned and not worn outside the factory premises. Changing Rooms should be provided.

2.6.2.3 Only personnel authorised by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas.

2.6.3 Medical Checks

2.6.3.1 There should be pre-employment medical checks and at regular intervals thereafter, and steps should be taken to see that no person with a disease in a communicable form, or with open lesions on the exposed surface of the body, is engaged in the manufacture of medicinal products. Visual inspection staff should pass an annual eye examination.

2.6.3.2 Staff should be required to report infections and skin lesions and a defined procedure followed when they are reported. Supervisory staff should look for the signs and symptoms of these conditions.

CHAPTER 3:

PREMISES AND EQUIPMENT

3.1 PRINCIPLES

3.1.1 Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build up of dust or dirt and, in general, any adverse effect on the quality of products and safety of personnel.

3.2 PREMISES

3.2.1 General Requirements

3.2.1.1 Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.

3.2.1.2 Construction should ensure that it prevents the entry of insects, animals (especially rodents) or birds and that the premises can be easily cleaned and disinfected. A Pest and Insect Control programme should be in place at all times. Toxic baits should be carefully controlled and used in such a way that they cannot present a hazard to products or materials.

3.2.1.3 The building must at all times be maintained in good order with repairs being carried out in such a way that they do not present a hazard to the quality of the products.

3.2.1.4 Waste materials should be continually removed from the premises and written sanitation procedures should be available detailing schedules, methods, materials and equipment available. Responsibility should be assigned in writing. Cleaning and disinfection should be on-going on a regular basis and must include change rooms, wash rooms, toilets and refreshment areas.

3.2.1.5 Adequate lighting and ventilation should be provided in all areas and equipment for controlling dust, humidity, pressure and temperatures should be appropriate for the processes taking place in any particular area. Environmental conditions should be monitored regularly and recorded.

3.2.2 Production Areas

3.2.2.1 Production areas should have a logical layout in order to prevent mix-ups and should have sufficient space to carry out the production in an orderly manner.

3.2.2.2 Production areas should be separated in such a way as to suit the operations taking place and should not be used as a right of way for personnel who do not work in them

3.2.2.3 Production of potent products should be in separate facilities which have been purposely designed to accommodate them and which protect the personnel from the product and vice versa.

3.2.2.4 Production of penicillins, biologicals, certain antibiotics, certain hormones and certain cytotoxics should take place in dedicated facilities designed specially for their manufacture. The principle of campaign working in the same facilities can be accepted provided specific precautions are taken and the process and its effect have been validated. Refer to appendices covering Penicillins, Cephalosporins and Sex Hormones. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of medicinal products.

3.2.2.5 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimise the risk of confusion between different medicinal products or their components, to avoid cross-contamination and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.

3.2.2.6 Production areas should be ventilated with air control facilities appropriate to the products handled, to the operations undertaken and to the external environment. Particular attention should be paid to dust-generating operations e.g. dispensary.

3.2.2.7 Filtration of outside air and air returned to the atmosphere should be the minimum requirement. Air can be blown into the factory and extracted but product must not migrate into passages or other areas. This can be achieved by e.g. blowing air into the passages and extracting it from each department through suitable filters which prevent contamination of the airducts.

3.2.2.8 Production areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate both to the products handled, to the operations undertaken within them and to the external environment.

3.2.2.9 Dust extraction and collection should be in place where dust is generated. All drains should have trapped gullies. Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaning and disinfection.

3.2.2.10 All pipes, fittings and other services should be designed and sited in such a way that they do not create places that are difficult to clean. Floors, walls and ceilings should be of materials that facilitate cleaning.

3.2.2.11 In-process controls may be done within the production area provided they do not carry any risk for the production.

3.2.3 Storage Areas

3.2.3.1 Storage areas should be designed or adapted to ensure good storage conditions. They must be clean and dry and maintain acceptable temperature limits.

3.2.3.2 Special storage areas such as flammable stores, cold rooms or low humidity rooms should be provided for materials that require these conditions. The environment should be continuously monitored and equipped with alarms to alert personnel in case of failure, so that alternative arrangements can be made.

3.2.3.3 There should be sufficient space for proper segregation of the various categories of materials and products. Acceptance and despatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow incoming material containers to be cleaned prior to storage.

3.2.3.4 Warehouses that are not computer controlled should provide separate areas clearly demarcated and preferably physically separated for the following categories of material - sampling, quarantined, raw, packaging, intermediate, finished products, rejected, recalled and returned materials or products. Areas must be restricted to authorized personnel.

3.2.3.5 Computer controlled warehouses must have a system which gives equivalent security.

3.2.3.6 Printed packaging materials and highly potent substances should be controlled and kept under safe and secure conditions.

3.2.3.7 Warehouses should be secured against theft and the higher scheduled medicines and raw materials should be locked in separate secured areas.

3.2.4 Quality Control Laboratories

3.2.4.1 Quality Control Laboratories should be separated from production areas. This is particularly important for laboratories for the control of biologicals, microbiologicals and radio-isotopes, which should also be separated from each other.

3.2.4.2 Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples and records.

3.2.4.3 Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.

3.2.4.4 Special requirements are needed in laboratories handling particular substances, such as biological or radioactive samples.

3.2.5 Ancillary Areas

3.2.5.1 Rest rooms, smoking areas and refreshment rooms should be separate from other areas.

3.2.5.2 Facilities for changing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not directly communicate with production or storage areas and should be well ventilated.

3.2.5.3 Maintenance workshops should as far as possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

3.2.5.4 Animal houses should be well isolated from other areas with a separate entrance for animal access and separate air handling facilities.

3.3 EQUIPMENT

3.3.1 Manufacturing equipment should be designed, located and maintained to suit its intended purpose.

3.3.2 Equipment should be installed and located in such a way as to prevent any risk of error or of contamination.

3.3.3 Repair and maintenance operations should not have any effect on the quality of the Products. Adequate records should be kept.

3.3.4 Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labelled as defective.

3.3.5 Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in a clean and dry condition. Adequate cleaning records indicating previous product made, should be kept.

3.3.6 Equipment for the purpose of washing and cleaning should be chosen and used in such a way so as not to be a source of contamination itself.

3.3.7 Inasmuch as water is used more copiously and widely than any other substance in pharmaceutical manufacturing, its quality is of the utmost importance. The two most important attributes over which control must be exercised are the content of solids and the number of micro-organisms.

3.3.8 Water used for the manufacture of medicines should be purified by ion exchange treatment, reverse osmosis or distillation. Ion-exchange columns and reverse osmosis units require special attention in that they afford sites for micro-organisms to lodge, to multiply and to enter the water. Frequent monitoring and regeneration of these units is called for.

3.3.9 Distilled, deionized and, where appropriate, other water pipes should be sanitized according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.
3.3.10 Production equipment should not adversely affect the quality of the products. The parts of the production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product. The product should not come into contact with other materials such as coolants and lubricants.

3.3.11 Balances and measuring equipment of an appropriate range and precision should be available for production and control operations.

3.3.12 Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. More frequent verification of some weighing equipment may be advisable. Adequate records of such tests should be maintained.

3.3.13 Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a medicinal product. If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written programme designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained.

3.3.14 Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Input to, and output from the computer or related system, of formulae or other records or data shall be checked for accuracy. A backup file of data entered into the computer or related system shall be maintained, except where certain data such as calculations are eliminated by computerization or other automated processes. In such instances either a written record of the programme (source code) shall be maintained or the system should be validated. Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasure or loss, shall be maintained.

3.3.15 Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.

3.3.16 Where applicable, liquid products should pass through suitable filtration equipment before being filled. The type of filter will vary from product to product but no asbestos filters should be used. For instance, syrups may be passed through in-line strainers while solutions are generally pumped through a filterpress. Filtration can be fine enough to exclude bacteria, if this is necessary. Filters should not shed fibres or adversely affect the product.

CHAPTER 4:

MATERIALS MANAGEMENT

4.1 PRINCIPLES

4.1.1 There should be written procedures for the control, purchasing, receipt, storage, handling and issuing of raw materials, packaging material components, intermediate and finished products. All materials should be handled and stored in a manner to prevent contamination. deterioration and intermixinq.

4.2 PURCHASING

4.2.1 All materials should be purchased against an approved and adequate specification which defines not only the grade and quality of the material, but also the nature of the packaging and container to be used.

4.2.2 Materials should be purchased and sourced only from approved suppliers and manufacturers. Choice of vendor should be based mainly on quality considerations.

4.2.3 Raw materials and packaging components should only be purchased by buyers who are adequately trained and who possess sufficient technical knowledge.

4.3 RECEIVING

4.3.1 Upon receipt and before acceptance, each container or grouping of containers should be examined visually for appropriate labelling, (including name, batch number, expiry date, supplier) damage and contamination, and quality control informed as necessary. The number of containers should be compared with the order document and invoice. Containers should be dusted or cleaned if required, and protected from contamination during storage.

Materials should only be taken into stock if all the relevant documentation (eg. delivery note and COA) is accompanied.

4.3.2 All materials subject to quality control should be stored under quarantine and withheld from use, until the lot has been tested or examined, as appropriate, and released by quality control.

4.3.3 Each container or grouping of containers should be identified with standard nomenclature and a distinctive code for each lot in each shipment received, which should be used in recording the disposition of each lot. Each lot should be appropriately labelled and identified as to its status (i.e. quarantined, approved or rejected). This may be done manually or the status may be controlled by appropriate and validated computer systems.

4.4 STORAGE

4.4.1 Materials which are in quarantine, approved or rejected should be segregated from each other. Such segregation may be accomplished by one or more of the following means:

·storage in physically separated areas
·clear and easily distinguishable status labelling
·a system of control, e.g. by computers, bar-codes or other means, which reliably prevents the inadvertent use of unapproved material.

4.4.2 Materials should be stored under suitable conditions, taking into account the following requirements:

·storage temperature
·humidity
·direct light
·exposure to air

4.4.3 Containers should be stored off the floor and suitably spaced from other materials, walls and from other batches of the same material.

4.4.4 Materials approved for use should be rotated so that the stock with the earliest expiry date is used first.

4.4.5 Materials should be resettled or re-examined, as appropriate, and approved or rejected by quality control if necessary e.g. after storage for long periods or after exposure to adverse conditions. An adequate system for monitoring the storage period should be maintained.

4.4.6 Storage of printed packaging materials requires strict and careful control, e.g.:

·storage in separate locked areas with each component stored separately with suitable identification
·under supervision of a suitably trained and responsible person
·obsolete components should be immediately destroyed.

4.4.7 Access to all storage and holding areas should be limited to authorized personnel.

4.5 ISSUING

4.5.1 Issuing of materials should be performed by suitably trained and responsible persons.

4.5.2 Records should be maintained for quantities received, approved, issued and returned, to enable clear reconciliations to be performed. Discrepancies require thorough investigation.

4.5.3 Rejected materials should be identified and controlled under a system which prevents their use in operations for which they are unsuitable. A separate area should be used. Only materials approved by quality control should be used.

4.5.4 Issuing of printed packaging materials requires strict and careful control, eg.:

·transport in sealed containers
·excess components should be destroyed if intermixing could have occurred
·returned components should be identified and stored in such a way so as to prevent mix-ups.

CHAPTER 5:

MANUFACTURING

5.1 PRINCIPLE

5.1.1 Manufacturing operations must follow clearly defined written procedures in order to produce products of the requisite quality and must comply with their authorized manufacturing documents as well as all legal requirements.

5.2 VALIDATION (SEE CHAPTER 9)

5.2.1 Before any manufacturing operation can be considered as routine it should be validated.

5.2.2 Validation studies of manufacturing methods should be conducted in accordance with defined procedures. Results and conclusions must be recorded.

5.2.3 New manufacturing procedures should be subject to methods to demonstrate the suitability of such procedures for routine processing. The defined process must be shown to yield a product consistently of the required quality.

5.2.4 Significant amendment to the manufacturing process which may affect product quality and/or the reproductivity of the process should be validated. This includes changes to materials and equipment.

5.2.5 Periodic re-validation should become a routine procedure to ensure that processess and procedures remain capable of achieving the intended results.

5.3 DISPENSING

5.3.1 Starting material should only be purchased from approved suppliers and in accordance with the registration dossier.

5.3.2 Starting materials in the storage area should be appropriately labelled. Labels should bear at least the following information:

(a) The designated name of the product and the internal code reference, where applicable

(b) a batch number given at receipt

(c) where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected)

(d) where appropriate, an expiry date or a date beyond which retesting is necessary.

5.3.3 There should be appropriate procedures or measures to assure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified.

5.3.4 Only starting materials which have been released by the Quality Control Department and which are within their shelf-life should be used.

5.3.5 Starting materials should only be dispensed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.

5.3.6 Each dispensed material and its mass or volume should be independently checked and signed for by a pharmacist or other legally authorized person.

5.3.7 Materials dispensed for each batch should be kept together and conspicuously labelled as such.

5.3.8 The addition of each material to the mix should be checked and signed for by a pharmacist or other legally authorized person.

5.4 MANUFACTURING OPERATIONS

5.4.1 Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination. Materials for a particular batch should, as far as possible, be kept together.

5.4.2 All manufacturing areas and equipment should be checked for cleanliness prior to starting production.

5.4.3 At every stage of processing, products and materials should be protected from microbial and other contamination.

5.4.4 At all times during processing, all materials, bulk containers, major items of equipment and, where appropriate, rooms used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication should also mention the stage of production.

5.4.5 Labels applied to containers, equipment or premises should adhere well and be clear, unambiguous and in the company's agreed format. It is often helpful, in addition to the wording on the labels, to use colours to indicate status (for example: green for released, red for rejected).

5.4.6 Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.

5.4.7 Normally, non-medicinal products should not be produced in areas and with the equipment destined for the production of medicinal products.

5.4.8 Access to production premises should be restricted to authorized personnel.

5.4.9 Any deviation from instructions or procedures should be avoided as far as possible. If deviations occur, they should be approved in writing by an authorized person(s), with the involvement of the Quality Control Department, when appropriate.

5.4.10 Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits. Any such discrepancies should be investigated and explained.

5.5 IN-PROCESS CONTROL

5.5.1 Production staff should follow defined and authorized procedures for each stage of each manufacturing process.

5.5.2 At all key steps of manufacture there should be some form of control to ensure compliance with the authorized procedure. Critical steps should be signed for.

5.5.3 In-process laboratory tests may need to be carried out before moving to the next step in production or as soon as possible after completion of that step. Formal approval of some results may be necessary.

5.5.4 All inappropriate labels must be removed from containers or equipment before these items enter the manufacturing area.

5.5.5 Environmental control should be carried out and recorded, when necessary.

5.6 CONTAMINATION

5.6.1 Contamination of raw material or of a product by another material or product must be avoided. The risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapours, sprays or organisms from materials and products in process, from residues in equipment, from water and from operators' clothing. The significance of this risk varies with the type of contaminant and of product being contaminated. Amongst the most hazardous contaminants are highly sensitizing materials, biological preparations such as living organisms, some hormones, cytotoxics, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection, those given in large doses and/or given over an extended period.

5.6.2 Cross-contamination should be avoided by appropriate technical or organizational measures, for example:

(a) production in segregated areas (required for products such as penicillins, some hormones, live vaccines, live bacterial preparations and some other biologicals - see Appendices), or by campaign production (separation in time) followed by appropriate cleaning

(b) providing appropriate air-locks and air extraction

(c) minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air

(d) keeping protective clothing inside areas where products with special risk of cross-contamination are processed

(e) using cleaning and decontamination procedures of known effectiveness. (Ineffective cleaning of equipment is a common source of cross- contamination). Vacuum and wet cleaning methods are preferred

(f) using "closed systems" of production

(g) testing for residues and use of cleaning status labels on equipment.

5.6.3 Measures to prevent cross-contamination and the effectiveness of the measures should be checked periodically according to set procedures.

5.6.4 Microbial contamination should be controlled by air filtration, effective cleaning, disinfection and ensuring only the minimum number of personnel required enter the area. The area must at all times be

neat and tidy to prevent accumulation of materials that could promote microbial growth. Insects, animals and birds must be totally excluded.

5.6.5 All personnel (including those concerned with cleaning and maintenance) should receive regular training in the disciplines necessary to prevent microbial and other contamination.

5.6.6 When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitizing materials.

5.6.7 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation.

5.6.8 Intermediate and bulk products should be kept under appropriate storage conditions and for controlled periods.

5.5.9 Any necessary in-process controls and environmental controls should be carried out and recorded.

5.7 REPROCESSING

5.7.1 Material may be re-worked or recovered by an appropriate and authorized method, provided that the material is suitable for such reprocessing, that the resultant product meets its specification, that there is no significant change in product quality and that Quality Control authorization is obtained. Documentation should accurately record the reworking processes carried out. The reprocessing of rejected products should be exceptional.

5.7.2 Residues and re-worked or recovered material which might adversely affect product quality, efficacy or safety should not be used in subsequent batches.

5.7.3 The treatment of product residues and reworked or recovered material and the means of their inclusion in a subsequent batch should be specifically authorized and documented.

5.7.4 Limits, approved by Quality Control, should be established for the amount of any such material which may be added to a subsequent batch.

5.7.5 Batches incorporating residues should not be released until the batches from which the residues originated have been tested and found suitable for use.

5.7.6 Methods of re-processing should be specifically authorized and fully documented, once any potential risks have been evaluated and found negligible.

5.7.7 The need for additional testing including stability of any Finished Product which has been re-processed (or to which residues have been added) should be considered.

CHAPTER 6

PACKAGING

6.1 PRINCIPLES

6.1.1 Packaging operations must follow clearly defined written procedures in order to produce finished products of the requisite quality and must comply with their authorized packaging documents as well as all legal requirements. Special attention must be paid to labels and labelling throughout the entire packaging cycle.

6.2 COMPONENT ISSUE

6.2.1 The purchase, handling and control of primary and printed packaging materials shall be accorded attention similar to that given to starting materials.

6.2.2 Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorized access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. If the quantity or volume of loose printed packaging material is too large to be placed in separate closed containers eg. several pallets of cartons, adequate alternative control measures must be taken to ensure no mix-ups occur.

Packaging materials should be issued for use only by authorized personnel following an approved and documented procedure.

6.2.3 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

6.2.4 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded.

6.3 PACKAGING OPERATIONS

6.3.1 When preparing a programme for the packaging operation, particular attention should be given to minimising the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.

6.3.2 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used, if these are not required for the current operation. The line-clearance should be performed according to an appropriate check-list and signed for. Certain checks eg. printed packaging material, printing operations and bulk identity should be performed and signed for by a pharmacist or legally authorized person.

6.3.3 The name and batch number of the product being handled should be displayed at each Packaging station or line.

6.3.4 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the packaging instructions.

6.3.5 Normally, filling and sealing should be followed as quickly as possible by labelling. If it is not the case, appropriate security procedures should be applied to ensure that no mix-ups or mislabelling can occur.

6.3.6 The correct performance of any printing operation (for example code numbers, expiry dates) to be done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand which should be re-checked at regular intervals.

6.3.7 Special care should be taken when using cut-labels and when over-printing is carried out off-line. Roll-feed labels are normally preferable to cut-labels, in helping to avoid mix-ups.

6.3.8 Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.

6.3.9 Printed and embossed information on packaging materials should be easily legible and resistant to fading or erasing.

6.3.10 Containers for filling should be clean before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments, metal particles and unwanted moisture.

6.3.11 All pipelines and other equipment for transporting product to the packaging line should be thoroughly cleaned, inspected and labelled according to a specific written procedure.

6.3.12 Hand packing operations require increased vigilance to prevent inadvertent mix-ups.

6.3.13 Products which have been involved in any deviation from standard procedure or other unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorized personnel. Detailed record should be kept of this operation.

6.3.14 On completion of a packaging run, the quantities of finished product should be reconciled with the amount of bulk product issued, the amount of packaging material issued. and the material remaining.

6.3.15 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product or printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for. Reconciliation of printed packaging materials may not be necessary if other suitable means of preventing the introduction of foreign components are in use, e.g. bar-code readers

6.3.16 At the end of the pack-out the packaging line should be inspected to ensure that all material relating to that particular product or run has been removed and that all equipment is cleaned. Special attention should be devoted to ensuring that no tablets, capsules or other small items have fallen into parts of the equipment. Special attention to ensure that no labels remain in the equipment or on the floor should be part of the inspection.

6.3.17 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded.

6.3.18 Special care must be taken to control the return of any unused packaging materials to the packaging materials warehouse.

6.4 IN-PROCESS CONTROL

6.4.1 During the packaging process the packing line should be continually monitored to ensure that the integrity of the finished product is not in any way compromised. Written procedures and tabulated check lists should be signed at regular intervals by competent and suitably trained people.

6.4.2 Automated controls and monitors should be checked regularly during the production run and validated from time to time.

6.4.3 On-line control of the product during packaging should include at least checking the following:

·general appearance of the package
·fill masses/volumes or quantity comply
·whether the packages are complete
·whether the correct products and packaging materials are used
·whether any over-printing is correct
·seal integrity
·correct functioning of line monitors.

6.4.4 Samples taken away from the packaging line should not be returned.

6.5 CONTAMINATION

6.5.1 Every effort should be made to ensure that packaging takes place in an orderly and tidy manner that will ensure there are no mix-ups between one product and another.

6.5.2 Products that are similar in appearance should not be packaged in close proximity to one another at the same time.

6.5.3 Packaging lines should be well separated and, if possible, physical barriers that will prevent the migration of material from one line to another should be in place.

6.5.4 Special precautions should be taken to prevent the inadvertent transfer of components by personnel moving between packing lines, e.g. inspectors and maintenance staff.

6.6 FINISHED PRODUCT RELEASE

6.6.1 Finished products must be placed in quarantine in such a way that they cannot be removed for use until such time as they are released.

6.6.2 Samples of the product taken at intervals during the packaging process must be retained for examination by the quality control laboratory and for retention purposes.

6.6.3 Documentation should be reconciled, completed/and sent for a complete documentation audit by quality assurance.

6.6.4 When all required parameters are satisfied, including the document audit, Quality Control may recommend release of the product from its quarantine status.

6.6.5 The finished product should be released for sale by a pharmacist.

CHAPTER 7:

QUALITY CONTROL

7.1 PRINCIPLES

7.1.1 In order to achieve reliable results, Quality Control laboratories should have sufficient resources and appropriate facilities, with properly trained, managed and motivated staff, and adopt good quality control laboratory practices. Materials and products should not be released for use or supply until their quality has been judged satisfactory. Quality Control should be independent from Production. Quality Control should adopt procedures necessary to ensure that the relevant tests and checks are carried out.

7.2 RESPONSIBILITIES

7.2.1 The Quality Control department is responsible for approving or rejecting raw materials, intermediates, finished products and components for use or supply to the market

7.2.2 Finished product assessment should embrace all relevant factors, including production conditions, results of in-process testing, a review of manufacturing and packaging documentation, compliance with Finished Product Specification and examination of the final finished pack. Where the local applicant or holder of a registration certificate makes use of a contract laboratory (overseas), the local applicant or holder of a registration certificate or the local laboratory as listed in the registration certificate, should do at least a visual identification of the final product.

7.2.3 Quality Control is not confined to laboratory operations but must be integrated into the Quality Assurance activities. It is involved in all decisions which may concern the quality of the product (i.e. quality planning, co-ordination and control activities). It further includes the review of all plant systems and procedures, audits, organization and documentation.

7.2.4 The Quality Control department will also have the following responsibilities:

·sampling of materials subject to quality control and the keeping of retention samples and records
·monitoring the stability of products
·investigation of complaints related to the quality of the product
·the testing or supervision of the testing of all materials and products
·the control over labeling of containers for materials and Products

All these operations should be carried out in accordance with written procedures, and where necessary, recorded.

7.2.5 The Quality Control department may also have responsibilities in the following areas :
·validation of critical equipment and procedures
·approval of third party contractors and vendors
·approval of all deviations and reworks

7.3 EQUIPMENT

7.3.1 Control laboratories should be designed, equipped, maintained and of sufficient space to suit the operations to be performed in them, and include provision for the storage of documents and samples.

7.3.2 Chemical, biological and microbiological laboratories should be separated from each other and from manufacturing areas. Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.

7.3.3 Control laboratory equipment and instrumentation should be appropriate to the testing procedures undertaken.

7.3.4 Equipment and instruments should be serviced and calibrated at suitable specified intervals and readily available records maintained for each instrument or piece of equipment.

7.3.5 Written operating instructions should be readily available for each instrument.

7.3.6 As necessary, analytical methods should include a step to verify that the equipment is functioning satisfactorily.

7.3.7 Control laboratories and equipment should be kept clean, in accordance with written standard operating procedures and schedules. Records/logs should be kept.

7.3.8 Personnel should wear clean protective clothing and personal protective equipment appropriate to the duties being performed.

7.4 PERSONNEL

7.4.1 The Quality Control laboratory should be under the authority of a person with appropriate qualifications and experience and with sufficient responsibility and authority to carry out the required duties adequately.

7.4.2 All relevant quality control staff should be suitably educated, trained and motivated to perform their tasks adequately.

7.5 SAMPLING

7.5.1 Samples should be taken in such a manner that they are representative of the batch of material from which they are taken, in accordance with approved written sampling procedures. These procedures should include:

·the method of sampling
·the equipment to be used
·the amount of sample to be taken
·instructions for any required sub-division of the sample

·the type and condition of sample container to be used
·any special precautions to be observed, especially in regard to sampling of sterile or noxious materials.
·cleaning and storage of sampling equipment.

Any sampling by production personnel should only be done in accordance with these approved procedures.

7.5.2 Each sample container should bear a label indicating its contents, with the batch or lot number reference and the date of sampling. The sampler should initial on the label and there should be an indication from which container the sample was taken. It should also be possible to identify the bulk containers from which samples have been drawn and which containers have been sampled.

7.5.3 Care should be taken to avoid contamination, or deterioration whenever a material or product is sampled. Sampled containers should be resealed in such a way so as to prevent damage to, or contamination of, or by, the contents.

7.5.4 Retention samples from each batch of finished products should be retained until one year after the expiry date. Finished products should be kept in their final packaging and stored under the recommended conditions. Samples of starting materials (other than solvents, gases and water) should be retained until at least the expiry date of the batch in which they are used. Reference samples of materials and products should be of a size sufficient to permit at least one full re-examination.

7.6 TESTING

7.6.1 Analytical methods should be suitably validated. Only methods approved for use should be used. All tests required to be performed should be carried out.

7.6.2 Before the material is released or rejected, the results obtained should be checked to make sure that they are consistent with all other information. Any calculations should be documented and critically examined.

7.6.3 All the in-process controls, even those made in the production area by production personnel, should be done according to methods approved by Quality Control and the results recorded.

7.6.4 Microbiological testing and testing using animals should be performed and controlled in a manner that assures their suitability and reliability.

7.7 STANDARDS, REAGENTS

7.7.1 Special attention should be given to the quality of laboratory reagents, volumetric glassware and solutions, reference standards and culture media.

7.7.2 Reagents made up in the laboratory should be prepared by persons competent to do so, following laid-down procedures. As applicable, labelling should indicate the concentration, standardisation factor, shelf-life, and storage conditions. If relevant, a date for re-standardisation should be recorded. The label should be signed, and dated, by the person preparing the reagent.

7.7.3 Reference standards, any secondary standards prepared from them and purchased reagents should be dated where necessary and be stored, handled and used following written procedures, so as not to prejudice their quality. In certain cases it may be necessary to carry out an identification test and/or other testing of reagent materials upon receipt or before use. A record of these tests should be maintained.

7.7.4 Both positive and negative controls should be applied to verify the suitability of microbiological culture media. The size of the inoculum used in positive controls should be appropriate to the sensitivity required.

7.8 DOCUMENTATION

7.8.1 Quality Control procedures should be established, validated, implemented and recorded so as to assure the adequate and reliable performance of all quality control operations.

7.8.2 The following master documentation should be readily available to the Quality Control Department:

·specifications
·sampling procedures
·testing procedures and records (including analytical worksheets and/or laboratory notebooks)
·analytical reports and/or certificates
·data from environmental monitoring, where required
·validation records of test methods, where applicable
·procedures for and records of the calibration of instruments and maintenance of equipment.

7.8.3 The following test records should be kept:

·name and quantity of product or material and code reference where applicable
·dates of receipt, sampling and testing
·manufacturer and/or supplier of product or material
·supplier's batch or lot number

·tests performed
·reference to the relevant specifications and test methods used and to any certificates of analysis
·test results including observations and calculations
·initials of analyst and the person who verified the testing and calculations where appropriate
·decision statement regarding release, rejection or other status and signature of responsible person taking the decision.

7.8.4 In addition to the above records, analysts' laboratory records should also be retained, with the basic data and calculations from which test results were derived (e.g.. weighings, readings, recorder charts, etc.).

7.8.5 It is useful to record test results in a manner that will facilitate comparative reviews of those results and the detection of trends.

7.8.6 Any Quality Control documentation relating to a batch record should be retained for at least one year after the expiry date of the batch.

7.9 STABILITY

7.9.1 A written programme of on-going, follow-up stability should be designed and implemented so as to monitor the quality of the various marketed products throughout their intended shelf-life.

7.9.2 Tests should be performed that are indicative of stability and if necessary additional tests monitoring possible degradation and deterioration should be included.

7.9.3 Stability samples should be stored in their final, marketed containers and storage conditions should be consistent with those approved for the product in question.

7.9.4 Results from stability trials should be used to confirm or modify the prevailing shelf-life and storage conditions.

CHAPTER 8:

DOCUMENTATION

8.1 PRINCIPLES

8.1.1 Documentation is an essential part of the Quality Assurance System. Its purposes are to define the system of control, to reduce the risk of error inherent in purely oral communication, to ensure that personnel are instructed in the details of, and follow, the procedures concerned, and to permit investigation and tracing of defective products. The system of documentation should be such that the history of each batch of product, including the utilisation and disposal of starting materials, packaging materials and intermediate, bulk and finished products, may be determined.

8.1.2 Every applicant or holder of a registration certificate should be in possession of Master documentation, whether he manufactures the product or makes use of a third party manufacturer.

8.1.3 There should be authorised (signed and dated) specifications for a least raw materials, formula of the product, manufacturing method, printed packaging material, final product specification, in process tests, test methods and packaging material.

8.1.4 Master documents should be authorised, and the name of the applicant or holder of a registration certificate should be visible.

8.1.5 Master documents should be kept at the registered premises of the applicant or holder of the registration certificate.

8.1.6 Master documents should be properly controlled, and access thereto limited.

8.1.7 The registration dossier should be compliant with Master documentation.

8.1.8 There should be a written procedure for updating of master documentation and the system should endure that current, approved master documentation is being used.

8.1.9 A formal system should be in place to control changes to master documentation. Changes to master documents should be communicated to the appropriate departments and written approval prior to implementation of changes should be obtained from the regulatory authority where applicable.

8.1.10 Possession of mater documentation is a pre-requisite of medicines.

8.1.11 All relevant documentation, including the registration dossier and master documentation, should be handed to the new proposed applicant, should the current applicant or holder of a registration certificate apply to the regulatory authority for a change of applicancy.

8.2 PREPARATION, ISSUE AND USE OF DOCUMENTS

8.2.1 To facilitate proper and effective use, documents should be designed and prepared with care, and with particular attention to the following points:

(a) the company's name, the title (which should be unambiguous), nature and purpose of the document should be clearly stated. The document should be laid out in an orderly fashion, and be easy to check. Each page should be sequentially numbered. Where a document has been revised, systems should exist to prevent inadvertent use of superseded documents.

(b) the way the document is to be used, and by whom, should be clearly apparent from the document itself.

(c) where documents bear instructions they should be written in the imperative as numbered steps. They should be clear, precise, unambiguous and in a language the user can understand. Such documents should be readily available to all concerned with carrying out the instructions.

(d) documents which require the entry of data should:

·provide sufficient space for the entry
·allow adequate spacing between entries
·show headings clearly indicating what is to be entered.

(e) persons making entries should do so in clear legible writing, and should confirm the entry by adding their initials or signatures. Ticking should be avoided.

(f) all entries should be made in ink or other indelible medium.

(g) the size and shape of documents and the quality and colour of the paper used should be considered in relation to the typing / printing, reproduction and filing facilities available.

(h) reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process. If working documents are computer generated these should be checked against an authorised master and signed for correctness.

8.2.2 Documents should contain all necessary, but no superfluous data. Any headings, or places for entries, which cease to be used should be removed at the earliest opportunity.

8.2.3 Documents should be approved, signed and dated by appropriate, competent and authorized persons.

8.2.4 Documents (other than records) should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of the registration dossier.

8.2.5 Records should be completed at the time each action is taken in such a way that all significant activities concerning the manufacture of medicinal products are traceable.

8.2.6 Data may be recorded by electromagnetic or photographic means, but detailed procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data processing methods, only authorised persons should be able to enter or modify data in the computer; access should be restricted by passwords or other means and entry of critical data should be independently checked. Batch records electronically stored should be protected by back-up transfer on magnetic tape, microfilm, paper or other means. It is particularly important that, during the period of retention, the data can be rendered legible within an appropriate period of time.

8.2.7 If an error is made or detected on a document it should be corrected in such a manner that the original entry is not lost and the correction initialed and dated. Where appropriate, the reason for the correction should be recorded. No correction fluid should be used.

8.2.8 Documents should be kept up to date. Any amendments should be formally authorised and signed. In the case of permanent amendments, the amended document should be replaced at the earliest opportunity by a newly prepared document.

8.2.9 The documentation system should include provision for regular review and revision as necessary.

8.2.10 An out-dated or superseded document should be removed from active use. The marked "Superseded" copy should be retained for reference purposes.

8.2.11 When a document has been revised, systems should exist to prevent inadvertent use of superseded documents.

8.2.12 Documents and other records, including original data such as laboratory notebooks should be retained for at least one year after expiry date of the batch. Documents should be easily retrievable.

8.3 MASTER SPECIFICATIONS

8.3.1 Starting Materials

8.3.1.1 There should be an authorised specification for each starting material.

8.3.1.2 Each specification should be dated and include:

(a) a designated name, with reference to monograph specifications where appropriate, and, preferably, a code reference unique to the material

(b) a reference to any alternative proprietary designation of the material

(c) a description of the physical form of the material

(d) sampling instructions

(e) tests and limits for identity, purity, physical and chemical characteristics, microbiological standards (where appropriate) and assay

(f) details of, or reference to, the test methods to be used to assess compliance with the specification

(g) approved supplier(s) of the material

(h) safety precautions to be observed

(i) storage conditions

j) frequency of re-testing the stored material

NOTE - Certain of the requirements may not necessarily appear on the prime specification document. There may be, for example, standard company sampling procedures and lists of approved suppliers to which the specification refers.

8.3.2 Packaging Materials

8.3.2.1 There should be packaging material specifications, approved by the person responsible for Quality Control.

8.3.2.2 Each specification should be dated and include:

(a) a designated name, with preferably a code-reference unique to the material. This reference may also appear on printed materials

(b) a description of the nature, dimensions and material of construction of the component with the quality standards, control limits, mould references, drawings and details of text, as applicable

(c) details of, or reference to the test methods to be used to assess compliance with the specification

(d) approved supplier(s) of the component
(e) sampling instructions

(f) storage conditions

(g) frequency of re-inspection of the stored component.

NOTE - Certain of these requirements may not necessarily appear on the prime specification document. See Note under 'Starting Materials' above.
See definition of 'Packaging Material' in Glossary. The need for detailed specifications may not apply to 'Other Packaging Materials'.

8.3.2.3 A file of reference specimens of current printed packaging materials should be maintained. This should include a colour standard

8.3.3 Intermediates and Bulk Products

8.3.3.1 These specifications should, as appropriate, be similar to specifications for starting materials and Finished Product specifications.

8.3.3.2 These specifications should be available if these products are imported, or if data obtained from these products are used for evaluation of the finished product eg. cores of coated tablets.

8.3.4 Finished Products

8.3.4.1 There should be specifications, approved at least by the person responsible for Quality Assurance, defining the nature and quality of each finished product.

8.3.4.2 Each specification should be dated and include:

(a) the designated name of the product and a code reference where applicable

(b) a description of the physical form of the product and a reference to container and package details

(c) sampling instructions

(d) tests and limits for identity, purity, physical and chemical characteristics, microbiological standards (where appropriate) and assay, with details of (or reference to) the test methods to be used

(e) safety precautions to be observed

(f) storage conditions and the claimed or approved shelf life.

(g) frequency of re-examination of the stored product to confirm the established shelf-life (for stability purposes).

NOTE - Certain of these requirements may not necessarily appear on the prime document. See Note under 'Starting Materials' above.

8.4 MASTER MANUFACTURING INSTRUCTIONS

8.4.1 A formally authorised Master Formula and Method should exist for each product and batch size to be manufactured.

8.4.2 The Master Formula should be dated and include:

(a) the name of the product with a code reference relating it to its specification

(b) a description of the pharmaceutical form and strength of the product and batch size

(c) a list of all starting materials to be used (see 8.4.3) with the amount of each, whether or not they appear in the Finished Product. All quantities should be stated in a uniform system of measurement, with a statement of any calculated overage. Where material of variable potency is to be used the permissible limits of variation and the total potency required for a batch should be stated

(d) a statement of the total expected final yield with the acceptable limits and of relevant intermediate yields where applicable.

8.4.3 Each starting material should be designated in the Master Formula by:

(a) the Approved or Monograph Name, and / or any other descriptive name, by which it can be specifically identified and which is used whenever that material is referred to

(b) a code reference which is unique to that material.

8.4.4 The Method should be dated and, as appropriate, include:

a) a statement of the manufacturing location and the equipment to be used

(b) the methods, or reference to the methods, to be used for preparing the equipment (e.g. cleaning, assembling, calibrating, sterilising)

(c) Detailed stepwise processing instructions, including:
·a check that the materials used are those intended
·any required pre-treatment of materials
·sequences for adding materials
·mixing and other processing times (as appropriate)
·temperatures (as relevant)
·safety precautions to be observed
·critical time limitations.

(d) a statement of the theoretical and/or expected amount of product at pertinent stages of manufacture

(e) details of any in-process controls, with instructions for sampling and with control limits

(f) requirements for bulk storage of the product, including containers, labels, storage time limits and special storage conditions.

8.5 MASTER PACKAGING INSTRUCTIONS

8.5.1 A formally authorised Master Packaging Instruction should exist for each pack size and type. It should be dated and (as appropriate) include, or have a reference to:

(a) the name of the product

(b) a description of its pharmaceutical form and strength where applicable

(c) the pack size expressed as number, mass or volume of the product in the final container

(d) a complete list with quantities, sizes and types of all the packaging materials required for a standard batch size

(e) the code or reference number of each material which relates it to its specification

(f) a specimen or facsimile of relevant printed packaging material, where practicable

(g) a description of the packaging operation with an indication of the equipment to be used

(h) details of any required preparation of packaging materials (e.g. washing, blowing, sterilising)
(i) details of any over-printing necessary

(j) special precautions to be observed

(k) details of any in-process controls to be applied, with instructions for sampling and with control limits.

(l) line clearance checks prior to starting the packaging operation

NOTE - It is useful to be able to refer to superseded Master Packaging Instructions.
Where products may be stored in partially packaged form, requirements for such storage should be laid-down in the master documentation, or for example, in standard procedures.

8.6 BATCH RECORDS (STARTING MATERIALS)

8.6.1 The receipt of the delivery of each starting material should be recorded. The record should include:

(a) date of receipt

(b) name of material

(c) name of material on delivery note and/or containers - if different from (b)

(d) supplier's name

(e) supplier's batch or reference number

(f) total quantity and number of containers received

(g) the batch identifying number assigned on, or after, receipt.

8.6.2 The testing of each starting material should be recorded and should be in accordance with the master specifications. The testing record should include:

(a) date of sampling and date of testing

(b) name and quantity of material

(c) the batch identifying number

(d) results of all tests

(e) identity of person(s) who performed tests

(f) a cross reference to any relevant certificate of analysis

(g) analyst's signature and the signed release or rejection (or other status decision) by Quality Control

(h) a clear statement of the assigned potency where this can vary.

NOTE - It is useful to record analytical data in a manner that will facilitate comparative reviews of past results and the detection of trends.

8.6.3 Stock records should be maintained of starting materials that will permit stock reconciliations to be made.

NOTE - Special requirements for substances scheduled six and higher are controlled by regulations in Act 101 of 1965.
8.6.4 A sample of the starting material sufficient in size to permit analytical re-examination should be retained as part of the starting material record.

8.7 BATCH RECORDS (PACKAGING MATERIALS)

8.7.1 The receipt of the delivery of each packaging material should be recorded. The record should include:

(a) date of receipt

(b) name and quantity of material

(c) supplier's name and any reference or batch number

(d) any batch identifying number assigned on, or after, receipt.

8.7.2 The testing and inspection of packaging materials should be recorded and be in accordance with the master specifications. The testing record should include:

(a) date of sampling and the date of testing (or inspection)
(b) name of material

(c) the batch identifying number

(d) results of testing and inspection

(e) name of person(s) who carried out testing or inspection

(f) analyst's signature and the signed release or rejection (or other status decision) by Quality Control.

NOTE - It is useful to record these data in a manner that will facilitate comparative reviews of past results and the detection of trends.

8.7.3 Stock records should be maintained of packaging materials that will permit stock reconciliations to be made.

NOTE - Lesser standards of control and documentation may be applied to packaging materials which can have limited influence on product quality. See also 'Packaging Materials' in Glossary.

8.8 BATCH RECORDS (MANUFACTURING)

8.8.1 Batch Manufacturing Records should be kept for each batch manufactured and should carry a batch reference number and be based upon the currently approved version of the Master Formula and Method. The method of preparation should be designed to avoid transcription errors. Photocopying or some similar method of preparing the basic document is to be preferred.

8.8.2 If Batch Manufacturing Records do not include complete details of the Method, the operator must have ready access to the currently approved Method.

8.8.3 Before any manufacture proceeds there should be recorded checks that the equipment and work-station are clear of previous products and documents and of materials not required for the process in hand and that equipment is clean and suitable for use.

8.8.4 During manufacturing the following should be entered onto the Batch Manufacturing Records, at the time that each action was taken and, after completion, the record should be dated and signed in agreement by the person responsible for processing operations:

(a) the batch identifying number of each of the starting materials used and the amount used

(b) where the Master Formula permits variation in the quantity of starting material, a record of the amount actually used

(c) dates of commencement and completion of manufacture and of significant intermediate stages

(d) where more than one batch of a given starting material is used, a record of the actual amount of each batch

(e) the batch identifying number and amount of any recovered or re-work material added and at what stage of the manufacturing process it was added to the mix

(f) the initials of the person(s) who weighed or measured each material and the initials of the person(s) who checked each of these operations, this check being not only of the quantity but also of the labelled identity and batch number of the material

NOTE - Critical steps such as weighing, measuring and 'adding to the mix' should be checked and signed for by a pharmacist or other legally authorised person.

(g) the amount of product obtained at pertinent intermediate stages of manufacture

(h) the initials of the person responsible for each critical stage of manufacture

(i) the results of all in-process controls, with the initials of the person(s) carrying them out

NOTE - The in-process control document could be a separate document.

(j) reference to the precise items of major equipment used, where several of the same type are available for use (i.e. where equipment is replicated). This information may be recorded in 'Plant Usage Logs'. A cross-reference to this should be included in the Batch Manufacturing Record [BMW]

(k) details of, and signed authorisation for, any deviation from the Master Formula and Method

(l) the final batch yield and the number of bulk containers

(m) signed agreement by the process supervisor that apart from any deviation noted in (k) above, manufacture has proceeded in accordance with the Master Formula and Method, and that process or yield variations are adequately explained

8.9 BATCH RECORDS (PACKAGING)

8.9.1 Batch Packaging Records should be kept for each batch or part-batch processed and should be based upon the currently approved version of the Master Packaging Instruction and prepared from it by a method designed to avoid transcription errors (photocopying or some similar method is to be preferred). The Record should carry the quantity of bulk product to be packed, the planned quantity of finished product and should bear a batch reference number, which is specific to a particular packaging run. The batch number which appears on the finished product should be this number, or one which may be easily related to it.

NOTE - The bulk product and packaging reference numbering system must make it possible to relate a packaging operation to a bulk batch and the bulk batch to any packaging operation(s).

8.9.2 If the Batch Packaging Records do not include details of the method of packaging, these should be readily available to the operator(s).

8.9.3 Before any packaging is undertaken checks should be made that each packaging line or station is clear of previous product, packaging components records or materials not required for the planned packaging operations, and that equipment is clean and suitable for use. These checks should be recorded and each packaging line opened and closed by a pharmacist, other legally authorised person or quality control.
8.9.4 During packaging, the following should be entered onto the Batch Packaging Records, at the time that each action is taken:

(a) the batch number and expiry date of the Bulk Product to be packaged

(b) dates and times of commencement and completion of packaging and of significant intermediate stages

(c) the initials of the person(s) who issued the bulk product and printed packaging materials and of the person(s) who confirmed their correct identity and quantity

NOTE - The identity of the bulk product and printed packaging material should be checked and signed for by a pharmacist or other legally authorised person.

(d) the total quantities of the packaging materials used, with a batch identifying reference to primary and printed packaging materials (specimens of printed packaging materials used including specimens of the overprinting should be attached, or alternatively there should be an arrangement which will permit later reference to specimens of the printed packaging materials used)

(e) the results of any in-process controls, together with the initials of the person responsible for carrying them out

(f) the initials of the persons who carried out each significant stage of the packaging operation

(g) a record of the packaging machines, line or area used.

8.9.5 Records should be kept of the amount of bulk product supplied, printed materials issued and finished packs produced and reconciliations performed where required. (Alternative measures to ensure correctness of finished pack may be used).

8.9.6 Notes on any special problems including details of any deviations from the packaging instructions with written authorisation by an appropriate person should be kept.

8.10 OTHER PROCEDURES AND RECORDS

8.10.1 Intermediate Bulk and Finished Product Test Records

8.10.1.1 These records should include:

(a) the date of manufacture

(b) the date of testing

(c) the batch number and expiry date

(d) the name, code reference and quantity of the material and/or product

(e) the tests done and the results

(f) analyst's signature and the signed release or rejection (or other status decision) by Quality Control.

NOTE - The method of recording should facilitate comparative reviews of past results and the detection of trends.

8.10.1.2 A sample of the final packaged product sufficient in size to permit full re-examination as necessary should be retained as part of the record. If this is not practicable or economic (due, for example, to an unusually large pack size) then a smaller sample in a similar type of pack may be retained.

8.10.2 Receipt Records

8.10.2.1 There should be written procedures and records for the receipt of each delivery of each starting and primary and printed packaging material. The records of the receipts should include:

(a) the name of the material on the delivery note and/or the containers

(b) the 'in-house' name of material (if different from (a))

(c) date of receipt

(d) supplier's name and, if possible, manufacturer's name

(e) manufacturer's batch or reference number

(f) total quantity and number of containers received

(g) the batch identifying number assigned after receipt

(h) any relevant comment (e.g. state of the containers).

8.10.2.2 There should be written procedures for the internal labeling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

8.10.3 Distribution Records

8.10.3.1 To facilitate effective recall, records of distribution should be kept showing the date and the name and addresses of all persons to whom the manufacturer supplies each specific batch of product.

8.10.4 Complaints Records

8.10.4.1 A record should be maintained of all complaints relating to product or packaging quality. This record should show the nature of the complaint, results of investigations and action taken. The record should be maintained in such a manner that significant recurrent complaints can be recognised and appropriate action taken eg. tracking of trends.

8.10.5 Other Documents

8.10.5.1 Where relevant to the scale of an operation, the maintenance of departmental and equipment logs (i.e. running, dated records of equipment usage, products manufactured and cleaning of equipment and manufacturing areas) is recommended.

8.10.5.2 Where appropriate, there should be written procedures and the associated records of actions taken or conclusions reached for:
-validation
-maintenance, cleaning, sanitation
-personnel matters including training, clothing, hygiene
-environmental monitoring
-pest control
-recalls

8.10.5.3 Clear operating directions should be available for major items of manufacturing or testing equipment.

8.10.6 Retention of Records

8.10.6.1 Batch Manufacturing and Packaging Records plus the relevant test records, must be retained until at least one year after the expiry date of the batch. Finished product samples should be retained at least until the expiry date of the product, plus one year. Starting material records and samples should be retained until at least the expiry date of the batch in which they are used. Finished product reference samples should be stored under ambient conditions, or as directed on the label.

8.11 ANALYTICAL RECORDS

8.11.1 Sampling and Approval Documentation

8.11 .1.1 There should be documentation systems set up with the object of ensuring that:

(a) starting and packaging materials are in fact sampled and tested in accordance with previously specified procedures

(b) materials are not taken into usable stock until the specified checks and tests have been performed and the material formally approved by Quality Control (alternative arrangements may be made when an acceptable certificate of analysis is available)

(c) intermediate, bulk and finished products and any re-worked or recovered materials are sampled and tested in accordance with previously defined procedures and that products will not be released for sale or supply until all data on the intermediate, bulk and finished product have been reviewed and approval given by Quality Control.

8.11.2 Sampling

8.1 1.2.1 There should be written procedures for sampling, which include details of the person authorized to take samples, the methods and equipment to be used, the amounts to be taken and any precautions to be observed to avoid contamination of the material or any deterioration in its quality.

8.11.3 Testing

8.11.3.1 There should be written procedures for testing of products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded and the records, together with all supporting documentation should be kept.

8.11.4.1 Written release and rejection procedures should be available for materials and products and in particular for the release for sale of the finished product by a pharmacist. This release should include the completion of a check list which will ensure that all important release criteria have been met.

8.12 OTHER DOCUMENTATION REQUIRED

8.12.1 Site Master File
A description of the manufacturing facility, including a company profile plus a description of the premises, equipment, personnel and standard operating procedures relating to manufacture and the quality system. This must be lodged with the Medicines Control Council.

8.12.2 Validation Master Plan (VMP)
Each applicant should have a VMP (See Chapter 9).

8.12.3 PLANNED PREVENTATIVE MAINTENANCE PROGRAMME
A Planned Preventative Maintenance Programme and Standard Operating Procedure for carrying out the maintenance, should be in place. It should refer to all relevant equipment and apparatus to be included in the programme. Responsible persons, should be listed, carrying out maintenance in

accordance with the specified time schedule. Records should be kept as evidence of maintenance checks and repairs.

8.12.4 Contract Manufacture, Analysis and Services
Technical Agreements outlining who is responsible for specific activities relating to the manufacture, analysis, servicing and quality control at each stage of the process must be compiled and signed by the responsible persons in each company. These may form part of the contract or may be separate agreements. Copies must be available for audit purposes.

CHAPTER 9:

VALIDATION

9.1 PRINCIPLES

9.1.1 One of the axioms of manufacturing is that no two objects are ever made exactly alike. Five factors contribute to these variations, namely variations inherent in process methods; materials; the manufacturing environment; the human element; and inspection methods.

9.1.2 As long as these five sources of variation fluctuate in a normal or expected manner, a stable pattern of **change causes of** variation develops (i.e. the variations lie within the so-called "normal curve"). When only change causes are present in a process, that process is considered to be in control. However, when an **assignable cause of variation** is also present the variation will be excessive, and the process is then classified as being out of control (i.e. beyond the expected or "normal curve" variation).

9.1.3 A process is in a **state of control** when all the assignable causes of variation have been eliminated, any only chance causes of variation are present. Such a process has thus been demonstrated to be capable of consistency delivering specified results, i.e. the process has been **validated.**

9.1.4 Statistical process control methods may be used to demonstrate that a process had been validated (i.e. is in a state of control). The control chart method of analysis and presentation of data may for instance be used to document the variations that occur in the central tendency and dispersion of a set of observations relating to a specific quality characteristic.

9.1.5 A process which is in a state of control contributes to productivity and profitability by reducing waste; increasing the yield of saleable product; and reducing the cost of inspection and test activities. Moreover, appropriate validation studies will facilitate pre-registration audits and expedite product registration. Validation therefore makes good business sense.

9.1.6 Validation is an integral part of current good manufacturing practice; it is, therefore, also an element of the quality assurance programme associated with a particular product or process.

9.1.7 Validation involves the accumulation of documentary evidence relating to a process, item of equipment, or facility. This is achieved by means of **validation protocol** which should exist for every product and which details the tests to be carried out, the frequency of testing, and the results anticipated (acceptance criteria).

9.1.8 A **prospective validation** programme is one that is implemented before the equipment or facility comes on stream, or before the product is manufactured.

9.1.9 A **retrospective validation** programme is based on a review of historical manufacturing and testing data.

9.1.10 A **concurrent validation** programme refers to the ongoing review and evaluation of prospective or retrospective validation data.

9.1.11 A validation programme should be co-ordinated by a multidisciplinary committee comprised of the different functions that are involved in the programme. Typically, the members of this **validation committee** would be drawn from departments such as production, quality assurance, microbiological and analytical quality control, pharmaceutical development, engineering, and maintenance. The committee approves and issues written protocols, and reviews the data obtained in order to approve or reject the programme results.

9.1.12 Validation and qualification should be conducted in accordance with defined written standard operating procedures.

9.2 VALIDATION MASTER PLAN

The validation programme should be co-ordinated by means of a formal policy document, usually referred to as a **validation master plan** (VMP).

9.2.1 Each company should have a Validation Master Plan which describes its overall philosophy, intention and approach to be used for establishing performance adequacy, and which identifies which items are subject to validation and the nature and extent of such testing and the applicable validation and qualification protocols and procedures.

9.2.2 The VMP should be a concise and easy to read document which will serve as a guide to the validation committee, and personnel who are responsible for implementing validation protocols. The VMP should also be viewed as being a source document for use by regulatory auditors.

9.2.3 The VMP should typically include at least the following sections:

* Approval page and table of contents
* Introduction and objectives
* Plant and process description
* Personnel, planning and scheduling
* Responsibilities of committee members
* Process control aspects
* Equipment, apparatus, processes and systems to be validated
* Acceptance criteria
* Documentation required including reference to validation protocols
* SOP's
* Training requirements

9.2.4 The Validation Protocol

9.2.4.1 The Validation protocol should clearly describe the procedure to be followed for performing validation. The protocol should include at least the objectives of validation and qualification study, site of the study, the responsible personnel, description of equipment to be used (including calibration before and after validation). SOP's to be followed, standards and criteria for the relevant products and processes, the type of validation, and time/frequency should be stipulated. The processes and/or parameters to be validated (e.g. mixing times, drying temperatures, particle size, drying times, physical characteristics, content uniformity etc.) should be clearly identified.

9.2.4.2 A written report should be available after completion of the validation. The results should be evaluated, analysed and compared with acceptance criteria. All results should meet the criteria of acceptance and satisfy the stated objective. If necessary, further studies should be performed. If found acceptable, the report should be approved and authorised (signed and dated).

9 2 4 3 The report should include the title and objective of the study, refer to the protocol, details of material, equipment, programmes and cycles used and details of procedures and test methods. The results should be compared with the acceptance criteria.

9.2.4.4 Included in the final report, should be recommendations on the limits and criteria to be applied to all future production batches and could form part of the basis of a batch manufacturing document.

9.2.4.5 There should be levels where validation and qualification should be performed, and the level should determine the intensity of these products. It should be least for liquid preparations (solutions) and most for patenteral medicines, and for solid dosage forms it should depend on the criticality of the product as far as the patient is concerned.

9.3 QUALIFICATION

Before a process can be validated the equipment, facilities, and services used in that process must themselves be validated. Such an operation is referred to as **qualification.** Qualification is, therefore, an integral part of process validation which, in turn, is part of good manufacturing practice.
9.3.1 An **installation qualification** (IQ) protocol is used to document the specific (static) attributes of a facility or item of equipment, in order to prove that the installation of the unit has been correctly performed and that the installation specifications of the manufacturer have been met. The IQ protocol should be numbered, dated, and approved for issue by appropriately authorised personnel. The document may comprise the following:

- introduction and objectives
- plant inventory number
- standard operating procedure number
- purpose of the facility or equipment
- design and construction details
- details of services required and provided
- addenda such as chart recorder traces, technical drawings, etc acceptance criteria

The IQ data should be reviewed and approved before operational qualification commences.

9.3 2 An **opperational qualification** (OQ) protocol is used to document specific (dynamic) attributes of a facility or item of equipment to prove that it operates as expected throughout its operating range. As with the IQ protocol, to OQ protocol should be numbered, dated and formally approved. The tests should be designed to demonstrate that the unit performs properly at the limits of its operating conditions, as well ad within its normal operating range. If measurements are made on a statistical basis, then this must be fully described in the protocol. In addition to the operational tests, an OQ protocol may typically include:

- introduction and objectives
- brief identification information
- visual inspection parameters
- functioning of switches and indicator lights
- check and calibration of sensors, probes, gauges, recorders, air flow rates, direction, pressures, temperatures, etc.
- filter integrity and efficiency tests
- cleaning procedures
- details of qualification instrumentation used
- acceptance criteria
- actions resulting from the OQ (what to do when out of spec. results are obtained)
- requalification timescales and triggering factors

The OQ data should be formally reviewed and approved before process validation can commence.

9.3.3 A **performance qualification** (PQ) protocol may be used in cases where performance data are gathered over a long period of time. Under these circumstances, it is difficult to "sign off" the operational qualification (OQ) as complete. One solution is to define and approve the OQ at a single point in time, and to create a PQ protocol which is then used as a the vehicle for amassing the ongoing data.

9.4 PROCESS VALIDATION

When qualification is complete, process validation (PV) can begin. In some cases, PV may be conducted concurrently with IQ, for example, where an item of equipment is dedicated to one process producing one product. Process validation is organised and administered in the same way as qualification, by the writing and issuing of process validation protocols and the accumulation and review of data against agreed acceptance criteria.

Validation should be considered in the following situations:

Validation should be considered in the following situations:

* totally new processes
* new equipment
* processes and equipment which have been altered to suit changing priorities
* processes where the end product test if poor and an unreliable indicator of product quality

9.4.1 Validation In Development (Prospective Validation)

9.4.1.1 When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.

In this phase the extent to which deviations from the chosen processing parameters can influence product quality should also be evaluated.

9.4.1.2 In general the final batch size should not be more than ten times the batch size of the representative development batches.

9.4.2 Validation In Production (Concurrent validation)

The validation in the production unit mainly comprises the determination and evaluation of the process parameters of the facilities applied for the scale-up to final batch size. The control of all critical process parameters, the results of the in-process controls, final controls and stability tests should prove the suitability of the important individual steps of a procedure.

At least three batches (including at least two production batches in the final batch size) should be validated, to show consistency. Worst case situations should be considered.

9.4.2.1 When certain processes or products have been validated during the development stage, it is not always necessary to re-validate the whole process or product if similar equipment is used or similar products have been produced, provided that the final product conforms to the in-process control and final product specifications.

9.4.2.2 There should be a clear distinction between in-process controls and validation. In-process tests are performed each time on a batch-to-batch basis using specifications and methods devised during the development phase. The objective is to monitor the process continuously.

9.4.2.3 Validation of the process can, however, be partly based on the processing and evaluation of in-process data provided it is evident that the reliability of the process can be unequivocally and accurately judged in terms of the results from these in-process control tests and final end product tests.

9.4.2.4 Validation is a once-off procedure that should only be repeated if major changes to equipment or processes have taken place. The objective is to establish a valid process. In-process control and validation co-exist in Good Manufacturing Practice or Quality Assurance systems. In-process data can be used (after processing of the data) during the validation study, or it may form the basis of a retrospective validation exercise. (See below). Thus, the results of in-process controls can be used to provide some of the evidence required for validation but are no substitute for validation.

9.4.2.5 Processes and procedures should undergo periodic critical re-validation to ensure that they remain capable of achieving the intended results.

9.4.2.6 As a rule re-validation is required under the following circumstances:

- change of formulae, procedures or quality of raw materials
- change of equipment, installation of new equipment, major revisions to machinery or apparatus and breakdowns
- major changes to process parameters
- changes to facilities and installations which influence the process
- on appearance of negative quality trends
- on appearance of new findings based on current knowledge, e.g. sterilisation where the frequency of checking is dependent on sophistication of in-process methodology

NOTE: The extent of re-validation will depend on the nature and significance of the changes.

9.4.3 Retrospective Validation

9.4.3.1 The analysis of in-process and end product testing has been widely used retrospectively in process validation. Usually statistical packages as well as manual reviews (including the monitoring of trend analysis) are used. In some cases retrospective validation is sufficient to establish a process as valid.

9.4.3.2 Retrospective validation may be allowed, when the formulation procedure and equipment have not been altered. A critical examination of the in-process control data and of the analytical results should be performed. Where existing data is not adequate, additional tests should be performed.

9.5 VALIDATION OF FACILITIES AND EQUIPMENT

9.5.1 New facilities and equipment which are components of a production process or are used for in-process control must be qualified before being put into operation. This is to ensure that they fulfill the relevant requirements and that no negative influence on product quality or measured values arises.

9.5.2 Specification qualification, design qualification, installation qualification, operational qualification and performance qualification should be considered when new equipment is acquired. Equipment and apparatus should be capable of meeting the original design specifications.

9.5.3 All instrumentation attached to equipment should be checked for accuracy, reliability and reproducibility. Such qualification studies could be carried out on-site or off-site, either by the user of the supplier.

9.5.4 Qualified and validated equipment should be monitored from time to time, to ensure that the fixed processing parameters are being maintained. This could be achieved by suitable instrumentation of different types, measuring temperatures, pressures, humidity, fill volumes etc. International standards should be used as reference point and all calibration data should be accurately documented.

9.5.5 Retrospective validation of old facilities and validation arising from changes should be evaluated in terms of criticality and the processes that are ultimately affected in the production of quality product.

9.6 VALIDATION OF ANALYTICAL METHODS

9.6.1 Analytical testing procedures including stability testing methods must be validated to demonstrate their reliability. This should be done during product design.

9.6.2 Revalidation may be necessary in the following circumstances:

* changes in the synthesis of a drug substance;
* changes in the composition of a finished product;
* changes in the analytical procedure
* changes in the manufacturing process that will effect the method

The degree of revalidation required depends on the nature of the changes. Certain other changes may require validation as well.

9.6.3 Method validation should not be confused with system suitability tests. System suitability testing verified the suitability if an analytical system at the time the test is performed.

9.6.4 Methods, (other than pharmacopoeal methods), should be validated. Typical validation characteristics which should be considered, include accuracy, precision, (repeatability and intermediate precision), specificity, detection limit, quantitation limit, linearity and range. Robustness should be considered at an appropriate stage in the development of an analytical procedure.

9.7 CLEANING VALIDATION

9.7.1 There should be written Standard Operating Procedures, detailing cleaning processes for different sections in the manufacturing facility, with appropriately documented and completed cleaning logs.

9.7.2 There should be written a SOP's detailing the cleaning process for equipment and apparatus.

9.7.3 There should be a written SOP detailing how cleaning processes will be validated, referring to accountabilities, acceptance criteria and revalidation requirements. Acceptance limits should be scientifically justifiable. The complexity and design of the equipment, training or operators, size of the system, and time delay between end of processing and cleaning should be kept in mind when designing the cleaning SOP. Microbiological aspects of cleaning (bioburden control), should further be considered. Written protocols to be followed during validation should detail sampling procedures (direct sampling, rinse samples, in-process control monitoring), analytical methods (specificity and sensitivity) of analytical methods to be used.

9.7.4 Evidence should be provided to ensure that equipment is consistently cleaned from product, detergent and microbial residues to an acceptable level.

9.7.5 Cleaning validation is particularly relevant in the case of highly active substances.

9.8 COMPUTER SYSTEM VALIDATION

See Chapter 19.

9.9 GENERAL

The following aspects could be considered during the validation of specific dosage forms.

9.9.1 **Validation of tabletting:** In the case of an oral tablet manufactured by granulation and compression, the critical process parameters may include (but not be limited to):

- particle size distribution of the active
- blending time for the powder
- granulating time and speed
- amount of granulating fluid-binder concentration
- drying time - final moisture content
- granule particle size distribution
- granule active content and homogeneity
- blending time of external phase
- tablet hardness with respect to water content, friability, disintegration, and dissolution
- lubrication level with respect tablet hardness, disintegration, dissolution and die-ejection force

- tablet weight and thickness control uniformity of content
-

If the tablet is film coated, the following additional parameters may require validation:

- spray rate of coating solution
- inlet and outlet air temperatures
- coating weight of polymer with respect to table appearance, friability, disintegration, and dissolution

9.9.2 **Validation of sterile products:** The general pattern of process validation is the same as for non-sterile, and similar critical process parameters need to be defined and controlled. The key additional requirement is the absence of microbial contamination. This necessitates validation of the sterilisation process for terminally sterilised products, or of the sterilisation, filling and sealing processes for aseptically prepared products. Attention should also be given to water systems and air handling systems.
In the case of steam sterilised products:

- bioburden before sterilisation
- heat distribution
- influence of container size (minimum of three batches of each size)
  influence of chamber loading patterns (minimum of three batches of each loading pattern)

In the case of aseptically filled products:

- assurance that the product and packaging materials are sterile
- assurance that product sterility is maintained during the filling and sealing process
- filter bubble point tests (at least on three product batches)
- determination of pressure drop, stability time, pressure hold time, and pressure decay before and after a production run.

CHAPTER 10:

RETURNED GOODS

10.1 PRINCIPLE

10.1.1 A clearly defined policy must be followed to ensure that returned goods are of an acceptable quality and have not expired before they are taken back into stock; otherwise they must be destroyed.

10.2 PROCEDURES

10.2.1 Goods which have been rejected, recalled or returned should be placed in adequately segregated storage to avoid confusion with other materials and products and to prevent redistribution, until a decision has been reached as to their disposition. Any action taken should be appropriately recorded.

10.2.2 A Finished Product returned from the Manufacturer's own stores or warehouse (because, for example, of soiled or damaged labels or outer packaging) may be relabelled or bulked for inclusion in subsequent batches, provided that there is no risk to product quality and the operation is specifically authorised and documented. If such products are re-labelled, extra care is necessary to avoid mix-up or mis-labelling.

10.2.3 Finished Products returned from the market and which have left the control of the manufacturer should be destroyed unless without doubt their quality is satisfactory; they may be considered for resale, relabelling or bulking with a subsequent batch only after they have been critically assessed by the person responsible for Quality Control. The nature of the product, any special storage conditions it requires, its condition and history and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for re-issue or re-use, although basic chemical re-processing to recover the active ingredient may be possible.

CHAPTER 11 :

COMPLAINTS, ADVERSE EVENTS, RECALLS AND WITHDRAWALS

11.1 PRINCIPLES

11.1.1 The full significance of a complaint may only be appreciated by certain responsible persons and then possibly only with the knowledge of other related complaints. A procedure must therefore exist to channel complaint reports appropriately.

11.1.2 A complaint, [or otherwise] reported product defect, or adverse event* may lead to the need for a recall. Any action taken to recall a product suspected or known to be defective or hazardous, should be prompt and in accordance with a pre-determined plan. The procedures to be followed should be specified in writing and made known to all who may be concerned.

11.1.3 Definitions
Adverse event* or experience:
Any untoward medical occurrence in a patient treated with a pharmaceutical product/device, reported from any source. This does not imply that a causal relationship exists with this treatment.

Adverse Drug Reaction:
A response to a drug which is noxious or unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function i.e. an adverse event for which a causal relationship is suspected between drug and event.

Unexpected Adverse Drug Reaction
An adverse reaction, the nature or severity of which is not consistent with applicable product information or labelling i.e. those recorded on the Package Insert [PI]

11.2 COMPLAINTS

11.2.1 A system should be established for dealing with complaints which should include written procedures indicating the responsible person(s) (e.g.pharmacist and/or deputy pharmacist) through whom the complaints are to be channeled. The responsible person must have appropriate knowledge and experience and the necessary authority to decide the action to be taken.

11.2.2 All complaints concerning a product defect should be recorded with all the original details and thoroughly investigated. The responsible person should decide whether, and what, subsequent action is necessary.

11.2.3 Complaint records should be regularly reviewed for any indication of specific recurring problems requiring attention and possibly the recall of marketed products.

11.2.4 Written records involving a medicine shall be maintained until at least one year after the expiration date of the medicine, or one year after the date that the complaint was received, whichever is longer.

11.2.5 The written record shall include the following information, where known:

·date of receiving complaint
·the name and strength of the medicine and lot number
·name of complainant, nature of complaint
·detailed record of the investigation
·details of the action taken to prevent recurrence of the problem that led to the negative effect on the product
·reply to complainant.

11.2.6 If a product defect is discovered or suspected in a batch, consideration should be given to whether other batches should be checked in order to determine whether they are also affected. In particular, other batches which may contain reworks of the defective batch should be investigated.

11.2.7 All the decisions and measures taken as a result of a complaint should be recorded and referenced in the corresponding batch records.

11.2.8 Where an investigation is not conducted, the written record shall include the reason that an investigation was found not to be necessary and the name of the responsible person making such a determination.

11.2.9 Trend analysis should be performed in an event to identify possible recurrent causes leading to a negative effect on a product.

11.3 ADVERSE EVENTS

11.3.1 A system should be established for dealing with adverse events which should include written procedures indicating the responsible person(s) (pharmacist and/or deputy pharmacist) through whom the reports and activities are to be channeled. The responsible person must have appropriate knowledge and experience and the necessary authority to decide the action to be taken.

11.3.2 All adverse events concerning product quality must be thoroughly investigated. The responsible person should decide whether, and what, subsequent action is necessary. This action should be recorded and the record filed with the details of the original adverse event report.

11.3.3 Adverse event records should be regularly reviewed for any indication of a trend that may warrant a recall or withdrawal.

11.4 RECALLS

11.4.1 WITHDRAWAL implies the total withdrawal of the product from the market.

11.4.2 RECALL refers to the removal from the market of a specific batch or batches of the product.

11.4.3 The recall of a particular batch or batches of a product from the market may be occasioned by the manufacturer or distributor, either following reports of adverse reactions to a particular batch of a product, or as the result of on-going stability studies, or by the authorities (Department of Health/Medicines Control Council) as a result of adverse reaction reports or for other reasons such as formulation, labeling or other errors.

11.4.4 The managing director or nominated deputy should initiate and co-ordinate all recall activities which should involve the head of Quality Management. In the event of an adverse event a Crisis Committee involving key personnel should be set up and involved.

11.4.5 There should be a written recall procedure which is capable of being initiated promptly and put into operation at any time, inside or outside normal working hours. It should include emergency and 'out of hours' contacts and telephone numbers.

11.4.6 The recall procedure should be shown to be practicable and operable within reasonable time (e.g. by conducting internal 'dummy runs'). It should be revised as necessary to take account of changes in procedures or responsible person(s).

11.4.7 The notification of recall should include:

(a) the name of the product, including the INN and Trade Names, its strength and pack size, and main therapeutic class
(b) the product batch number(s)
(c) the nature of the defect and the reason for the recall or withdrawal decision [including the discovery of counterfeit medicines*]

(d) the action to be taken
(e) the urgency of the action (with reasons, indication of health risk, as appropriate)
(f) the date of the recall or withdrawal

11.4.8 Account should be taken of any goods which may be in transit when the recall is initiated.

11.4.9 The distribution records should be readily available to the person(s) responsible for recalls and contain sufficient information on wholesalers and customers (e.g. addresses, telephone numbers inside or outside working hours, batches and amounts delivered) including exported products and medical samples.

*In the case of counterfeit medicines the MCC should be informed immediately as well as the appropriate Industry Action Committee.

11.4.10 Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate.

11.4.11 All Regulatory Authorities of all countries to which products may have been distributed should be promptly informed if products are intended to be recalled because they are, or are suspected of being defective.

11.4.12 The progress of the recall process should be recorded and a final report issued, including a reconciliation between the delivered and recovered quantities of the products.

Enclosure:
Manufacturer's Post-Withdrawal Decision Checklist

CHAPTER 12:

CONTRACT MANUFACTURE ANALYSIS AND SERVICING

12.1 PRINCIPLES

12.1.1 The relative responsibilities of the Contract Giver and the Contract Acceptor relating to specific activities in manufacture, analysis and the provision of services should be clearly understood and agreed, with the object of avoiding misunderstandings which could result in a product or work of unsatisfactory quality. The Contract Giver (the Applicant) bears the ultimate responsibility for ensuring that the product specification complies with relevant legal requirements, that the product as manufactured meets its specification, and that the specified quality is maintained during storage, transport and distribution.

12.2 MANUFACTURE AND/OR PACKAGING

12.2.1 A Contract Giver should assure himself that the Contract Acceptor has adequate premises, equipment, and staff with sufficient knowledge and experience, to carry out satisfactorily the work placed with him. In order to do this the Contract Giver should audit the Contractor Acceptor's premises, equipment and systems both before the contract is given and at regular intervals thereafter. Audit reports should be issued and kept on record. A contract Giver may only use the contract manufacturer or packer as approved in the registration dossier. A Contract Giver shall not authorise a Contract Acceptor to commence manufacture/packaging/testing of a medicine, until he has assured himself, and authorised in his own handwriting, that all the necessary master documents and/or specifications, generated by the Contract Acceptor for use in his own facility, are in accordance with the particulars contained in the Contract Giver's (applicant or holder of a registration certificate) master documentation and registration dossier. The specification/master documents should be in compliance with the requirements as stipulated in Chapter 8. The Contract Acceptor shall not commence manufacture/packaging/testing of a medicine until he is in possession of specification/master documents that have been authorised by the Contract Giver.

12.2.2 The Contract Acceptor should refrain from any activity which may adversely affect products manufactured for a Contract Giver. A Contract Acceptor must ensure that all legal requirements of the relative Acts are met, prior to accepting contract work (e.g. registerability of medicines).

12.2.3 The technical arrangements made in connection with a contract should be in writing. The limits of the responsibilities accepted by each of the parties should be clearly laid down in a Technical Agreement which can be included in the body of the contract or as an Addendum to the contract. The technical agreement should cover all aspects relating to responsibilities w.r.t setting of specifications, acquisition of material (e.g. raw or starting material, packaging components, printed packaging material), as well as the lines of reporting and communication.

This should be in compliance with the organogram, job descriptions and standard operating procedures.

The technical agreement should address all aspects relating to change control. The Technical agreement may refer to standard operating procedures agreed to by both parties, agreeing to the process to be followed should any changes take place during the manufacturing process. These changes should be controlled in accordance with the minor/major change policy of the Medicines Control Council, as communicated to the industry. The applicant or holder of a registration certificate must be informed of any change that took place, as well as the Registrar of Medicines. Where relevant, permission must be obtained from the Medicines Control Council, prior to implementation of the change. Where necessary, master documentation and registration dossiers should be updated in accordance with standard operating procedures and policy.

Where changes took place during manufacture/packaging/testing, a detailed deviation report should be written, describing the change, the reasons for the change, who was responsible or managed the

change, the implication of the change and the effect the change will have on the product, approval of the change etc. and be discussed with the applicant or holder of a registration certificate.

12.2.4 Any change in technical arrangements should be agreed upon by both parties and should be laid down in writing.

12.2.5 The parties to a manufacturing contract should each appoint competent persons to:

·draw up the Technical Agreement for manufacture
·agree upon arrangements for in-process control tests, for testing of raw materials, components and Finished Products and for reworking if necessary
·define the mechanism by which a batch is released for sale after review of the manufacturing, packaging and analytical records.

12.2.6 A Contract Acceptor should not pass to a third party any of the work entrusted to him by a Contract Giver without the latter having evaluated the arrangements and given his consent.

12.2.7 Arrangements made with a third party should ensure that the exchange of information is on the same basis as between the Contract Giver and the original Contract Acceptor.

12.2.8 If a Contract Giver supplies materials, the Contract Acceptor should be given a signed statement from the Contract Giver that the Vendor has been audited and is approved, as well as a copy of the Certificate of Analysis of the raw/starting material (at least the active raw/starting material). The Contract Giver should supply the Contract Acceptor with specifications/master documentation for all materials handled by the Contract Acceptor. If this is not possible for reasons of commercial or research confidentiality, he should be given sufficient information to enable him to process the material correctly, and details of:
·any potential hazard to premises, plant, personnel, or to other materials or products
·the legal status of the materials and resultant products.

12.2.9 If a Contract Acceptor supplies materials, the Contract Giver should specify the quality required in the specification/master document.

12.2.10 A Contract Acceptor should check that all products or materials delivered to him are suitable for the purpose intended.

12.2.11 A Contract Giver should ensure that all products or materials delivered to him by the Contract Acceptor comply with the specifications. If products are delivered directly from a Contract Acceptor to the market, the Contract Giver should provide for this check to be made before they are released for sale. Note: The Contract Giver is legally responsible for the final release of each batch for sale.

12.2.12 Manufacturing and analytical records and reference samples should be kept by, or be readily available to the Contract Giver. The documents kept should facilitate recall from sale of any batch of the product. The responsibility for arranging and managing a recall or withdrawal of any batch of a product must be clearly specified in the Technical Agreement as well as the management of adverse event reporting.

12.2.13 The above guidelines should also be used for sale/distribution contracts where applicable. A Contract Acceptor, should on receipt of materials, take all material into his own system of receival of goods in accordance with the requirements of GMP.

12.2.14 Contract Givers must ensure that all the necessary documentation accompanies all material delivered to Contract Acceptors, as stock should not be received without the relevant and/or necessary documentation, e.g. invoices, delivery notes, instructions etc. Contract Acceptors may return goods delivered, should the necessary documentation not be included.

12.2.15 All containers delivered to Contract Acceptors, should be properly labelled in accordance with GMP requirements.

12.2.16 The guidelines under 12.2 should also be used for sale/distribution contracts where applicable, as well as the requirements in Chapter 18.

12.3 CONTRACT ANALYSIS

12.3.1 As appropriate, the above provisions may apply also to contract analysis.

12.3.2 Although analysis and testing may be undertaken by a Contract Analyst, the responsibility for Quality Control cannot be delegated to him.

12.3.3 The nature and extent of any contract analysis to be undertaken should be agreed upon and clearly defined in writing, and procedures for taking samples should be as set out.

12.3.4 The Contract Analyst should be supplied with full specifications/master documents of the materials to be tested as well as full details of the test methods relevant to the material under examination. These will need to be confirmed as suitable for use in the context of the contract laboratory.

12.3.5 Formal written arrangements should be made for the retention of samples and of records of test results.

12.3.6 Periodic audits should be carried out on the work performed by the contract laboratory. Audit reports should be kept on record.

12.3.7 The requirements of Chapter 7 applies.

12.4 SERVICE CONTRACTS

12.4.1 Where service or maintenance work is performed (e.g. on manufacturing or test equipment, sterilisers, controlled air supply systems) the Contract Giver should assure himself that the Contract Acceptor has sufficient equipment, staff, knowledge and experience to carry out the work correctly.

12.4.2 There should be a written contract which should clearly specify the work to be carried out and the form and detail of the report or certification required. The report or certificate should state clearly what work was done and the result achieved, and declare whether or not the equipment performs in compliance with specification.

12.4.3 A Standard Operating Procedure should specify the acceptable limits between services or maintenance of equipment, systems etc.

CHAPTER 13:

VETERINARY MEDICINES

13.1 PRINCIPLE

13.1.1 Medicinal products for veterinary use should be manufactured in accordance with the principles outlined in this Guide.

13.2 GENERAL REQUIREMENTS

13.2.1 Some veterinary medicines such as those used for mass external treatment of animals (e.g. sheep dips), have no direct equivalent amongst products for human use and the recommendations on manufacturing premises and equipment given elsewhere in the Guide may not be appropriate. Sufficient order, tidiness, cleanliness and product security is however always required in order to minimise the risk of formulation error, mix-up and contamination. In addition, the general systems and procedures in this guide still apply to veterinary medicines.

13.2.2 In the manufacture and filling of terminally sterilised parenteral veterinary medicines, particular attention should be given to the need to minimise microbiological contamination of the product before sterilisation. Pyrogen contamination (endotoxin level) should be controlled to the same limits as for human medicines.

13.3 SPECIAL REQUIREMENT

13.3.1 Manufacture of premixes for medicated feedingstuffs

- a medicated feeding stuff is any mixture of a veterinary product or products and feed or feeds which is ready prepared for marketing and intended to be fed to animals without further processing because of its curative or preventative properties or other properties as a medicinal product.

- a premix for medicated feedingstuffs is any veterinary medicinal product prepared in advance with a view to the subsequent manufacture of medicated feedingstuffs.

13.3.1.1 The manufacture of premixes for medicated feedingstuffs requires the use of large quantities of vegetable matter which is likely to attract insects and rodents. Premises should be designed, equipped and operated to minimize this risk and should also be subject to a regular pest control programme.

13.3.1.2 Because of the large volume of dust generated during the production of bulk material for premixes, specific attention should be given to the need to avoid cross contamination and facilitate cleaning, for example the installation of sealed transport systems and dust extraction, whenever possible. The installation of such systems does not, however, eliminate the need for regular cleaning of production areas.

13.3.1.3 Parts of the process likely to have significant adverse influence on the stability of the active ingredients(s) (e.g. use of steam in pellet manufacture) should be carried out in a uniform manner from batch to batch.

13.3.1.4 Consideration should be given to undertake the manufacture of premixes in dedicated areas which, if at all possible, do not form part of a main manufacturing plant. Alternatively, such dedicated areas should be surrounded by a buffer zone in order to minimize the risk of contamination of other manufacturing areas.

13.3.2 The manufacture of ectoparasiticides

13.3.2.1 Ectoparasiticides for external application to animals which are veterinary medicinal products, and subject to registration, may be produced and filled on campaign basis in pesticide specific areas. However, other categories of veterinary medicinal products should not be produced in such areas.

13.3.2.2 Adequate validated cleaning procedures should be employed to prevent cross contamination, and steps should be taken to ensure the secure storage of the veterinary medicinal product in accordance with the guide.

13.3.3 The manufacture of veterinary medicinal products containing penicillins

13.3.3.1 The use of penicillins in veterinary medicine does not present the same risks of hypersensitivity in animals as in humans. Although incidents of hypersensitivity have been recorded in horses and dogs, there are other materials which are toxic in certain species e.g. the ionophore antibiotics in horses. Although desirable, the requirements that such products be manufactured in dedicated, self-contained facilities may be dispensed with in the case of facilities dedicated to the manufacture of veterinary medicinal products only. However, all necessary measures should be taken to avoid cross-contamination and any risk to operator safety in accordance with the guide. In such circumstances, penicillin-containing products should be manufactured on a campaign basis and should be followed by appropriate, validated decontamination and cleaning procedures.

13.3.4 Retention of samples

13.3.4.1 It is recognized that because of the large volume of certain veterinary medicinal products in their final packaging, in particular premixes, it may not be feasible for manufacturers to retain samples from each batch in its final packaging. However, manufacturers should ensure that sufficient representative samples of each batch are retained and stored in accordance with the guide.

13.3.4.2 In all cases, the container used for storage should be composed of the same material as the market primary container in which the product is marketed.

13.3.5 Sterile veterinary medicinal products

13.3.5.1 Where this has been accepted by the competent authorities, terminally sterilised veterinary medicinal products may be manufactured in a clean area of a lower grade than specified for "Sterile preparations", but at least in a grade D environment.

CHAPTER 14:

RADIOPHARMACEUTICALS

Radiompharmaceutical products should be manufactured in accordance with the principles outlined in this guide.

14.1 PRINCIPLES

14.1.1 Radiopharmaceutical 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.

14.1.2 The manufacturing and handling of radiopharmaceuticals 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 radiopharmaceuticals. Due to their short half-life, some radiopharmaceuticals 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.

14.2 REGISTRATION REQUIREMENTS

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

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

14.2.3 Radiopharmaceuticals, 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.

14.2.4 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.

14.3 PERSONNEL

14.3.1 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.

14.4 PREMISES AND EQUIPMENT

14.4.1 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 radiopharmaceuticals.

14.4.2 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.

14.4.3 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.

14.4.4 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.

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

14.5 PRODUCTION AND HANDLING OF RADIOACTIVE PREPARATIONS

14.5.1 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.

14.5.2 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.

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

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

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

14.5.5 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.

14.6 QUALITY CONTROL

14.6.1 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.

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

14.7 PACKAGING OF RADIOPHARMACEUTICALS

14.7.1 Due to the short half-life of certain radiopharmaceuticals 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.

14.7.2 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.

14.7.3 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.

14.8 NON-RADIOACTIVE KITS

14.8.1 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.

14.8.2 The preparation of these radiopharmaceuticals 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.

14.9 DISTRIBUTION AND RECALLS

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

CHAPTER 15:

BIOLOGICAL MEDICINES

15.1 PRINCIPLES

15.1.1 Biological medicines comprise those derived or extracted from living organisms or tissues and those which contain living or inactivated organisms in the end product.

15.1.2 There are 4 sub-categories, namely:
ANTIGENS: These include vaccines, toxoids, allergens, venoms, etc.

ANTIBODIES: These include antitoxins, antisera, immunoglobulins, etc.

BLOOD FRACTIONS: These include all preparations and components of human blood, made from donor pools exceeding 12 donors.

OTHER: This includes in-vivo diagnostics, venom, etc.

15.1.3 The methods employed in the manufacture of biological medicinal products are a critical factor in shaping the appropriate regulatory control. Biological medicinal products can be defined therefore largely by reference to their method of manufacture. Biological medicinal products prepared by the following methods of manufacture will fall under this chapter.

(a) Microbial cultures, excluding those resulting from r-DNA techniques.

(b) Microbial and cell cultures, including those resulting from recombinant DNA or hybridoma techniques.

(c) Extraction from biological tissues.

(d) Propagation of live agents in embryos or animals.

(Not all aspects of this chapter may necessarily apply to producers in category (a).

15.1.4 The manufacture of biological medicinal products involves certain specific considerations arising from the nature of the products and processes. The way in which biological medicinal products are produced, controlled and administered make some particular precautions necessary.

Unlike conventional medicinal products, which are reproduced using chemical and physical techniques capable of a high degree of consistency, the production of biological medicinal products involves biological processes and materials, such as cultivation of cells or extraction of material from living organisms. These biological processes may display inherent variability, so that the range and nature of by-products are variable. Moreover, the materials used in these cultivation processes provide good substrates for growth of microbial contaminants.

Control of biological medicinal products usually involves biological analytical techniques which have a greater variability than physico-chemical determinations. In-process controls therefore take on a greater importance in the manufacture of biological medicinal products.

15.1.5 The principles of good manufacturing practice still apply, but it is important to be aware of the difficulties posed by the different nature of biological materials. The use of material from living organisms requires increased emphasis on some aspects of manufacturing different from those of other pharmaceuticals.

15.2 PERSONNEL

15.2.1 All personnel (including those concerned with cleaning, maintenance or quality control) employed in areas where biological medicinal products are manufactured should receive additional training specific to the products manufactured and to their work. Personnel should be given relevant information and training in hygiene and microbiology.

15.2.2 Persons responsible for production and quality control should have an adequate background in relevant scientific disciplines, such as bacteriology, biology, biometry, chemistry, medicine, pharmacy, pharmacology, virology, immunology and veterinary medicine, together with sufficient practical experience to enable them to exercise their management function for the processes concerned.

15.2.3 The immunological status of personnel may have to be taken into consideration for product safety. All personnel engaged in production, maintenance, testing and animal care (and inspectors) should be vaccinated where necessary with appropriate specific vaccines and have regular health checks. Apart from the obvious problem of exposure of staff to infectious agents, potent toxins or allergens, it is necessary to avoid the risk of contamination of a production batch with infectious agents. Visitors should generally be excluded from production areas.

15.2.4 Any changes in the immunological status of personnel which could adversely affect the quality of the product should preclude work in the production area. Production of BCG vaccine and tuberculin products should be restricted to staff who are carefully monitored by regular checks of immunological status and chest X-ray.

15.2.5 In the course of a working day, personnel should not pass from areas where exposure to live organisms or animals is possible to areas where other products are handled. If such passage is unavoidable, clearly defined decontamination measures, including changes of clothing and shoes and, where necessary, showering should be followed by staff involved in any such production.

15.3 PREMISES AND EQUIPMENT

15.3.1 The degree of environmental control of particulate and microbial contamination of the production premises should be adapted to the product and the production step bearing in mind the level of contamination of the starting materials and the risk to the finished product.

15.3.2 The risk of cross-contamination between biological medicinal products, especially during those stages of the manufacturing process in which live organisms are used, may require additional precautions with respect to facilities and equipment, such as the use of dedicated equipment, production on a campaign basis and the use of closed systems. The nature of the product as well as the equipment used will determine the level of segregation needed to avoid cross-contamination.

15.3.3 In principle, dedicated facilities should be used for the production of BCG vaccine and for the handling of live organisms used in production of tuberculin products.

15.3.4 Dedicated facilities should be used for the handling of Bacillus anthracis, Clostridium botulinum and Clostridium tetani until the inactivation process is accomplished.

15.3.5 Production on a campaign basis may be acceptable for other spore forming organisms provided that the facilities are dedicated to this group of products and not more than one product is processed at any one time.

15.3.6 Simultaneous production in the same area using closed systems of biofermenters may be acceptable for products such as monoclonal antibodies and products prepared by DNA techniques.

15.3.7 Processing steps after harvesting may be carried out simultaneously in the same production area provided that adequate precautions are taken to prevent cross-contamination. For killed vaccines and toxoids, such parallel processing should only be performed after inactivation of the culture or after detoxification.

15.3.8 Positive pressure areas should be used to process sterile products but negative pressure in specific areas at point of exposure of pathogens is acceptable for containment reasons. Where negative pressure areas or cabinets are used for aseptic processing of pathogens, they should be surrounded by a positive pressure sterile zone.

15.3.9 All filtration units should be specific to the processing area concerned and recirculation of air should not occur from areas handling live pathogenic organisms.

15.3.10 The layout and design of production areas and equipment should permit effective cleaning and decontamination (e.g. by fumigation). The adequacy of cleaning and decontamination procedures should be validated.

15.3.11 Equipment used during handling of live organisms should be designed to maintain cultures in a pure state and uncontaminated by external sources during processing.

15.3.12 Pipework systems, valves and vent filters should be properly designed to facilitate cleaning and sterilization. The use of 'clean of place' and 'sterilize in place' systems should be encouraged. Valves on fermentation vessels should be completely steam sterilizable. Air vent filters should be hydrophobic and validated for their scheduled life span.

15.3.13 Effluents which may contain pathogenic microorganisms should be effectively decontaminated.

15.3.14 Due to the variability of biological products or processes, some additives or ingredients have to be measured or weighed during the production processes (e.g. buffers). In these cases, small stocks of these substances may be kept in the production area.

15.4. ANIMAL QUARTERS AND CARE

15.4.1 Animals are used for the manufacture of a number of biological products, for example polio vaccine (monkeys), snake antivenoms (horses and goats), rabies vaccine (rabbits, mice and hamsters) and serum gonadotrophin (horses). In addition, animals may also be used in the quality control of most sera and vaccines e.g. pertussis vaccine (mice), pyrogenicity (rabbits), BCG vaccine (guinea-pigs).

15.4.2 Quarters for animals used in production and control of biological products should be separated from production and control areas. The health status of animals from which some starting materials are derived and of those used for quality control and safety testing should be monitored and recorded. Staff employed in such areas must be provided with special clothing and changing facilities.

15.5 DOCUMENTATION

15.5.1 Specifications for biological starting materials may need additional documentation on the sources, origin, method of manufacture and controls applied, particularly microbiological controls.

15.5.2 Specifications are routinely required for intermediate and bulk biological medicinal products.

15.6 PRODUCTION

15.5.1 THE POSSIBILITY OF CONTAMINATION

15.5.1.1 Due to the inherent characteristics of biological material special care should be taken during collection and processing to avoid microbial growth and contamination, which could lead to sub-standard or hazardous products or substantial losses.

15.6.2 THE POSSIBILITY OF INFECTION

15.6.2.1 A particular hazard associated with biological materials is that an element of a pool of starting material may contain an infectious agent. This is a hazard to staff who will have to process the material and appropriate precautions must be taken. Processing steps must be designed to inactivate and eliminate both the known and the potential infectious agents which may be present in the material. No completely reliable test exists for the presence of any pathogenic bacteria or virus so that good manufacturing practices are essential to reduce the chances of this hazard.

15.6.3 WHERE THE PRODUCT ITSELF IS AN INFECTIOUS AGENT

15.6.3.1 Many highly effective vaccines consist of living organisms which have been selected for minimal pathogenicity and maximal immunogenicity (attenuated). Facilities and staff for propagating, processing and filling each product must be physically separated from those used for other products.

15.6.3.2 Similarly, as these products do not undergo a terminal sterilization procedure and do not usually contain preservative materials, it is extremely important that premises and staff are isolated from facilities handling or testing infectious virulent materials (e.g. challenge strains or diagnostic facilities). The checks on the health of staff in these production areas must also be more stringent than those for other production staff.

15.6.3.3 For products containing living organisms, tests for the absence of contaminants are more complex and must include tests to demonstrate the maintenance of attenuation.

15.6.3.4 Where an inactivated infectious agent is included in a product, it is impossible to reliably detect extremely low levels of infectivity, thus it is necessary to estimate the infectivity of the preparation at various times during inactivation, and to use this data to calculate a time when the theoretical infectivity of the preparation reaches an acceptable level.

15.6.4 STARTING MATERIALS

15.6.4.1 The source, origin and suitability of starting materials should be clearly defined. Where the necessary tests take a long time, it may be permissible to process starting materials before the results of the tests are available. In such cases, release of a finished product is conditional on satisfactory results of these tests.

15.6.4.2 Where sterilization of starting materials is required, it should be carried out where possible by heat. Where necessary, other appropriate methods may also be sued for inactivation of biological materials (e.g. irradiation).

15.6.4.3 Where a biological medicine is derived or extracted from living organisms or tissues, there is always the probability of batch to batch variation of the starting material. Genetic variation in a pool of material from a number of individuals or organisms, can occur. This may be prevented through strict controls over each seed lot. It may be necessary to ensure purity of the seed lot prior to each production sequence through finger-printing methods such as DNA sequencing.

15.6.4.4 The yield and / or quality may also be affected by e.g. minor differences in growth conditions of a cultivated starting material.

15.6.4.5 Due to deterioration of material during collection, storage or processing, aberrant forms of the products can result and the yield can vary from batch to batch.

15.6.5 SEED LOT AND CELL BANK SYSTEM

15.6.5.1 In order to prevent the unwanted drift of properties which might ensue from repeated subcultures or multiple generations, the production of biological medicinal products obtained by microbiological culture, cell culture or propagation in embryos and animals should be based on a system of master and working seed lots and/or cell banks.

15.6.5.2 The number of generations (doublings, passages) between the seed lot and the cell bank and the finished product should be consistent with the registration dossier. Scaling up of the process should not change this fundamental relationship.

15.6.5.3 Seed lots and cell banks should be adequately characterized and tested for contaminants. Their suitability for use should be further demonstrated by the consistency of the characteristics and the quality of the successive batches of the product. Seed lots and cell banks should be established, stored and used in such a way as to minimize the risks of contamination or alteration.

15.6.5.4 Establishment of the seed lot and cell bank should be performed in a suitably controlled environment to protect the seed lot and the cell bank and, if applicable, the personnel handling it. During the establishment of the seed lot and cell bank, no other living or infectious material (e.g. virus, cell lines or cell strains) should be handled simultaneously in the same area or by the same persons.

15.6.5.5 Evidence of the stability and recovery of the seeds and the banks should be documented. Storage containers should be hermetically sealed, clearly labelled and kept at an appropriate temperature. An inventory should be meticulously kept. Storage temperature should be recorded continuously for freezers and properly monitored for liquid nitrogen. Any deviation from set limits and any corrective action taken should be recorded.

15.6.5.6 Only authorized personnel should be allowed to handle the material and this handling should be done under the supervision of a responsible person. Access to stored material should be controlled. Different seed lots or cell banks should be stored in such a way to avoid confusion or cross-contamination. It is desirable to split the seed lots and cell banks and to store the parts at difference locations so as to minimize the risks of total loss.

15.6.5.7 All containers of master or working cell banks and seed lots should be treated identically during storage. Once removed from storage, the containers should not be returned to stock.

15.6.6 OPERATING PRINCIPLES

15.6.6.1 The growth promoting properties of culture media should be demonstrated.

15.6.6.2 Addition of materials or cultures to fermenters and other vessels and the taking of samples should be carried out under carefully controlled conditions to ensure that absence of contamination is maintained. Care should be taken to ensure that vessels are correctly connected when addition or sampling takes place.

15.6.6.3 Centrifugation and blending of products can lead to aerosol formation and containment of such activities to prevent transfer of live microorganisms is necessary.

15.6.6.4 If possible, media should be sterilized in situ. In-line sterilizing filters for routine addition of gases, media, acids or alkalis, defoaming agents etc. to fermenters should be used where possible.

15.6.6.5 Careful consideration should be given to the validation of the necessary virus removal or inactivation undertaken.

15.6.6.6 In cases where the virus inactivation or removal process is performed during the manufacture, measures should be taken to avoid the risk of recontamination of treated products by non-treated products.

15.6.6.7 A wide variety of equipment is used for chromatography, and in general such equipment should be dedicated to the purification of one product and should be sterilized or sanitized between batches. The use of the same equipment at difference stages of processing should be discouraged. Acceptance criteria, life span and sanitization or sterilization method of columns should be defined.

15.7 QUALITY CONTROL

15.7.1 In-process controls play an especially important role in ensuring the consistency of the quality of biological medicinal products. Those controls which are crucial for quality (e.g. virus removal) but which cannot be carried out on the finished product, should be performed at an appropriate stage of production.

15.7.2 It may be necessary to retain samples of the intermediate products in sufficient quantities and under appropriate storage conditions to allow the repetition or confirmation of batch control.

15.7.3 Continuous monitoring of certain production processes is necessary, for example fermentation. Such data should form part of the batch record.

15.7.4 Where continuous culture is used, special consideration should be given to the quality control requirements arising from this type of production method.

15.7.5 SPECIAL REQUIREMENTS FOR FINAL TESTING

15.7.5.1 Biological medicines require biological tests to ensure efficacy and safety. In-vitro tests are not sufficient and in-vivo animal testing is required. Animal testing should be conducted in accordance with regulations.

15.7.6 WASTE DISPOSAL

15.7.6.1 Infectious material and toxins must be adequately inactivated before disposal. The inactivation system used must be validated.

CHAPTER 16

MANUFACTURE OF HERBAL MEDICINAL PRODUCTS INCLUDING HOMEOPATHIC PRODUCTS

16.1 PRINCIPLE

Because of their often complex and variable nature, and the number and small quantity of defined active ingredients, control of starting materials, storage and processing assume particular importance in the manufacture of herbal medicinal products.

16.2 PREMISES

16.2.1 STORAGE AREAS

16.2.1 Crude (i.e. unprocessed) plants should be stored in separate areas. The storage areas should be well ventilated and be equipped in such a way as to give protection against the entry of insects or other animals, especially rodents. Effective measures should be taken to prevent the spread of any such animals and microorganisms brought in with the crude plant and to prevent cross-contamination. Containers should be located in such a way as to allow free air circulation.

16.2.1.2 Special attention should be paid to the cleanliness and good maintenance of the storage areas particularly when dust is generated.

16.2.1.3 Storage of plants, extracts, tinctures and other preparations may require special conditions of humidity, temperature or light protection; these conditions should be provided and monitored.

16.2.2 PRODUCTION AREAS

16.2.2.1 Specific provisions should be taken during sampling, weighing, mixing and processing operations of crude plants whenever dust is generated, to facilitate cleaning and to avoid cross-contamination, as for example, dust extraction, dedicated premises, etc.

16.3 DOCUMENTATION

16.3.1 SPECIFICATIONS FOR STARTING MATERIALS

16.3.1.1 Apart from the data described in General Guide, specifications for medicinal crude plants should include, as far as possible:

- the botanical name (with, if appropriate, the name of the originator of the classification, e.g. Linnaeus;
- the details of the source of the plant (country of region, and where applicable, cultivation, time of harvesting, collection procedures, possible pesticides used, etc.);
- whether the whole plant or only a part is used;
- when a dried plant is purchased, the drying system should be specified;
- the description of the plant and its macro and microscopical examination;
- the suitable identification tests including, where appropriate, identification tests for known active ingredients, or markers. A reference authentic specimen should be available for identification purposes;
- the assay, where appropriate of constituents of know therapeutic activity or of markers;
- the methods suitable to determine possible pesticide contamination and limits accepted;
- the tests to determine fungal and/or microbial contamination, including aflatoxins and pest-infestations, and limits accepted;
- the tests for toxic metals and for likely contaminants and adulterants;
- the tests for foreign materials.

16.3.1.2 Any treatment used to reduce fungal/microbial contamination or other infestation should be documented. Specifications for such procedures should be available and should include details of process, tests and limits for residues.

16.3.2 PROCESSING INSTRUCTIONS

16.3.2.1 The processing instructions should describe the different operations carried out upon the crude plant such as drying, crushing and sifting, and include drying time and temperatures, and methods used to control fragment or particle size. It should also describe security sieving or other methods of removing foreign materials.

16.3.2.2 For the production of a vegetable drug preparation, instructions should include details of base or solvent, time and temperatures of extraction, details of any concentration stages and methods used.

16.3.3 SAMPLING

16.3.3.1 Due to the fact that crude drugs are an aggregate of individual plants and contain an element of heterogeneity, their sampling has to be carried out with special care by personnel with particular expertise. Each batch should be identified by its own documentation.

16.3.4 QUALITY CONTROL

16.3.4.1 Quality Control personnel should have particular expertise in herbal medicinal products in order to be able to carry out identification tests and recognize adulteration, the presence of fungal growth, infestations, non-uniformity within a delivery of crude plants, etc.

16.3.4.2 The identity and quality of vegetable drug preparations and of finished product should be tested as described in the note for guidance "Quality of herbal remedies".

CHAPTER 17:

MEDICAL GASES

17.1 PRINCIPLE

17.1.1 Gases, either in compressed or liquefied form, intended for medical use should be manufactured, filled, stored, distributed and documented in accordance with the general principles outlined in this Guide, appropriately interpreted to suit the special context of gaseous products.

17.2 GENERAL REQUIREMENTS

17.2.1 Although order, tidiness, cleanliness and security sufficient to avoid the risk of error, mix-up or contamination are required, certain recommendations given elsewhere in the Guide (for example on premises and equipment) may not always be applicable to a product which is never in direct contact with the factory environment. Nevertheless, particularly to encourage desirable attitudes towards medicinal products, areas where medical gases are filled should be maintained at an appropriate standard of cleanliness and order.

17.2.2 The gas production plant should be continually monitored for the quality and impurity levels of the gas produced, and similar tests should be carried out on bulk storage vessels at specified regular intervals.

17.2.3 The gas production, treatment and filling plant should be designed, installed and maintained so as to avoid contamination of the gas. Filters are necessary after driers to prevent contamination with particles of desiccant.

17.2.4 The areas used for filling of medical gases should be segregated from areas used for filling gases for other (e.g. industrial) purposes. The "medical" nature of such areas should be emphasized.

17.2.5 Staff employed in the production, filling and testing of medical gases should be made aware of the special importance of their work and the potential hazards to patients.

17.3 PIPELINES

17.3.1 Gas pipelines should be colour coded to BS 1710 (Identification of Pipelines) and HTM 22 (Piped Medical Gases, etc.). All gas outlets should be conspicuously marked to indicate the name of the gas supplied to the outlet. Cleaning and purging of pipelines should follow written procedures, and checks for the absence of cleaning agents or other contaminants should be carried out before the line is released for use.

17.4 FILLING AREAS

17.4.1 Filling areas should be of sufficient size, and have an orderly lay-out which will permit:

·allocation of separate marked areas for different gases and different cylinder sizes
·clearly identifiable segregation of empty cylinders from full cylinders
·clear distinguishing of the stage reached by given cylinders (e.g. "awaiting filling", "filled", "awaiting test and/or inspection", "released").

17.4.2 The method used to achieve these various levels of segregation will depend on the nature, extent or complexity of the over-all operation, but marked-out floor areas, partitions, barriers, labels and signs should be used, as appropriate.

17.5 PREPARATION OF RETURNED CYLINDERS

17.5.1 New cylinders and cylinders returned for re-filling should be checked as clean and suitable before re-use. Cylinders returned from customers should be prepared for re-filling as follows:
·cylinders due for statutory hydraulic testing, or which require repainting, or which are damaged in any way must receive the appropriate treatment before filling. If a cylinder is to be re-painted in a different colour, for use with a different gas, the old paint must be completely removed before re-painting

·old date / batch labels, and any markings applied by the customer, must be removed

·any water or debris in the valve outlets must be removed by an airjet or other suitable means before the cylinder valve is opened.

1 7.6 FILLING

17.6.1 Before a cylinder is filled, steps should be taken to avoid the risk of contamination of the new gas with any possibly contaminated gas remaining in the cylinder, by employing appropriate blow-down, purging and evacuation procedures. Checks should be made to ensure compliance with points under 17.5.1 above, and in particular to ensure that the cylinder is colour-coded (ref. BS 1319 1976), labelled, stenciled or otherwise marked in accordance with the nature of the gas to be filled.

17.7 LOT IDENTIFICATION

17.7.1 In addition to identification labelling or marking, all filled cylinders should have attached a lot identifying label. If, because of the continuous nature of gas production, it is not possible to relate this directly to a bulk batch of gas, it should at least be indicative of date, time and place of filling, and permit access to a relevant test record.

17.8 RELEASE

17.8.1 Following filling, all cylinders should be leak-tested by an appropriate method, and held in quarantine until released by Quality Control, after checks have been made to ensure:

·that all necessary tests have been carried out, and that the recorded results are within specification
·that the cylinders have not exceeded the hydraulic test date, are in good condition and correctly painted and are properly identity- and batch-labelled and stenciled
·that the cylinder valve is in good condition and the protective cap or sleeve over the outlet has been properly applied.

17.8.2 It is not normally necessary or appropriate to retain finished product samples.

17.9 STORAGE

17.9.1 Gas cylinders should be stored under cover, and not subjected to extremes of temperature. Areas where they are stored should be clean, dry, well ventilated and free from combustible materials.

17.9.2 Storage arrangements should permit segregation of different gases and of full / empty cylinders and permit rotation of stock.

17.9.3 Cylinders should be stored so that they remain clean, dry and with their markings unobscured.

17.9.4 Storage arrangements for gas-mixtures should be such so as to avoid separation of the mixture into its component gases.

CHAPTER 18:

GOOD PHARMACEUTICAL WHOLESALING PRACTICE

18.1 PRINCIPLES

18.1.1 Good wholesaling practices should be seen as an extension of the manufacturer's endeavors to assure the maintenance of product quality by having adequate storage conditions, record keeping and compliance with legal requirements. The recommendations of relevant sections of this Guide in relation to buildings, pest control, stock records and stock rotation should be followed.

18.2 GENERAL REQUIREMENTS

18.2.1 Key personnel involved in the warehousing of medicinal products should have the ability and experience appropriate to the responsibility of ensuring that the products or materials are properly handled.

18.2.2 The area should be protected against unauthorized entry.

During operating hours, the business must at all times be conducted under the continuous personal supervision of a pharmacist.

Proper training relating to quality, handling, quantity relations, storage requirements, distribution and safety must be provided for all personnel.

Sufficient security must be provided to prevent pilferage and/or unauthorided entry.

18.3 STORAGE

18.3.1 The warehouse, storage areas and surroundings should be maintained in a clean and tidy condition, free from accumulated waste. Spilled substance should be promptly cleaned up and rendered safe.

All waste material should be removed on a regular basis.

Programmes for regular cleaning must be drawn up and followed.

18.3.2 Stocks should be received in a separate reception area, and examined for correctness against order and for absence of damaged containers.

18.3.3 Medicinal products should be stored apart from other goods which could cause harmful cross-contamination.

Sufficient lighting should be provided to enable all operations to be carried out accurately and safely.

All products should be stored off the floor.

18.3.4 All products should be protected from excessive local heating, and from undue exposure to direct sunlight, and (unless they are known to be unaffected) from freezing. Minimum and maximum temperatures should be monitored.

18.3.5 Special storage facilities should be provided as necessary to protect products from deterioration and to comply with the manufacturer's directions and with legal requirements.

18.3.6 Refrigerated storage areas should be equipped with temperature recorders or other temperature monitoring devices. Control should be adequate to maintain all parts of the storage area within the specified temperature range.

Temperature should be monitored and recorded periodically. Records of temperature should be reviewed regularly.

Written procedures must be available detailing the action to be taken in the event of a temperature violation occurring.

All thermoliable products must be distributed under temperature-controlled conditions to maintain the cold chain.

18.3.7 There should be a system to ensure stock rotation, with regular and frequent checks that the system is operating correctly. Products beyond their expiry date or shelf-life should be removed from usable stock and neither sold nor supplied.

18.3.8 Stock which is damaged or withheld from supply, and which is not immediately destroyed, should be kept apart from saleable stock, so that it cannot be sold in error, and so that leakage from any broken package cannot contaminate other goods.

18.3.9 Stocks of sterile products with broken seals, damaged packaging, or suspected of possible contamination must not be sold or supplied.

18.4 TRANSPORT

The sale of medicine shall only take place to persons legally entitled thereto. Deliveries should be made only to other authorised wholesalers or to persons authorised to supply medicinal products.

18.4.1 Products should be transported in such a way that:

·the identification of the product is not lost
·the product does not contaminate, and is not contaminated by, other products or materials
·adequate precautions are taken against spillage or breakage
·the cold chain, if required, is preserved
·the specific storage conditions of the product are not grossly exceeded or exceeded for an unacceptable length of time
·medicinal products requiring controlled temperature storage should also be transported by appropriate specialized means.

18.5 DOCUMENTATION AND CONTROL

18.5.1 Goods which have been rejected, recalled or returned should be placed in adequately segregated storage to avoid confusion with other materials and products and prevent redistribution, until a decision has been reached as to their disposition. Records of all goods returned should be kept.

18.5.2 There should be a written procedure for implementing a manufacturer's product recall, and records of any recalled products received into the warehouse should be kept. It is useful to have a record keeping system by batch which would assist with effective recall from the retailer. A person should be designated as responsible for execution and co-ordination of recalls.

18.5.3 There should be a written procedure for the handling of spillages of harmful Products (e.g. cytotoxics, hormones, penicillins).

18.5.4 There should be a written procedure for the handling of product complaints.

18.5.5 Legal requirements regarding the documentation and control of scheduled medicines should be adhered to.

There must a system for the recognition of and prompt and correct handling by the pharmacist of Schedule 6 or 7 substances and for those products requiring storage at specific temperature ranges.

Schedule substances should only be purchased from manufacturers or distributors registered as such with the South African Pharmacy Council.

All applicable documentation and receipts for Scheduled substances should be retained on the premises for the statutory period of time.

Records should be kept of each purchase and sale. Records should ensure the traceability of the origin and destination of products.

All documentation should be made available on request to the authorities.

Accurate and accessible records of all sales of Scheduled substances must be made, indicating the date oft supply, customer, customer address, product name and quantity.

A valid written order must be obtained prior to sale and/or despatch of Schedule 6 or Schedule 7 substances. The order must comply with statutory regulations.

All records must be kept for the statutory period of time.

The sale of medicines should only take place to persons legally entitled thereto. Proof of registration of the purchaser with the relevant statutory body must be in possession of the wholesaler before medicines are sold.

Stock that can no longer be used must be destroyed in an appropriate manner, such as not to cause a harmful or potentially harmful hazard, and to prevent accidental usage.

18.5.6 Goods which have left the care of the wholesaler should only be returned to saleable stock if:

·the goods are in their original unopened containers and in good condition and bear the valid registration numbers
·it is known that the goods have not been subject to adverse conditions
·they have been examined and assessed by a person authorized to do so. This assessment should take into account the nature of the product, any special storage conditions it requires, and the time elapsed since it was issued. If necessary, advice should be sought from the person responsible for the Quality Control of the manufactured product.

18.5.7 It is useful to employ a batch-tracking system which enables the supply of specific batches to be traced.

CHAPTER 19 :

ELECTRONIC DATA PROCESSING

19.1 PRINCIPLES

19.1.1 The introduction of Electronic Data Processing into systems of manufacturing, storage and distribution does not alter the need to observe the relevant principles, given elsewhere in the Guide. Where Electronic Data Processing replaces a manual operation in a system there should be no adverse impact on product quality or Good Manufacturing Practice.

19.2 RESPONSIBILITIES

19.2.1 The responsibilities of key personnel described in the Guide are not changed by the use of computers, and it is essential that there is the closest co-operation between Production, Quality Control and Electronic Data Processing Departments.

19.2.2 Persons with appropriate expertise should be responsible for the design and introduction of a proposed computer system. These or other expert persons should be retained to review the system at appropriate intervals.

19.2.3 Employees whose duties involve the use of a computer system should be appropriately trained in its correct use. Written operating procedures should be readily available to these employees. On-line help screens could be used for this purpose. Records of operator training should be kept.

19.3 VALIDATION

19.3.1 The development, implementation and operation of a computer system should be carefully documented at all stages and each step proven to achieve its written objective under challenging test conditions.

19.3.2 The extent of validation necessary will depend on a number of factors:

i) the use to which the system is to be put.
ii) whether the validation is to be prospective or retrospective
iii) whether novel elements are incorporated

Validation should be considered as part of the complete life cycle of a computer system. The cycle includes the stages of planning, specification, programming, testing, commissioning, document operation, monitoring and modifying.

19.3.3 A control document (system specification) should be prepared specifying the objectives of a proposed computer system, the data to be entered and stored, the flow of data, how it interacts with other systems and procedures, the information to be produced, the limits of any variable and the operating program(s) and test programs. Examples of each document produced by the program should be included. A functional specification should also be prepared to provide instructions for testing, operating and maintaining the system and the names of the person or persons responsible for its development and operation.

19.3.4 Computers should be protected from disturbances caused by fluctuations in the electrical supply and from loss of memory due to supply failure, electrical / magnetic disturbances or high temperatures.

19.3.5 Before a system using a computer is brought into use it should be tested and confirmed as being capable of achieving desired results. If a manual system is being replaced it is advisable to run the two in parallel for a time, as part of this testing and validation.

1 9.3.6 At installation and after a suitable period of running a new system, it should be independently reviewed and compared with the system specification and functional specification to ascertain whether it is meeting all of its requirements.

1 9.3.7 Alterations to a system or to a computer programme should only be made in accordance with a defined procedure which should including provision for checking, approving and implementing the change. Such an alteration should be implemented with the agreement of the person responsible for the part of the system concerned, and the alteration should be recorded.

1 9.3.8 Data collected directly from manufacturing or monitoring equipment should be checked periodically to confirm that it has been accurately and reliably transferred. Similarly, data or control signals transmitted from a computer to equipment involved in the manufacturing process should be checked periodically to ensure accuracy and reliability.

1 9.4 SECURITY

1 9.4.1 Data should only be entered or amended by persons authorized to do so. Suitable methods of deterring unauthorized entry of data include the use of keys, pass cards, personal codes and restricted access to computer terminals. The method of final release by computer of a batch for sale or supply should uniquely identify the person effecting the release. There should be a defined procedure for the issue, cancellation and alteration of authorization to amend data, including the changing of personal codes.

1 9.4.2 The entry of critical data into a computer by an authorized person (e.g. entering a master processing formula) should require independent verification and release of use by a second authorized person.

1 9.4.3 The computer program should create a complete record ("audit trail") of all entries and amendments to the data base.

1 9.4.4 Adequate alternative arrangements should be available, i.e. disaster recovery procedure, for systems which need to be operated in the event of a break-down. The procedures to be followed if the system fails or breaks down, should be defined and tested. Regular backups of all files should be stored in a secure location to prevent willful or accidental damage. Any failure and remedial action taken should be recorded.

1 9.4.5 It should be possible to obtain printed copies of electronically stored data.

1 9.4.6 Stored data should be checked for accessibility, durability and accuracy, especially after any relevant changes have been made to the computer equipment or its programmes.

1 9.4.7 Care should be taken to ensure that computer systems are not contaminated by computer viruses.

CHAPTER 20 :

SECURITY GUIDELINES

20.1 PRINCIPLE

20.1.1 Adequate security measures are essential to protect pharmaceutical installations against unauthorized entry or deliberate adulteration of products.

20.1.2 Legitimate procedures should be followed for the removal/transportation of stock and materials to prevent pilferage or theft.

20.2 SECURITY PERSONNEL

20.2.1 Sufficient resources should be provided to establish an adequate security force on a 24 hour, 7 days per week basis.

20.2.2 A security manager should be appointed in writing to identify, evaluate and propose corrective measures to reduce risk to acceptable levels. He should be conversant with the Criminal Procedures Act and Labour Legislation.

20.2.3 Security staff should be security vetted and should be adequately trained and knowledgeable about Company procedures and practices as they impact on security operations.

20.3 ENTRY TO SITE

20.3.1 A risk evaluation is recommended to identify potential means of unauthorized entry during daylight as well as after hours.

20.3.2 The following security measures may be appropriate:

·a perimeter fence of good quality
·adequate security lighting
·limited and restricted access to all production and storage areas (especially scheduled) medicines
·adequate gates of sound construction, that are lockable
·security guards patrolling the grounds during the day and night. A telephone for the use of night security staff to use in the event of unlawful entry or fire, or an adequate electronic alarm system
·guard dogs and handlers for night patrol.

20.4 ENTRY TO BUILDINGS

20.4.1 The contents of the building are important in determining the level of protection required. The following security measures may be appropriate:

·robust outside doors
·good quality locks
·inaccessible windows
·installations of burglar alarms which should elicit a response and be regularly tested.

20.4.2 Consideration should be given to restricting and controlling entry to vital areas within buildings where high risk items are kept and the use of high security rooms and alarms.

20.5 INTERNAL SECURITY

20.5.1 There should be established procedures covering a number of security related activities, e.g.

·Locking of areas, control and storage of keys including the use of a key register
·Authorization of personnel who need access to vital or high-risk areas

Listing certain areas as "Restricted area - for authorized personnel only"
·control of all unnecessary staff movement between departments including personnel who are authorized to be in one area from moving freely to other high-risk areas
·control over the movement of customers and visitors
·control of the movement of stock ensuring that there is no opportunity for pilferage in transit. This also applies between the factory and the customer
·random physical checking of inventories
·the checking of waste as it is removed from production areas and the independent checking of cleaning and security staff where outside contractors are used
·checking of batch yields by a responsible person during processing and immediately on completion in case low yields may be the result of pilferage
·the searching of staff on leaving the premises or at any other time. Refer to Criminal Procedures Act
·screening of staff on employment, including careful checking of references
·particular attention should be paid to delivery services and other vehicles entering and leaving the premises.

CHAPTER 21:

SAFETY AND ENVIRONMENTAL PROTECTION

21.1 PRINCIPLES

21.1.1 The purpose of safety guidelines is to provide for the safety of persons at a workplace or in the course of their employment or in connection with the use of machinery.

21.1.2 Good Environmental Practice entails the minimization of waste at source and the disposal of waste in a manner harmless to the environment.

21.1.3 This chapter provides guidelines for practices and procedures which constitute Good Environmental Practice.

21.2 SAFETY

21.2.1 It is important to maintain a high level of safety awareness in pharmaceutical factories. To this end the importance of training cannot be over-emphasized.

21.2.2 Safety in the workplace is controlled by the Occupational Safety and Health Act (85 of 1993).

21.2.3 Factories are inspected on an annual basis by the Occupational Safety Association (NOSA). Regular safety self-inspections should also be undertaken.

21.2.4 The following should always be considered:

·buildings, machinery, vehicles, equipment etc. should be kept in a good state of repair
·fire preventative measures, as well as action steps in case of fire should be in place
·the dangers associated with electricity should be highlighted
·the nature of work/material will determine the level of personal protection necessary (helmets, safety glasses, headcovers, masks, respirators, ear protection, overalls, gloves, safety shoes etc.)
·first aid equipment and medicine should be available and accessible for the treatment of injured persons. Qualified first aid personnel should be available.

21.2.5 Special attention should be given to the manufacture, storage, use and handling of, and the exposure of employees and other persons to, hazardous materials; and the performance of work in hazardous or potentially hazardous conditions or circumstances.

21.3 ENVIRONMENTAL PROCEDURES

21.3.1 In addition to all applicable legal requirements, pharmaceutical companies may institute additional in-house requirements.

21.3.2 Procedures and controls to minimize the discharge to the environment of hazardous substances may include the following:

·procedures and controls regarding the discharge of hazardous substances into sewage and storm water drains where the material could accumulate or interfere with treatment processes
·emission to the atmosphere from process vents, storage vessels, area ventilating systems, incinerator stacks and fugitive emissions
·contamination of soil, water or the atmosphere due to spill, leakage from any source (storage tanks etc.), malfunction of control equipment, fire or explosion or from inadequate or improper treatment, storage or disposal practices.

21.3.3 Where possible, the company should have methods of rendering waste substances harmless to the environment.
21.3.4 There should be procedures to control the generation, transportation, storage, treatment or disposal of hazardous wastes. The most effective control of hazardous waste is the reduction or elimination of the waste. To that end, re-use, recycling, reclamation, inactivation or destruction is more desirable than land disposal or deep well injection. Other techniques should be thoroughly investigated before land disposal is selected.

21.3.5 Emergency procedures to minimize hazards associated with discharges to the environment should be developed. Procedures to co-ordinate internal and external emergency groups should be considered.

21.3.6 The capabilities of vendor suppliers and contract-acceptors should also be evaluated from an environmental point of view.

21.3.7 Monitoring programs should be developed to determine that compliance with legal and/or in-house specifications is maintained.

21.3.8 Procedures should be developed for the operation and maintenance of pollution control and monitoring equipment and should include preventative maintenance and training programmes.

21.3.9 Records should be retained in accordance with legal and/or in-house requirements.

21.3.10 The integrity of underground storage tanks and associated piping and equipment should be routinely verified. Alternatives to underground storage of potentially hazardous substances should be considered.

21.3.11 The preferred strategy for all waste management is reduction of waste at source.

CHAPTER 22:

STERILE PRODUCTS

22.1 INTRODUCTION

These standards do not replace any of the general GMP standards but must be seen as supplementary to them, the focus being on small volume injectable manufacture by aseptic process or terminal sterilization. The manufacture of sterile preparations has special requirements in order to minimise risks of microbiological contamination, and of particulate and pyrogen contamination. Terminal sterilization is generally achieved on one of three ways:

- ethylene oxide fumigation
- gamma irradiation
- steam sterilization (Autoclaving)

while aseptically prepared products are rendered sterile in bulk form through filtration and then processed into pre-sterilized containers under conditions which minimise the potential for change microbial contamination.

The major elements to be considered in aseptic processing include:

1. training of personnel;
2. layout and specifications for buildings and facilities;
3. particulate and microbial environmental monitoring programs;
4. systems for water, steam, air and other process gases;
5. descriptions of and procedures for manufacturing operations include people, materials, material flow, solution preparation and associated acceptance criteria;
6. use and validation of sterilization processes, including sanitization practices;
7. validation methods and data requirements for medial fills and container/closure systems;
8. operating practices for disposition of product, investigation reviews, and release/reject decisions.

22.2 DEFINITIONS

AIRBORNE PARTICULATE CLEANLINESS CLASSES

The airborne particulate 4 classes or grades shown below apply to the manufacture of sterile products.

Grade A: The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, aseptic connections. Normally such conditions are provided by a laminar air flow work station. Laminar air flow systems should provide an homogeneous air speed of 0.30 m/s for vertical flow and 0.45 m/s for horizontal flow.

Grade B: In case of aseptic preparation and filling the background environment for grade A zone.

Grade C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products.

The airborne particulate classifications for these grades are given in the following table.

ENVIRONMENTAL GRADES FOR CLEAN ZONES/AREA:

	at rest		in operation(c)	
GRADE	Maximum permitted number of particles/m^3 equal to or above			
	0,5um	5um	0,5um	5um
A	3 500	-	3 500	-
B(a)	3 500	-	350 000	2 000
C(a)	350 000	2 000	3 500 000	20 000
D(a)	3 500 000	20 000	-	-

Notes:

a) In order to reach B, C and D air grades, the number of air changes should generally be higher than 20 per hour in a room with a good air flow pattern and appropriate filters; HEPA for grades A, B and C.

b) Appropriate alert and action limits should be set for the particular operation.

The guidance given for the maximum permitted number of particles in the "at rest" condition corresponds approximately to the US Federal standard 209 E as follows: Class 100 (grades A and B). Class 10000 (grade C) and Class 100000 (grade D).

c) Recommended limits for contamination may be exceeded on isolated occasions and require only an examination of the production conditions and the control system. If frequency is high or shows an upward trend then action should be taken.

ASEPTIC AREA

A room or suite of rooms or special area within a clean area, designed, constructed, serviced and used with the intention of preventing microbial contamination of the product.

ASEPTIC FILLING

That part of aseptic processing whereby the product is sterilised separately, then filled and packaged using sterilised containers and closures in critical processing zones.

ASEPTIC PROCESSING AREA (APA)

Controlled environment, consisting of several zones, in which the air supply, equipment and personnel are regulated to control microbial and particulate contamination to acceptable levels.

BATCH

A defined quantity of material, or bulk, intermediate or finished product that is intended or purported to be uniform in character and quality, and which has been produced during a defined cycle of manufacture. To complete certain stages of manufacture it may be necessary to divide a batch into a number of sub-

batches, which are later brought together to form a final uniform batch. A batch is sometimes described as a lot.

For the purpose of a sterility test, a batch is a collection of sealed containers prepared in such a manner that the risk of microbial contamination may be considered the same for each of the units in it. It may be defined as one of the following:

(a) one sterilizer load

(b) the quantity of containers filled aseptically in one working session at one work station. A working session should be deemed to terminate whenever there is a significant change in circumstances which could affect the risk of product contamination (for example, a change of filling equipment, a change in the team of operators or a machine break-down). What in fact constitutes 'a significant change' should be documented and agreed upon in advance by the persons responsible for Production and Quality Control.

(c) in the case of aseptically filled products which are subsequently freeze-dried, a batch should be one freeze-drier load if this is less than in (b) above.

BIOBURDEN

The total number of viable microorganisms on or in health care product prior to sterilization.

BIOLOGICAL INDICATOR MICRO-ORGANISM

Micro-organism of a known sterilization resistance, that is used to develop and/or validate a sterilization process. The micro-organisms are frequently used on a carrier, which is supporting material on which test organisms are deposited.

BLOW/FILL/SEAL TECHNOLOGY

Blow/fill/seal units are specialist purpose built equipment in which, in one continuous operation, containers are formed from thermoplastic granule, filled and then sealed.

BUBBLE POINT PRESSURE TEST

Membrane filters have discrete pores or capillaries penetrating from one side of the membrane to the other. When a membrane has been completely wetted, liquid is held in these capillary pores by surface tension. The Bubble Point of a membrane is defined as the minimum gas pressure required to break this surface tension and force the liquid out of the capillaries. Bubble point is a measure of relative pore size.

CHANGING ROOM

A room or suite of rooms designed for the changing of clothes and from which a clean or aseptic area is entered.

CHEMICAL DISINFECTANT

A chemical or chemical solution capable of destroying micro-organisms through dehydration (alcohols), alkylation (aldehydes), protein denaturation (phenols), oxidation (iodine/chlorine) and wall permeability (quaternary ammonium compounds).

CLEAN ROOM

A room with defined environmental control of particulate and microbial contamination, constructed in such a way as to reduce the generation and retention of contaminants within the area.

CRITICAL AREAS

Areas where sterilized products or containers/closures are exposed to the environment.

CRITICAL SURFACES

Surfaces which come into contact with sterilized product or containers/closures that may lead to contamination of product contact surfaces if not appropriately controlled.

D VALUE

Sterilization exposure under a defined set of conditions that result in one logarithmic (to the base 10) or 90% reduction in the population of a particular micro-organism.

DECONTAMINATION

The process of removing organisms and rendering the object safe for handling.

DISINFECTION

A process that kills or destroys most disease producing micro-organisms but rarely kills all spores: Disinfectants are used on inanimate objects as opposed to antiseptics which are used on living tissue.

FOGGING

Decontamination process performed by generating an aerosol or vapour of a disinfectant.

INTEGRITY TEST

Test to determine the functional performance of a filter system.

LAMINAR AIRFLOW

Air flowing in a single pass in a single direction, through a clean room or clean room area with uniform velocity along parallel flow-lines. Laminar air flow systems should provide a homogeneous air speed of 0.30m/s for vertical flow and 0.45m/s for horizontal flow.

LARGE VOLUME PARENTERALS

A sterile single dose injectable product intended for administration through the skin with a nominal fill volume of more than 100ml. It may be packed in glass or suitable plastic material.

MEDIA FILLS

Method of evaluating an aseptic process using a microbial growth medium. (Media fills are understood to be synonymous to simulated product fills, simulated filling operations, broth trials, broth fills, etc.)

POSITIVE PRESSURE

Atmospheric pressure which is higher than the immediate surrounding areas usually measured in inches of water or Pa.

QUALIFICATION

INSTALLATION QUALIFICATION (IQ)

Installation qualification (IQ) demonstrates that the unit under test is in compliance with all relevant criteria and safety standards, and is calibrated and regularly scheduled for preventive maintenance.

OPERATIONAL QUALIFICATION (OQ)

Operational qualification (OQ) testing demonstrates that the equipment functions as intended, that procedures exist describing operation of the equipment, and that personnel have been trained to set- up, operate and maintain the equipment.

PERFORMANCE QUALIFICATION (PQ)

Performance qualification (PQ) testing involves actual challenges to the system to substantiate its effectiveness and reproducibility.

SANITIZING

A process which results in a reduction in microbial population on an inanimate object to a relatively safe level.

SMALL VOLUME PARENTERAL

A sterile injectable product intended for administration under or through the skin with a nominal fill volume of 100 ml or less. It may be packaged in glass or suitable plastic material.

STEAM-IN-PLACE

Steam-in-place allows the entire healthcare product processing system to be steam sterilized as a single entity, eliminating or reducing the need for aseptic connections. Examples include tanks, filling lines, transfer lines, filtration systems and water for injection systems.

STERILE PRODUCTS

These may be classified broadly into two categories according to their manner of production, those that must be processed by aseptic means at some or all stages, and those which are sterilized when sealed in their final container (terminally sterilized) which are in a state free of viable micro-organisms.

STERILIZING FILTER

A appropriate sterilizer is to be used from an approved vendor who has the necessary supporting data on file.

STERILITY

The complete absence of living organisms.

NOTE:- The state of sterility is an absolute. There are no degrees of sterility. However the judging of sterility is probabilistic. While the probability may be reduced to a very low number, it can never be reduced to zero.

VALIDATION

The action of proving that any material, process, procedure, activity, system, equipment or mechanism used in manufacture or control can, will and does achieve the desired and intended result(s).

22.3 **FACILITIES**

Layout and construction features which shall be considered in the design of an APA include:

a) wall and floor surfaces which can be cleaned and which resist disinfectants;
b) avoidance of ledges and other horizontal surfaces which could collect particulates or disturb air flow;
c) installation of pipes, ducts and other utilities in a manner to avoid recesses and other surfaces difficult to clean;
d) adequate space for gowning areas, garment storage, soiled garment disposal, and hand washing;
e) separation of gowning and preparation areas from the APA by means of airlocks, pass-through windows for components, supplies and equipment;
f) maintain appropriate pressure differentials required for the given product and process;

22.3.1 The following minimum specification is described for facility design and controls. Additional requirements may be necessary for specific processes. Production of sterile preparations should be carried out in a clean area whose entry should be through airlocks for personnel or for goods. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has all been passed through filters of an appropriate efficiency.

22.3.2 There should be separate or defined areas of operation to prevent contamination. For aseptic processing there should be, as appropriate, an air supply filtered through high efficiency particulate air (HEPA) filters under positive pressure and systems for monitoring the environment and maintaining equipment used to control aseptic conditions. Monitoring results should be considered when reviewing batch documentation for finished product release.

22.3.3 In addition equipment for adequate control over air pressure, micro-organisms, dust, humidity and temperature should be provided where appropriate. Air filtration systems, including prefilters and particulate matter air filters, should be used where appropriate on air supplied to production areas.

22.3.4 Processing should be conducted in a cleanroom suite, constructed and operated in accordance with the air cleanliness standards. In order to control the microbiological and particulate cleanliness of the various grades/classes of operation, the areas should be monitored using various methods, eg. volumetric air sampling, settle plates, surface sampling (swabs, contact plates).

22.3.5 The filling of products to be terminally sterilized should be carried out in an appropriate environment for control of viable and non-viable airborne particulate matter. Extra precautions in the form of contained work stations and/or laminar air flow protection may be necessary when solutions intended for intravenous use are filled into wide-necked containers.

22.3.6 Equipment should be designed and installed so that it may be easily cleaned, disinfected or sterilized as required. Exposed surfaces should be smooth, impervious and unbroken in order to minimise shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents/disinfectants.

22.3.7 Non-sterile products should not be processed in the same area at the same time as sterile products.

22.3.8 Vaccines of dead organisms, or of bacterial extracts, may be filled (after inactivation) in the same premises as other sterile medicinal products. Spore forming organisms should be processed in separate premises or well isolated suites at least until any inactivation stage is completed. Live or attenuated vaccines should be processed and filled in premises separate from other processing or filling operations. Different live vaccines should be processed and filled separately from each other. Separation may be achieved in space or, given adequate cleaning and disinfection, in time. Special isolation facilities may be needed for highly contagious micro-organisms.

22.3.9 The processing of animal tissue materials and of micro-organisms (not required for the current manufacturing process), the performance of test procedures involving animals or micro-organisms, and any animal houses, must be well separated from premises for manufacturing sterile medicinal products, with completely separate ventilation systems, and separate staff.

22.3.10 Where equipment, such as filling equipment, connecting lines, and filter holders, is steam sterilized in autoclaves, it is important that established loading patterns of heat distribution be determined and the ability to achieve sterilization be monitored. One way of ensuring replication of the validated conditions is to follow established loading configuration diagrams and include them as part of the processing record.

22.3.11 Where equipment, such as large tanks and immobile piping is sterilized in place by the passage of pressurized steam, it is important that validation consider temperature and pressure at various locations. This will identify potential "cold spots" where there may be insufficient heat to attain sterility. Some in-line filters in piping systems cause a significant pressure differential across the filter, resulting in a temperature drop on the downstream side. One method of determining if such a drop in temperature will adversely affect the sterilization procedure involves the placement of suitable biological indicators at appropriate downstream locations. Validation could also include measurements of temperature and pressure at various points.

22.3.12 As far as possible, equipment fittings and services should be designed and installed so that maintenance and repairs may be carried out without additional personnel having to enter the clean aseptic rooms. If maintenance must be carried out within these areas, personnel concerned should receive appropriate training in the elements of microbiology and sterile area procedures. When within the areas they should be appropriately dressed, and use tools and equipment which have been sterilized or disinfected. Areas entered for maintenance should be cleaned and disinfected before processing recommences if the required standards of cleanliness and asepsis have not been maintained during the work.

22.3.13 Recording apparatuses should be accurately calibrated on installation and thereafter checked at scheduled intervals.

22.3.14 Validation of equipment performance on installation, is essential. Planned maintenance and frequent checks on performance are also important for critical items of equipment such as sterilizes, air filtration systems, and skills. Checks on steam and hot air sterilizes should include heat distribution and heat penetration studies. Filter efficiency tests should be conducted on air supply systems. Details of maintenance operations and performance checks should be recorded.

22.3.15 When blow/fill/seal units are used, particular attention should be paid to at least the following: equipment design and qualification, validation and reproducibility of cleaning and sterilization, background cleanroom environment in which equipment is located, operator training and clothing, interventions in the critical zone of the equipment, including any aseptic assembly prior to the commencement of filling.

22.3.16 Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimizing microbial and particle contamination of protective clothing. They should be effectively flushed with filtered air. Hand washing facilities should be provided only in the first stage change.

22.3.17 Airlocked doors should not be opened simultaneously. Airlocks should be equipped with interlocks to avoid simultaneous opening of doors.

22.3.18 Control of temperature and relative humidity, if necessary, within defined tolerances and, if possible, monitored continuously.

Aseptic processing facilities shall be designed to promote flow of components and materials in order to:

a) maintain the microbiological integrity of critical processing zones;
b) minimize the entry of contamination from outside the APA, and contain any such contamination so it does not reach critical processing zones; and
c) prevent mingling of clean and dirty items.

22.3.20 **Aseptic Processing Area (APA)**

Access to the aseptic processing area shall be restricted to qualified personnel with sufficient airflow and a positive differential air pressure existing relative to areas outside the APA to prevent contamination of the APA by adjacent areas.

22.3.21 **Processing Zones**

22.3.21.1 **Critical Processing Zones**
Critical processing zones shall be identified, and microbial and total particulate specifications shall be documented. These zones shall contain less than 3 500 particles of $\geq$ 0.5 um per cubic metre of air.

NOTE: This quality of air is commonly referred to as Class 100, Class M 3.5 or Class A/B in existing, commonly used national and international air quality standards.

All product contact and component sampling sites in the critical processing zone shall be monitored for environmental control during each operational shift.

22.3.21.2 **Other Processing Zones**

Other processing areas shall contain less than 350,000 particles of $\geq$ 0.5 um per cubic metre of air.

NOTE: This quality of air is commonly referred to as Class 10,000 Class M 5.5 or Class C in existing, commonly used national and international air quality standards.

22.3.21.3 **Non-sterile Support Areas**

Support areas shall contain less than 3,500,000 particles of $\geq$ 0.5 um per cubic metre of air.

NOTE: This quality of air is commonly referred to as Class 100,000, Class M 6.5 or Class D in existing, commonly used national and international air quality standards.

Personnel in support areas shall wear garments designed to minimize particulate generate, but these garments normally need not be sterile prior to use.

The disinfection and environmental monitoring of this area is less frequent than that utilized for the processing zones.

22.3.22 Temperature and humidity levels shall be specified, controlled and maintained to assure employee comfort while maintaining product attributes as this has a direct impact on aseptic techniques and the potential level of contamination.

These requirements should be met with a full complement of operational personnel and all equipment in operation.

22.4 AIR HANDLING SYSTEMS

The basic elements of environmental air systems and control programmes require proper design and control of the aseptic processing facilities including: relative humidity, room temperature, air velocity, HEPA filtration, laminar airflow, and room to room air balance.

22.4.1 Air quality and the monitoring of particulate matter (viable and non-viable) as a means to control physical and biological contamination in the manufacture of injectable products, is one part of the total system of control which should be designed to ensure compliance with the class limits as it applies to areas of manufacture and preparation of product and components. These include filtration though HEPA filters into clean rooms and suitable filtration into critical areas.

22.4.2 In the table below and at the end of this chapter are the basic environmental standards for various operations. These are arranged in classes.

ENVIRONMENTAL REQUIREMENTS FOR SPECIFIC OPERATIONS

OPERATIONS	WORK ZONE (CLASS)	CLEAN ROOM (CLASS)
Compounding and non-sterile filtration of bulk	-----	3
Preparation of containers and closures	-----	3
Washing, drying and depyrogenation of components	-----	3
Filling and sealing of products to be terminally sterilized.	2	3
Aseptic Fill	1/A	1/B
Aseptic Fill in form fill seal machine.	1/A	3
Aseptic addition to sterile manufactured product.	1/A	3

A filtered air supply should maintain a positive pressure relative to the surrounding areas of a lower grade under all operational conditions and should flush the area effectively. Adjacent areas of different grades should have a pressure difference of 15 pascals (guidance value).

22.4.3
It should be demonstrated that air-flow patterns do not present a contamination risk eg. that particles are distributed from a particle-generating person, operation, machine, etc. to a zone of higher product risk.

22.4.4 A warning system should be provided to indicate failure in the air supply. Indicators pressure differences should be fitted between areas where these differences are important. These pressure differences should be recorded regularly.

22.4.5 A determination of airflow patterns shall demonstrate that the airflow is appropriate to the process being performed and shall include investigations with the effects of turbulence which may interfere with the sweeping action of the air. These determinations shall be documented.

Airflow patterns, appropriate to the actual process being performed, should be tested for turbulence that would interfere with the sweeping action of the air.

22.4.6 **HEPA Filter Integrity**

Receipt of HEPA filters shall be accompanied by a supplier's certification that indicates the filter has an efficiency of 99.997% for the retention of 0.3 um or larger particles.

Upon installation, HEPA filters shall be integrity tested by a suitable method, e.g. cold DOP test.

Filters shall be velocity tested periodically, and airflow patterns shall be reassured whenever an airflow configuration change has been introduced. Tests shall be performed in the event of a change in the situation that might affect the integrity of the filter.

22.5 **SANITIZATION AND MONITORING**

22.5.1 Microbiological contamination should be controlled and monitored by appropriate procedures approved by Quality Control.

22.5.2 Cleanrooms and related areas should be cleaned frequently and thoroughly. Non-disposable "sticky mats" should be washed daily. Cleaning activities should be documented as per an approved procedure.

22.5.3 For Aseptic Processing where disinfection is employed to further reduce the surface contamination level, the choice of disinfectants and the way that they are used should be described in a procedure. In addition, detergents, disinfectants and antiseptics should be supplied sterile, or be sterile-filtered or otherwise sterilized at the use-dilution, or be sterilized as a concentrate and diluted only with sterile water. Diluted disinfectants or antiseptics should not be stored. Containers should not be topped up. Disinfectants/detergents used should be validated and approved. When disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly to detect the development of resistant strains. Disinfectants and detergents used in Class 1 and 2 areas should be sterilised prior to use.

22.5.4 Fogging should not be used as air contaminants are readily dissipated by natural or mechanical ventilation. Fumigation with humidified formaldehyde vapour may be employed to reduce microbiological contamination in places inaccessible to surface disinfection, however if fogging or fumigation is used, the process should be validated.

22.5.5 Cleanrooms and related areas should be monitored at planned intervals for airborne particulate contamination.

22.5.6 Cleanrooms and related areas should also be monitored at planned intervals for microbiological contamination using a combination of "settling plates", surface sampling and air sampling and the results obtained should be used to determine "warning", "action" and "shut-down" levels.

22.5.7 Gowning procedures should be proceduralized and monitored where aseptic filling procedures are practiced.

22.5.7.1 Written gowning procedures, training programmes, monitoring programmes and follow-up procedures shall be established.

At the time of entry into the gowning area, staff shall wear dedicated clothing (eg. plant uniform) and shoes.

Staff should enter the gowning area by way of an airlock.

NOTE: Generally, a mesh hair-net and beard cover, if required, are donned at the airlock. Disposable shoe covers may be used in addition to, or in place of, dedicated shoes.

Employees shall restrict movement in the APA in order to:

a) Avoid unnecessary movements which can generate particles or create turbulence;

b) Avoid reaching across open containers and exposed product and components;

c) Avoid blocking airflow over critical surfaces.

Employees shall regularly check gloves and gowns for proper fit and integrity. Gowned personnel should avoid unnecessary contact with walls, floors and cleaned surfaces with talking among personnel minimized.

Personnel conducting filling operations should not be exchanged during a shift with employees performing other functions within the APA. Operators working in non-sterile support areas shall not have access to the critical processing zone.

22.5.8 Monitoring should be frequent and should take place whilst normal production operations are in progress. In the case of aseptic filling it should provide the basis for the assessment of aseptic hygiene throughout the filling process. Results should be tabulated or graphed and assessed and prompt remedial action taken according to the monitoring standards established. Additional monitoring should be conducted after particular events such as spillages, cleaning, maintenance or fumigation.

22.5.9 Micro-organisms recovered from cleanrooms should be routinely identified, at least to genus level.

22.5.10 In a new unit, with a new process or with new operators, microbial monitoring should be sufficiently intensive to determine patterns and levels of contamination. Once suitable conditions have been established, monitoring may be reduced to a level which will demonstrate maintenance of those conditions.

22.5.11 There should be specific written procedures and documentation for:

- all cleaning and disinfecting of the APA
- Procedures shall include utilization of approved agents, the cleaning schedule, disinfectant application, post-disinfection cleaning if required, and employee safety precautions, including care and storage of cleaning aids. Only cleaning agents and disinfecting agents which have been tested, validated and approved, shall be used.
- the dismantling, cleaning and decontamination of all equipment.
- the cleaning of bulk containers and their subsequent inspection for release for use in processing.
- the control of external contamination of bulk containers during use.
- the assembly of filters and the connecting of hoses and pipelines.

22.5.12 Items brought into cleanrooms, including means of transport, should be of a standard of cleanliness compatible with the environmental standard for the room.
22.5.13 For Aseptic Processing when equipment maintenance or testing has been carried out within a Class 2 or cleaner area, and where the required standards of cleanliness and/or asepsis have not been maintained during this work, the area should be cleaned, and, where appropriate, disinfected and fumigated before processing recommences. This also applies to broth filling procedures which may contaminate the filling area.

22.5.14 The absence of disinfectant and cleaning agent residuals on product contact surfaces shall be confirmed. The manufacturers' instructions should be followed with respect to storage and use. Disinfectants shall be batched with a stated expiration date, and containers should not be refilled. Interchanging or rotating disinfectants should be reconsidered due to potential changes in environmental flora (isolates). A sporicidal agent may be necessary when environmental monitoring indicates the presence of sporeforming organisms, molds and fungi.

The effectiveness and frequency of the disinfection procedure shall be determined as part of the process validation. Evaluation of the efficacy of disinfectants should be related to the reduction of types and numbers of micro-organisms recovered from surfaces during routine environmental monitoring.

22.6 **PERSONNEL TRAINING**

22.6.1 Responsibility for monitoring the processing of sterile products should be delegated by management to a person competent through training and experience in the relevant aspects of microbiology, hygiene and the correct manufacture of sterile products. Only the minimum number of personnel required should be present in the clean area. Personnel involved with maintenance and cleaning should be trained prior to employment and supervised.

22.6.2 Personnel required to work in clean aseptic areas should be selected with care to ensure that they may be relied upon to observe the appropriate discipline and are not subject to any chronic disease or condition which would present an abnormal microbiological hazard to the product. The same principles should be applied to visitors to cleanrooms. Inspections and controls should be conducted from outside the area as far as possible.

22.6.3 All personnel (including those concerned with cleaning, testing and maintenance) should receive regular training in cleanroom procedures and in disciplines relevant to the correct manufacture of sterile products, including hygiene and the basic elements of microbiology.

22.6.4 When external staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their supervision.

22.6.5 Training should be carried out upon recruitment of staff and at regular, planned intervals in accordance with a formal training programme. Records, specific for each member of staff. should be maintained.

22.6.6 Personnel involved in the manufacture of sterile preparations should maintain high standards of personal hygiene and cleanliness and be instructed to report any condition (e.g. diarrhoea, coughs, colds, infected skin or hair, wounds) which may cause the shedding of abnormal numbers or types of contaminants. Actions to be taken about personnel who could be introducing undue microbiological hazard should be decided by designated competent person.

22.6.7 Clothing should be appropriate to the work zone environment in which the personnel will be working. In addition, the following requirements should be adhered to:

·bulky or fluffy personal clothing should be removed before aseptic or cleanroom garments are donned
·wristwatches and jewellery, other than a simple wedding ring should not be worn. Cosmetics which can shed particles should not be used
·beards and moustaches should be covered during the compounding of products
·persons engaged in aseptic processing should wear sterilized or disinfected footwear and should change garments at least every working session

·persons working in Class 2 rooms should wear a single- or two-piece trouser suit gathered at the wrists and with high neck. Headgear must totally enclose hair and beard and be of the helmet/cowl type, tucked into the neck of the suit. Footwear should totally enclose the feet, and trouser-bottoms should be tucked inside the footwear
·sterilize non powdered rubber or plastic gloves, when worn, should be disinfected regularly during operations using a suitable spray and changed at regular intervals or when damaged.

22.6.8 Outdoor clothing should not be brought into the changing rooms associated with clean or aseptic areas, and personnel entering these changing rooms should already be clad in standard factory protective garments. Changing and washing should follow a clearly displayed written procedure.

22.6.9 Clean and aseptic area clothing should be laundered or cleaned and thereafter handled in such a way that it does not gather contaminants which can later be shed. Separate laundry facilities for such clothing are desirable. It should be noted that some methods of sterilization may damage fibres and reduce effective garments. Washing and sterilization operations should follow a clearly displayed written procedure.

22.6.10 For each worker in a class 2 room, clean, sterile, protective garments should be provided at each work session.

22.7 MANUFACTURING REQUIREMENTS AND CONTROLS

22.7.1 Starting materials should be selected so as to contain only minimal quantities of micro-organisms or pyrogenic material. The material specification should include requirements for microbial monitoring. with limits as necessary.

22.7.2 Precautions should be taken during all processing stages, before and after sterilization to avoid contamination of the product with micro-organisms.

22.7.3 Activities and conversation in clean and aseptic areas should be kept to a minimum. Movements of personnel should be controlled and methodical, so as to avoid excessive shedding of particles and organisms due to over-vigorous activity and to avoid disruption of air flow patterns.

22.7.4 Containers and other materials liable to generate particles or fibres should not be taken into areas of Class 1 or Class 2.

22.7.5 The intervals between the washing and drying and the sterilization of components and equipment should be as short as possible and subject to a time limit appropriate to the storage conditions. The interval between sterilization and use of these materials should also be subject to a time limit.

22.7.6 Articles required in an aseptic area should be sterilized and passed into the area in such a way which will avoid contamination of the area.

22.7.7 The time between the start of the preparation of a solution and its sterilization (or sterile filtration) should be as short as possible and subject to a limit for each product that takes into account its composition and the prescribed method of storage.

22.7.8 Unless special storage precautions are taken, bulk solutions should have no greater volume than can be filled in one working day and should be filled into final containers and sterilized within one working day.

22.7.9 The microbiological load of products should be as low as practicable prior to sterilization eg. all solutions should be passed through a bacteria-retaining filter immediately before filling.

22.7.10 Each procedure used for the sterilization of a particular quantity or volume of a material, component, or product should have been demonstrated to be effective and reliable by suitable validation studies.

22.7.11 Batch processing records for sterile products should include details of the sterilization of the components and equipment used.

22.7.12 Water treatment plants should be designed, constructed, and maintained to ensure the reliable production of water of the required quality. They should not be operated beyond their designed capacity. The water should be produced, stored and distributed in such a manner as to discourage microbial growth (eg. by constant circulation at temperatures above 70°C, and avoidance of places where water may remain stagnant such as U-bends, 'dead ends' and ill-designed valves).

22.7.13 Water sources, water treatment equipment and treated water should be monitored regularly for chemical, microbial and pyrogen contamination as relevant. Records should be maintained of the results of the monitoring, and of any remedial action.

22.7.14 Unsterilized distilled water intended for further processing or sterilization should not stand for more than a short time unless special precautions are taken, such as storage above 65°C, to prevent both the growth of bacteria and the consequent development of pyrogens.

22.7.15 Where water or solutions are held in sealed vessels, any pressure relief outlets should be protected by hydrophobic microbial air filters.

22.7.16 Components and containers should be handled after the final cleaning process in such a way that they are not subject to recontamination. The final rinse should be with purified water of appropriate quality.

22.8 VALIDATION OF ASEPTIC PROCESS

22.8.1 Aseptic processing and filling equipment, used in aseptic work procedures and environments should be validated for their overall performance at the time of qualification and at regular intervals thereafter by test runs in which suitable sterilized agents which will not inhibit microbial growth are passed through the routine procedures up to the sealing of filled final containers. In the case of liquid processing the test agent should be soybean-casein digest medium and the filled sealed containers should be incubated for at least 14 days at 3$\pm$ 2 °C. When appropriate to the product, other media or temperatures may also be used. In the case of solid or semisolid processing, a process should be developed to imitate the filling operation as closely as possible. Full microbiological test controls should be carried out.

22.8.2 For each container type, at least 3 000 typical containers should be filled to the labelled quantity and sealed in an undivided test run. The test run should be carried out immediately after a regular production run and in "worse case" conditions. No growth should be observed in the incubated containers, but production may continue if not more than three containers show evidence of microbial growth after incubation (i.e. contamination rate of not more than 0,1 %).

22.8.3 Initial validation should employ at least three runs, which should not be continuous, but consideration should also be given to employing more than 3 000 units in subsequent runs in order to reach statistical significance in estimating the contamination rate.

22.8.4 Continuing validation should occur at least twice per year for each shift for each filling/sealing line. All personnel should take part in a media fill at least once per year. The duration of the run should be sufficient to cover all manipulations that are normally performed in actual processing at filling rates comparable to standard Production.

22.8.5 Medium should be made to contact the entire inside surface of the containers being filled at intervals during the incubation period, e.g. by swirling or tumbling. Media fertility and stasis tests should be carried out.

22.8.6 Consideration should be given to validating the ability of the medium used to grow micro-organisms recovered from environmental monitoring or from sterility testing.

22.8.7 When a new aseptic process is introduced, when any significant change is made in such a process or in the equipment, when staff are being trained and at regular intervals thereafter, the efficacy of

aseptic procedures should be validated, eg. by filling a sterile liquid nutrient medium or powder and testing for the incidence of contamination. Such fillings should be carried out under normal operating conditions.

22.8.8 Procedures shall be in place describing the operations of all critical equipment. The qualification of equipment generally includes calibration, installation qualification (IQ), operation qualification (OQ), and performance qualification (PQ).

22.8.9 Processing equipment such as sterilizers, component washers, filters, fillers, closure placement equipment, sealing machinery, and lyophilizers shall be qualified as part of the overall programme. Product contact surfaces shall be sterilized and process validated.

22.8.10 Process related utilities such as purified water, water-for-injection, pharmaceutical compressed air (and/or other gases), clean or water-for-injection steam, and clean-in-place/steam-in/place systems shall be validated.

22.8.11 The following measures should be addressed for steam-in-place systems:

a) displacement and elimination of entrapped air;
b) constant bleeds or steam traps at all low points to eliminate condensate buildup;
c) strict adherence to the steam-in-place procedures;
d) proper maintenance of the integrity of the system after the process;
e) strict adherence to the maximum filter specifications for temperature, pressure, and flow, and
f) avoidance of back pressure on filters during steam-in-place.

22.9 STERILIZATION PROCESSES

22.9.1 General

22.9.1.1 Sterilization can be affected by moist or dry heat, by ethylene oxide (or other suitable gaseous sterilizing agent), by filtration with subsequent aseptic filling into sterile final containers, or by irradiation with ionizing radiations (but not with ultraviolet radiation). Each method has its particular applications and limitations. Where possible and practicable, heat sterilization is the method of choice.

22.9.1.2 For effective sterilization, the whole of the material must be subjected to the required treatment, and the process must be designed and monitored to ensure that this is achieved.

22.9.1.3 Before any sterilization process is adopted, its suitability for the product and its efficacy in achieving the desired sterilizing conditions in all parts of each type of load to be processed should be confirmed. Such validation should be repeated at suitable scheduled intervals and whenever significant modifications have been made to the equipment. Records should be kept of the results.

22.9.1.4 Products which are intended to be sterile, should be preferably heat sterilized in final sealed containers. Each cycle of heat sterilization should be monitored by means of temperature probes to determine if the heat distribution in the sterilization vessel is uniform.

22.9.1.5 The charts of automatic recorders of cycle parameters should constitute part of the batch processing records of sterile products and should be marked to identify the batch or batches to which each applies.

22.9.1.6 Each separate sterilizing basket, package, pallet etc., of products or components undergoing sterilization should be fastened to ensure its integrity and should bear in a conspicuous position a visual indicator to demonstrate whether or not it has passed through a sterilization cycle.

22.9.1.7 To verify the continuing effectiveness of dry heat sterilizing cycles, suitable microbiological indicators of known high resistance to the dry heat sterilization process should be included in sterilizing cycles and placed at representative locations in typical loads. The indicators should be located in the most difficult-to-sterilize site within the sterilizer and, where appropriate, within the product.

22.9.2 **Moist Heat**

22.9.2.1 This method is suitable only for water-wettable materials and aqueous solutions. Other materials must be sterilized by other methods.
22.9.2.2 Moist heat sterilization is achieved by exposure to saturated steam under pressure in a suitably designed chamber. Under these conditions there is an exact relationship between steam temperature and pressure, but the pressure is used solely to obtain the temperature required and otherwise contributes nothing to the sterilization process. The temperature and not the pressure must be used to control and monitor the process.

22.9.2.3 Whilst temperatures and periods of treatment are recommended in official compendia, (eg.121 °C for 15 minutes), other combinations of temperature and time can be used provided they have been validated. It is important to recognize that the temperature-time relationship is complex, that at temperatures below 115 °C disproportionately long periods of time are required, and that as temperature is reduced, the process may become progressively less reliable.

22.9.2.4 Items to be sterilized (other than aqueous medicinal products in sealed containers) should be wrapped in a material which allows removal of air and prevents penetration by micro-organisms after sterilization. All parts of the load should be in contact with water or saturated steam at the required temperature for the required time.

22.9.2.5 Unless special precautions are taken, air must be displaced from the chamber, and from materials within the chamber, either by a period of free steaming before the sterilization cycle begins or by use of a vacuum pump.

22.9.2.6 Mixtures of steam with air may be used for sterilizing sealed containers of aqueous fluids provided that steps are taken to ensure homogeneity of the steam-air mixture throughout the chamber, and the process has been validated.

22.9.2.7 Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time-period is commenced. This time must be determined for each type of load to be processed before the method is adopted.

22.9.2.8 Care should be taken to ensure that steam used for sterilization is of suitable quality and does not contain additives at a level which could cause contamination of product or equipment.

22.9.3 **Dry Heat**

22.9.3.1 Dry heat is suitable for sterilizing equipment, non-aqueous liquids and other materials which can withstand the temperatures required. Various combinations of temperature and time are recommended in official compendia but other combinations of temperature and time can be used provided they have been validated.

22.9.3.2 Heating should be carried out in an oven or other equipment which will achieve sterilizing conditions throughout the load. The method of loading used should not be such as to lead to an uneven temperature distribution.

22.9.3.3 Before the timed sterilization period begins, sufficient time must be allowed for the temperature of the whole load to reach the requisite level. This time should be determined for each type of load to be processed, and the timed sterilization period should not start until the entire load is known to have reached that level .

22.9.4 **Filtration Sterilization**

22.9.4.1 Sterilization by filtration should only be employed when heat sterilization cannot be applied because of its detrimental effect on the active ingredients.

22.9.4.2 Solutions or liquids can be sterilized by filtration through a sterile filter of nominal pore size of 0,22 micron (or less), or with at least equivalent micro-organism retaining properties, into a previously sterilized container. Such filters can remove bacteria and moulds but not all viruses or mycoplasmas.

22.9.4.3 The integrity of the filter assembly should be checked by an appropriate method, such as a bubble-point pressure test or forward-flow pressure test immediately before and after use. Abnormal filtration flow-rates should be noted and investigated. Results of these filter-integrity checks should be recorded in the batch record.

22.9.4.4 Any potentially fibre or particle releasing filter should be followed by a downstream non-fibre releasing filter that will retain such particles.

22.9.4.5 If it is intended to use a filter for an extended period, the effectiveness of the process should be validated, taking into account such aspects as the microbial content of the solution, the capacity and efficacy of the filter and its housing, and the potential for growth of organisms on or through the filter. It is preferable not to use the filter for longer than one working day.

22.9.4.6 Due to the potential additional risks of the filtration method as compared with other sterilization processes, a second filtration via a further sterilized micro-organism retaining filter, immediately prior to filling, may be advisable.

22.9.4.7 The time interval between sterilizing a bulk solution by filtration and filling it into final containers should be kept to a defined minimum, appropriate to the conditions under which the filtered bulk is stored.

22.9.4.8 Filters should not adversely affect the quality or content of solutions by removal of ingredients from them or by release of substances into them. Asbestos filter pads should not be used for filtration of parenteral products. Filters should be treated as starting materials and subjected to quality control. Filters must be sterilized when aseptic filling is carried out.

22.9.4.9 Any new or modified filtration system for sterilization should be validated for integrity before it is placed in service and a record of such validation kept. Only positive pressure filtration should be employed.

22.9.4.10 Where the bulk batch is divided into lots for different sterilization or lyophilisation cycles, all such lots should be distinguishable from one another, by label and in the records.

22.9.5 Biological Indicators

22.9.5.1 Biological and chemical indicators used alone are not acceptable as proof of sterility.

22.9.5.2 Biological indicators (i.e. preparations of bacterial cultures, usually spores of selected resistant strains) are much less reliable than physical monitoring methods (except in ethylene oxide sterilization).

22.9.5.3 Strict precautions must be taken when handling biological indicators due to the hazard of introducing potential contaminants into an otherwise microbiologically clean area.

22.9.5.4 Microbiological indicators should be treated as starting materials and subjected to quality control.

22.9.6 Chemical Indicators

22.9.6.1 Chemical indicators are available for heat, ethylene oxide and radiation sterilization, usually in the form of adhesive tapes or patches, colour spot cards, small tubes or sachets. They change colour as a result of chemical reaction brought about by the sterilization process, but it is possible for the change to take place before the sterilizing time has been completed, and hence, with the exception of plastic dosimeters used in radiation sterilization, they are unsuitable as proof of sterilization.

22.9.6.2 Certain other substances with melting points which coincide with the sterilization temperature may be used as indicators in heat sterilization. They indicate that the temperature has been reached, but not that it has been maintained, or for how long.

22.9.6.3 Radiation-sensitive colour discs, not to be confused with plastic dosimeters, are used to differentiate between packages which have been subjected to irradiation and those which have not. They are not indicators of successful sterilization, and the monitoring of radiation sterilization by calibrated plastic dosimeters is the only way of ensuring that the sterilizing dose has been given.

22.9.7 **Ethylene oxide**

22.9.7.1 This method should only be used when no other method is practicable. During process validation it should be shown that there is no damaging effect on the product and that the conditions and time allowed for degassing are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material.

22.9.7.2 Direct contact between gas and microbial cells is essential: precautions should be taken to avoid the presence of organisms likely to be enclosed in material such as crystals or dried protein. The nature and quantity of the packaging materials can significantly affect the process.

22.9.7.3 Before exposure to the gas, the material should be brought into equilibrium with the humidity and temperature required by the process. The time required for this should be balanced against opposing need to minimise the time before sterilization.

22.9.7.4 Each sterilization cycle should be monitored with suitable biological indicators appropriately distributed through the load. The information so obtained should form part of the batch record.

22.9.7.5 Records should be obtained of the time taken to complete the cycle, the pressure, temperature and humidity within the chamber during the process, the gas concentration and total amount of gas used. The pressure and temperature recorded during the cycle should form part of the batch record.

22.9.7.6 After sterilization, the load should be stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to be reduced to defined validated levels.

22.9.8 **Radiation**

22.9.8.1 Radiation sterilization is used mainly for sterilization of heat sensitive materials and products.

22.9.8.2 During the sterilization procedure the radiation dose should be measured. For this purpose dosimetry indicators which are independent of dose rate should be used, giving a quantitative measurement of the dose received by the product itself. Dosimeter absorbance should be read within a short period after exposure to radiation.

22.9.8.3 The total radiation dose should be administered within a predetermined time span.

22.9.9 **Air Removal**

The removal of air from a steam-in-place system may be accomplished by one of two methods:

a) by gravity
b) through the use of vacuum

22.9.10 **Condensate Removal**

Condensate should be continuously removed from all low points to maintain sterilization conditions in the system.

22.9.11 **Post-sterilization system integrity**

System integrity shall be maintained after sterilization. The system should then be purged of steam and condensate and maintained under positive pressure until ready for use.

NOTE 15: The introduction of gas can dry the system prior to use, which is very important if the product to be processed is non-aqueous.

22.9.12 **Depyrogenation**

Data should be available that demonstrates a knowledge of the (or endotoxin) loading on components prior to treatment in a depyrogenation process. When a depyrogenation process is used, the data shall demonstrate that the process will remove a greater quantity of endotoxin than may have been originally present in the component or product.

NOTE: Plastic medical devices and/or containers may be depyrogenated by rinse processes, and/or high temperature moulding, and/or extrusion processes prior to filling. Rubber compound stoppers may be rendered pyrogen-free by multiple cycles of washing and rinsing prior to final steam sterilization. The final rinse should be water-for-injection quality.

22.9.13 **Gases**

Compressed air shall be dry and oil-free. All compressed gases that contact products, container/closures or product contact surfaces shall be filter sterilized.

22.9.14 **Processing Time**

The total time for the product filtration and filling operations, and holding time after filtration and prior to filling, shall be limited to a defined maximum. Elapsed time between component washing and sterilizing should be minimized.

22.9.15 **Sampling**

All product contact and component sampling sites in the critical processing zone shall be monitored for environmental control during each operational shift. If the environmental control programme indicates that specified limits are exceeded, corrective action shall be taken in accordance with written procedures.

Other processing zones shall be monitored frequently, with sampling frequency based on classification of the zones and testing data.

Sampling in critical processing zones shall be performed in a manner which presents a minimal contamination risk to the product.

Support areas shall be routinely monitored, but may be monitored on a less frequent basis than processing zones.

22.9.15.1 **Sampling Sites**

Sampling sites should be derived from and consistent with those used during validation activities. The individual sampling sites for each programme should be at the discretion of the manufacturer reflecting differences in facility/equipment design and processing parameters.

22.10 **QUALITY CONTROL**

22.10.1 **Sterility Testing**

22.10.1.1 A test for sterility must be carried out on samples from each batch of sterile products except for products for which approval to omit the test for sterility has been specifically granted by the inspecting authority.

22.10.1.2 Where a batch of product is sterilized as a series of lots, each of which is subjected to a separate sterilizing cycle or is subjected in processing to different treatment which may affect its sterility, eg. different lyophilisation cycles, each lot should be tested for sterility.

22.10.1.3 Samples for the test of sterility should be taken:

· in the case of aseptically prepared products, at regular intervals during the filling operation so as to be representative of the whole of the batch or filling session. In particular the samples should include containers filled at the beginning and end of the batch and after any significant interruption of work. Resampling for retesting must follow the same principle. Where possible, the first and last units filled should be part of the initial sample from all prescribed locations and at all prescribed times . These should be divided between test samples and retention samples.

·records should be kept of the results of all sterility tests and control tests. Contamination rates for different products and for different sterility test techniques should be calculated periodically and compared, and their significance assessed.

· for products which have been heat sterilized in their final containers, consideration should be given to taking samples from the potentially coolest part of the load.

22.10.2 **Pyrogen Testing**

22.10.2.1 The water used in the preparation of sterile products should be tested for pyrogens at least once per week and after any repair or disturbance to the system, using, for example the limulus amoebocyte lysate test. Sampling should include "worst case" situations, including start-up. Water for injection stored below 65 °C should be tested at least twice weekly for microbial and pyrogen contamination.

22.10.2.2 Appropriate samples for pyrogen testing should include those taken from the first units filled, the last units filled, the first units filled immediately following a break in the filling line (eg. a filter change) and the first units filled following prolonged downtime periods, i.e. one hour or more.

22.10.3 **Media Fills**

Media filling in conjunction with comprehensive environmental monitoring of the aseptic area can be particularly valuable in evaluating the aseptic processing of sterile products. The media fill should simulate the aseptic process as far as reasonably practical.

Scheduled media fill requalifications shall occur at least every six months for each aseptic process and filling line. The media fill run shall be of sufficient duration to cover all manipulations normally performed in actual processing. Media fill evaluations shall be incubated for at least 14 days at temperature ranges of 20-25 and 30-35. Requalification acceptance criteria shall meet the number of runs and total filled units which is summarized as follows:

a) For production batch sizes of less than 500 units, 3 media fill runs of the maximum batch size shall be conducted.

b) Alternatively, for small production batch sizes where infrequent batches (less than 4 per year) are filled, or for clinical batches, it shall be acceptable to requalify the process of line by performing a single media fill run, containing a quantity of units at least equal to the production batch, immediately after the production batch is filled.

c) For production batch sizes between 500 and 2,999 units 1 media fill run of at least the maximum batch size shall be conducted.

d) For production batch sizes greater than 3 000 units, 1 media fill run of at least 3 000 units shall be conducted.

Guidance values for microbiological monitoring of clean rooms in operation

	Maximum number of viable organisms (a)			
GRADE	air sample cfu/m^3	settle place (90mm) cfu/4 hour	contact place (55mm) cfu	glove print 5 fingers cfu
A	< 1 (b)	< 1 (b)	< 1 (b)	<1 (b)
B	10	5	5	5
C	100	50 (c)	25	-
D	200	100 (c)	50	-

Notes:

(a) Recommended limits for contamination may be exceeded on isolated occasion and require only an examination of the production conditions and the control system. If the frequency is high or shows an upward trend then action should be taken.

(b) Low values involved here are only reliable when a large number of samples is taken.

(c) For Grades C and D settle plates may be exposed for less than 4 hours.

Grade	Examples of operations
A	Aseptic preparation and filling. Filling of products to be terminally sterilized when products are unusually at risk.
B	Transfer and storage of containers of freeze-dried products and components for aseptic filling.
C	Preparation of solutions and components for subsequent sterile filtration and aseptic filling. Preparation of solutions and components for subsequent filling and terminal sterilization when products or components are considerably exposed or unusually at risk. Filling of products to be terminally sterilized.
D	Preparation of solutions and components for subsequent filling and terminal sterilization.

22.11 FINISHING OF STERILE PRODUCTS

22.11.1 Ampoules should be sealed by a "drawing-off" technique rather than by tip-sealing.

22.11.2 Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined delay.

22.11.3 Filled containers of parenteral products for administration to humans should be inspected individually. When this inspection is visual it should be done under suitable controlled conditions of illumination and background. Operators doing the inspection should pass regular eye-sight checks, with spectacles if worn, and be allowed adequate breaks from inspection.

22.11.4 Where automatic/electronic/photo-electric methods of inspection are used, the effectiveness of the equipment should be validated and its sensitivity monitored.
22.11.5 Tests to demonstrate the integrity of seals of closures on product containers should be carried out during the production of each batch. These results should form part of the batch processing records.

22.11.6 Wherever the nature of the product makes it possible, every filled and sealed container of parenteral product should be tested for physical defects and for particulate contamination.

22.11.7 It is appropriate to monitor and control the microbiological content of the water and other materials used in the leak test procedure.

22.12 BATCH RELEASE

22.12.1 The decision to release a batch of sterile product for use should take account of not only the specific production records and results of tests performed on that batch, but also the cumulative test records and information gathered from the monitoring of the environment, personnel, intermediate products, equipment and processes, both before and during the manufacturing of the batch.

CHAPTER 23

ISOLATOR TECHNOLOGY

23.1 PRINCIPLES

23.1.1 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.

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

23.2 DEFINITION OF TERMS

23.2.1 Isolator

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

23.2.2 Type 1 Isolator

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

23.2.3 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.

23.2.4 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.

23.2.5 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.

23.2.6 Background Environment

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

23.2.7 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.

23.2.8 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.

23.2.9 Decontamination

A process which reduces contaminating substances to a de-defined acceptance level.

23.2.9.1 Sanitisation

That part of decontamination which reduces viable micro-organisms.

23.2.9.2 Particulate Decontamination

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

23.2.9.3 Chemical Decontamination

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

23.2.10 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.

23.2.11 Exhaust Filter

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

23.2.12 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.

23.2.13 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'.

23.2.14 Sterilisation

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

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

23.2.16 Transfer Hatch

See Transfer Chamber.

23.2.17 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.

23.2.18 Transfer Device

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

23.2 19 Transfer Port

See transfer chamber.

23.2.20 Transfer System

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

23.2.21 Turbulent Flow

A flow of air which is non-laminar.

23.3 ISOLATOR DESIGN PRINCIPLES

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

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

23.3.2 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).

23.3.3 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.

23.3.4 Type 2 isolators should operate under negative pressure.

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

23.3.6 For operator protection, in the event of a breach in type 2 isolators a minimum breach velocity of O,7m sec- should be maintained.

23.3.7 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.

23.3.8 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.

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

23.3.10 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.

23.3.11 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.)

23.3.12 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),

23.3.13 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.

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

23.3.15 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.

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

23.3.17 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.

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

23.4 THE SITING OF ISOLATORS

23.4.1 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.

23.4.2 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 I/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).

23.4.3 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.

23.4.4 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.

23.5 FACTORY ACCEPTANCE TEST (FAT)

23.5.1 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.

23.6 INSTALLATION QUALIFICATION (IQ)

23.6.1 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.

23.7 OPERATIONAL QUALIFICATION (OQ)

23.7.1 Operational qualification (OQ) should be performed.

23.7.2 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.

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

23.7.4 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.

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

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

23.8 PERFORMANCE QUALIFICATION (PQ)

23.8.1 Performance qualification (PQ) should be performed.

23.8.2 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

23.9.1 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:

23.9.2 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.

23.9.3 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.

23.9.4 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

23.9.6 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.

23.10 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.

23.10.1 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.

23.10.2 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.

23.10.3 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).

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

23.11 GAS STERILISATION OF ISOLATOR SYSTEMS

23.11.1 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.

23.11.2 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.

23.11.3 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.

23.11.4 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.

23.11.5 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.

23.11.6 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.

TABLE 3

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				

CHAPTER 24

AEROSOLS & METERED DOSE INHALERS

24.1 PRINCIPLE

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.

24.2 GENERAL

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

24.2.1.1 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.

24.2.1.2 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.

24.3 PREMISES AND EQUIPMENT

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

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

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

24.4 PRODUCTION AND QUALITY CONTROL

24.4.1 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.

24.4.2 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.

24.4.3 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.

24.4.4 Precautions should be taken to ensure uniformity of suspensions at the point of fill throughout the filling process.

24.4.5 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.

24.4.6 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.

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MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

ADDENDUM 6

DISSOLUTION TESTING

This document has been prepared to serve as a recommendation to applicants wishing to submit applications for registration of medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request for any additional information to establish the safety, quality and efficacy of a medicine and may make amendments in keeping with the knowledge which is current at the time of consideration of data accompanying applications for registration of medicines. Alternative approaches may be used but these must be scientifically and technically justified. The MCC is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy. It is important for applicants to adhere to the administrative requirements to avoid delays in the processing of applications.

Guidelines and application forms are available from the office of the Registrar of Medicines.

REGISTRAR OF MEDICINES
MS M.P. MATSOSO
DATE: 29/4/2003

DISSOLUTION TESTING

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DISSOLUTION TESTING

1. INTRODUCTION

This guideline describes the setting of dissolution specifications as a quality control requirement and also describes how to conduct dissolution testing in support of a request for a waiver for bioequivalence testing.

Although intrinsic dissolution of the active pharmaceutical ingredient (API) is an important consideration when formulating solid oral dosage forms, the dissolution behaviour of solid oral dosage forms provides important information to ensure drug product quality. Hence, dissolution testing has been established as an extremely valuable tool to monitor batch-to-batch consistency and the primary utility of a dissolution test is therefore to establish dissolution specifications for relevant drug products for the purposes of quality assurance.

Dissolution testing can also be useful in providing information on drug product quality following certain post-approval changes made to the product, such as changes in formulation, manufacturing process, site of manufacture and the scale-up of the manufacturing process. The various classes of changes where dissolution can be used in support of a bio-waiver are described in the MCC's document on major and minor changes.

In addition, where solid oral dosage forms have been proportionally formulated in different strengths and the drug follows linear kinetics, dissolution data can be used in support of a bio-waiver for lower strengths of such dosage forms provided an acceptable bioequivalence study has been carried out on one strength, usually the highest strength.

Drug absorption from oral dosage forms depends on adequate release of the active pharmaceutical ingredient (API) from the product. Physico-chemical factors such as dissolution or solubility of the drug under physiologic conditions and its permeability through the membranes of the gastrointestinal tract play pivotal roles in this respect. Due to the critical nature of these factors, dissolution of a drug product *in vitro* can, in certain instances, be relevant to anticipate the *in vivo* performance.

2. SETTING DISSOLUTION SPECIFICATIONS FOR IMMEDIATE RELEASE SOLID ORAL DOSAGE FORMS

2.1 Objectives

i. To provide general recommendations for dissolution testing and setting dissolution specifications for quality control.

ii. To obtain information on test batches used in bioavailability/ bioeqivalence studies and pivotal clinical studies to support specifications for quality control.

iii. To be used as a tool in quality control to demonstrate batch-to-batch and lot-to-lot consistency during manufacture.

2.2 Dissolution Specifications

Primarily, *in vitro* dissolution specifications are used to ensure batch-to-batch consistency and to indicate potential problems of bioavailability.

i. For new drug products, dissolution specifications must be based on data obtained from acceptable clinical, pivotal bioavailability, and/or bioequivalence batches.

ii. In the case of multi-source pharmaceutical products the dissolution specifications are generally the same as the reference product.

These specifications should be confirmed by comparison of the dissolution performance of the multi-source pharmaceutical product and reference product from an acceptable bioequivalence study.

If the dissolution performance of the multi-source pharmaceutical product is substantially different from that of the reference product and the *in vivo* data remain acceptable, a different dissolution specification for the multi-source pharmaceutical product may be set.

iii. Once dissolution specifications are set, the drug product should comply with those specifications throughout its shelf life.

Setting dissolution specifications for multi-source pharmaceutical products may be classified in three categories as described below.

2.2.1 Drug Product Dissolution Test Available in an Acceptable Pharmacopoeia

In this instance the quality control dissolution test should be the test described in the BP, USP or EP. Use of any other pharmacopoeia must be justified and acceptable to the MCC.

It is recommended that a dissolution profile be generated by taking samples at 15-minute intervals or less using the specified pharmacopoeial method for test and reference products (12 units each).

Additional dissolution data may also be required when scientifically justified e.g. when the pharmacopoeia does not specify a dissolution test for all API's in a combination product.

2.2.2 Pharmacopoeial Drug Dissolution Test Not Available

Comparative dissolution testing using test and reference products under a variety of test conditions is recommended.

The test conditions may include different dissolution media (pH 1 to 6.8), addition of surfactant, or use of an official basket or paddle apparatus with varying agitation.

In all cases, profiles should be generated as previously recommended.

The dissolution specifications should be set based on available bioequivalence and other data. In addition, the method used must be justified and validated.

2.2.3 Special Cases.

For poorly water soluble drug products (e.g. glyburide), dissolution testing at more than one time point, and preferably a dissolution profile, is recommended for quality control purposes. Alternatively, the use of the USP apparatus 4 (Flow-Through Method) should be considered for the development of dissolution specifications for such products.

3 *IN VITRO* DISSOLUTION TESTING IN SUPPORT OF A BIO-WAIVER (Bioequivalence Surrogate Inference)

3.1 Immediate Release Drug Products with Class 1 API's

3.1.1 Objectives

To provide recommendations for requesting a waiver of *in vivo* bioequivalence studies for immediate release (IR) solid oral dosage forms where the API is classified as Class 1 according to the Biopharmaceutics Classification System (Reference 1).

3.1.2 Classification Criteria

In the Biopharmaceutics Classification System (BCS) an API is classified as having high or low solubility and high or low permeability.

i. An API is considered to be *highly soluble* when the highest dose strength is soluble in ≤250mL of aqueous buffer over the pH range of 1.0 to 8.0.

ii. An API is considered to be *highly permeable* when the extent of absorption in humans is determined to be greater than 90% of an administered dose in the absence of documented instability in the gastrointestinal tract, or whose high permeability has been determined experimentally (Reference 1) and reported in the literature.

According to the BCS, a Class 1 API is both *highly soluble* and *highly permeable*.

An immediate release (IR) dosage form can be classified as either rapidly or slowly dissolving and is considered *rapidly dissolving* when not less than 85% of the label amount of the API dissolves within 30 minutes using USP Apparatus 1 at 100rpm (or Apparatus 2 at 50rpm) in a volume of 900mL, or less, in each of the following three media:

- acidic media such as 0.1N HCl
- pH 4.5 buffer
- pH 6.8 buffer

3.1.3 Requirements for Bio-Waivers for Immediate Release Drug Products

When an immediate release drug product is *rapidly dissolving* and contains a Class 1 API i.e. the API is both *highly soluble* and *highly permeable,* a bio-waiver for the multi-source product may be granted on the basis of acceptable dissolution data.

Dissolution should be greater than 85% in 30 minutes in each of the following three media:

- acidic media such as 0.1N HCl
- pH 4.5 buffer
- pH 6.8 buffer

3.2 Proportionally Similar Dosage Forms

When a bio-waiver is requested for lower strengths of drug products which are proportionally formulated (see Guideline for Bioavailability and Bioequivalence....), the following dissolution testing is required:

i. Dissolution of test and reference products should be conducted in each of the following three media:
   - acidic media such as 0.1N HCl
   - pH 4.5 buffer
   - pH 6.8 buffer

ii. Dissolution profiles of test and reference products should be compared as described below for each of the three media.

   Similarity in dissolution profiles must be assessed using f_1 and f_2 but only f_2 data will be used as the acceptance criterion.

   An f_2 value $\geq$ 50 indicates sufficiently similar dissolution profiles such that further *in vivo* studies are not necessary.

iii. When both the test and reference products dissolve to the extent of 85% or more of the label amount in □15 minutes in all three dissolution media recommended above, comparison of test and reference dissolution profiles are not necessary.

iv. Dissolution data in support of bio-waivers for higher strength proportionally similar dosage forms will not normally be considered. However, is a successful biostudy was carried out on a lower strength for reasons of safety (see Guideline for Bioavailability and Bioequivalence....), then dissolution testing on higher strengths will be considered.

3.3 Comparison of a Foreign Reference Product with a Reference Product Registered and Marketed in South Africa

As an interim measure, bioequivalence studies submitted where a foreign reference product has been used will require comparative dissolution profiles between the foreign product and the innovator product marketed in South Africa.

i. Dissolution of test and reference products should be conducted in each of the following three media:
   - acidic media such as 0.1N HCl
   - pH 4.5 buffer

- pH 6.8 buffer

ii. Dissolution profiles of test and reference products should be compared as described in section 3.4 for each of the three media.

Similarity in dissolution profiles must be assessed using f_1 and f_2 but only f_2 data will be used as the acceptance criterion.

An f_2 value ≥50 indicates sufficiently similar dissolution profiles such that further *in vivo* studies are not necessary.

iii. When both the test and reference products dissolve to the extent of 85% or more of the label amount in □15 minutes in all three dissolution media recommended above, comparison of test and reference dissolution profiles are not necessary.

3.4 Comparison of Dissolution Profiles

A dissolution profile comparison may be carried out using a simple model independent approach to assess overall profile similarity as well as similarity or differences at each dissolution sample time point.

This approach uses a difference factor (f_1) and a similarity factor (f_2) to compare dissolution profiles (Reference 2). The difference factor (f_1) calculates the (%) difference between the two curves at each time point and is a measurement of the relative error between the two curves:

$$f_1 = \{[\Sigma_{t=1}^{n} |R_t - T_t|] / [\Sigma_{t=1}^{n} R_t]\}. 100$$

Where *n* is the number of time points, R_t is the dissolution value of the reference batch at time t, and T_t is the dissolution value of the test batch at time t.
The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves.

$$f_2 = 50. \log\{[1+ (1/n)\Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5}.100\}$$

A specific procedure to determine difference and similarity factor is as follows:

1. Determine the dissolution profile of two products (12 units each) of the test and reference products.

2. Using the mean dissolution values from both curves at each time interval, calculate the difference factor (f_1) and similarity factor (f_2) using the above equations.

3. For curves to be considered similar, f_1 values should be close to 0, and f_2 values should be close to 100. Generally, the f_1 values up to 15 (0 – 15) and f_2 values greater than 50 (50 – 100) ensure sameness or equivalence of the two curves and, thus, of the performance of the test and reference products.

This model independent method is most suitable for dissolution profile comparison when three to four or more dissolution time points are available. The following recommendations should also be considered:

1. The dissolution measurements of the test and reference batches should be made under exactly the same conditions. The dissolution time points for both profiles should be the same (e.g., 15, 30, 45, 60 minutes).

2. Only one measurement should be considered after 85% dissolution of both the products.

3. To allow use of mean data, the percent coefficient of variation at the earlier time points (e.g., 15 minutes) should not be more than 20%, and at other time points should not be more than 10%.

4 Dissolution Testing Requirements For Minor And Major Amendments To The Formulation Of Pharmaceutical Products And Related Manufacturing Procedures Including Their Site Of Manufacture.

When amendments are made to pharmaceutical products, manufacturing procedures and other associated processes including change of site their impact on quality must be demonstrated. The following describes the use of dissolution testing as an indicator of quality which may be applicable as describe below.

The following dissolution tests are recommended:

DISSOLUTION TESTING

4.1 Types of Dissolution Test

4.1.1 Case A Dissolution Testing

Dissolution testing should be conducted as a release test according to the original submission or in accordance with compendial requirements for that product.

4.1.2 Case B Dissolution Testing

Dissolution testing should be conducted as a multi-point test in the application/ compendial medium at 15, 30, 45, 60 and 120 minutes or until an asymptote is reached for the proposed and currently registered formulation.

4.1.3 Case C Dissolution Testing

Dissolution testing should be conducted as a multi-point test in water, 0.1N HCl and buffer at pH=4.5 and 6.8 for the proposed and currently registered formulations at 15, 30, 45, 60 and 120 minutes or until either 90% of drug from the drug product is dissolved or an asymptote is reached. In the case of poorly soluble drugs, comparisons can be made using alternative compendial methods and media that have been appropriately justified.

4.2 Types of Changes

4.2.1 Minor Changes

In the event that the minor change made is such that there is unlikely to be an effect on the quality and performance of a dosage form then Case A dissolution testing is appropriate.

4.2.2 Intermediate Changes

In the event that the changes made may have a significant impact on the quality and performance of a dosage form then Case B dissolution testing is appropriate. However if the change is made to a product containing a BCS class 1 compound then 85% must be dissolved in 15 minutes in the media used in the application or compendial requirements.

For low permeability, high solubility drugs, dissolution profiles should be generated in the application/compendial medium as previously described for Case B dissolution testing. For high permeability, low solubility compounds, multi-point dissolution profiles should be carried out according to Case C dissolution testing.

Profiles of the currently used product and the proposed product should be proven similar according to the f_2 requirements as describe in this Guideline.

4.2.3 **Major Changes**

In the case of changes that are highly likely to have a significant impact on formulation quality and performance, *in vivo* bioequivalence testing must be conducted. Case B or Case C dissolution testing may also be required. Biowavers may be considered if a proven *in vitro-in vivo* correlation (IVIVC) has been shown.

5. REFERENCES

1. Guidance for Industry. Waiver of In-Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), August 2000.

2. Mathematical Comparison of Dissolution Profiles. Pharm. Technol. 20:6 (1996) 64-74, J.W. Moore and H.H.Flanner.

MEDICINES CONTROL COUNCIL

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ADDENDUM 5

BIOAVAILABILITY AND BIOEQUIVALENCE DATA REQUIRED AS PROOF OF EFFICACY

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REGISTRAR OF MEDICINES
MS M.P. MATSOSO
DATE: 29/4/2003

BIOAVAILABILITY/BIOEQUIVALENCE

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1. INTRODUCTION

Adequate evidence/proof of efficacy and safety for all multisource products in the form of appropriate *in vivo* bioequivalence studies must be submitted with each application for the registration of a medicine.

To exert an optimal therapeutic action an active moiety should be delivered to its site of action in an effective concentration for the desired period. To allow reliable prediction of the therapeutic effect the performance of the dosage form containing the active substance should be well characterised.

Comparison of therapeutic performances of two pharmaceutical products containing the same active substance is a critical means of assessing the possibility of using either the innovator or a multi-source (generic) pharmaceutical product. Assuming that in the same subject a similar plasma drug concentration time course will result in similar drug concentrations at the site of action and thus in a similar effect, pharmacokinetic data instead of therapeutic results may be used to establish bioequivalence.

The objectives of this guideline are to:

i. Define when bioavailability or bioequivalence data will be required in order to prove safety and efficacy.

ii. Provide guidance on the design and conduct of studies and the evaluation of data.

iii. Provide guidance when *in vitro* instead of *in vivo* data may be used.

iv. Provide guidance when suitably validated pharmacodynamic methods can be used to demonstrate bioequivalence.

For pharmaceutical products where the active ingredient is not intended to be delivered into the general circulation, the common systemic bioavailability approach cannot be applied. Under these conditions availability (local) may be assessed by quantitative measurements which appropriately reflect the presence of the active ingredient at the site of action.

2 DEFINITIONS

2.1 Active Pharmaceutical Ingredient (API)

A substance or compound used or intended to be used in the manufacture of a pharmaceutical product and which is expected to have a medicinal or pharmacological effect when administered.

2.2 Pharmaceutical Product

Any preparation for human or veterinary use containing one or more active pharmaceutical ingredients with or without pharmaceutical excipients or additives that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

2.3 Pharmaceutical Equivalence

Pharmaceutical products are pharmaceutically equivalent if they contain the same amount of the same active pharmaceutical ingredient(s) in the same dosage form, if they meet the same or comparable standards and if they are intended to be administered by the same route.

Pharmaceutical equivalence does not necessarily imply bioequivalence as differences in the excipients and/or the manufacturing process can lead to differences in the product performance.

2.4 Therapeutic Equivalence

Two pharmaceutical products are therapeutically equivalent if they are pharmaceutically equivalent and, after administration in the same molar dose, their effects with respect to both efficacy and safety are essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical or *in vitro* studies.

2.5 Bioavailability

Bioavailability refers to the rate and extent to which the active pharmaceutical ingredient, or its active moiety, is absorbed from a pharmaceutical product and becomes available at the site of action.

It may be useful to distinguish between the "absolute bioavailability" of a given dosage form as compared with that (100%) following intravenous administration (e.g. oral solution *vs.* iv.), and the "relative bioavailability" as compared with another form administered by the same or another non-intravenous route (e.g. tablets vs. oral solution).

2.6 Bioequivalence

Bioequivalence is defined as the absence of a significant difference in the bioavailability between two pharmaceutically equivalent products under similar conditions in an appropriately designed study.

Comparative studies using clinical or pharmacodynamic end points may be used to demonstrate bioequivalence.

2.7 Pharmaceutical Dosage Form

A pharmaceutical dosage form is a pharmaceutical product formulated to produce a specific physical form (e.g. tablet, capsule, solution etc.) suitable for administration to human and animal subjects.

2.8 Multi-Source (Generic) Pharmaceutical Product

Multi-source pharmaceutical products are pharmaceutically equivalent products that may or may not be therapeutically equivalent.

2.9 Proportionally Similar Dosage Forms/Products

Pharmaceutical products are considered proportionally similar in the following cases:

i. When all active pharmaceutical ingredients and inactive components are in exactly the same proportion between different strengths (e.g. a 100mg strength tablet has all active and inactive pharmaceutical ingredients exactly half of a 200mg strength tablet and twice that of a 50mg strength tablet).

ii. When the active and inactive ingredients are not in exactly the same proportion but the ratios of inactive pharmaceutical ingredients to the total weight of the dosage form are within the limits defined by the Guideline for Major and Minor Amendments.

iii. When the pharmaceutical products contain high potency active pharmaceutical ingredients and these products are of different strengths but are of similar weight.

The difference in API content between strengths may be compensated for by weight changes in one or more of the inactive pharmaceutical excipients provided that the total weight of the pharmaceutical product remains within 10% of the weight of the pharmaceutical product on which the bioequivalence study was performed. In addition, the same inactive pharmaceutical excipients must be used for all strengths, provided that the changes remain within the limits defined by the Guideline for Major and Minor Amendments.

Exceptions to the above definitions may be considered provided justification is submitted.

3. DESIGN AND CONDUCT OF STUDIES FOR ORALLY ADMINISTERED PHARMACEUTICAL PRODUCTS

A bioequivalence study is basically a comparative bioavailability study designed to establish equivalence between test and reference products. In the following sections, requirements for the design and conduct of bioavailability or bioequivalence studies are formulated.

3.1 Design

The study should be designed in such a way that the formulation effect can be distinguished from other effects. If the number of formulations to be compared is two, a balanced two-period, two-sequence crossover design is considered to be the design of choice.

However, under certain circumstances and provided the study design and the statistical analyses are scientifically sound, alternatively well-established designs such as parallel designs for very long half-life substances could be considered.

In general, single dose studies will suffice, but there are situations in which steady-state studies may be required and must be justified.

To avoid carry-over effects, treatments should be separated by adequate wash-out periods.

The sampling schedule should be planned to provide an adequate estimation of Cmax and to cover the plasma drug concentration time curve long enough to provide a reliable estimate of the extent of absorption. This is generally achieved if the AUC derived from measurements is at least 80% of the AUC extrapolated to infinity.

If a reliable estimate of terminal half-life is necessary, it should be obtained by collecting at least three to four samples during the terminal log linear phase.

For long half-life drugs (> 24 hours) the study should cover a minimum of 72 hours unless 80% is covered before 72 hours.

For immediate release dosage forms, studies must be done under fasting conditions, unless food effects influence bioavailability. If the dosage directions specifically state administration with food, both fed and fasted studies are required. For modified release dosage forms the influence of food must be demonstrated to exclude any possibility of dose dumping, hence both fed and fasted studies are required.

3.2 Subjects

3.2.1 Number of Subjects

It is recommended that the number of subjects should be justified on the basis of providing at least 80% power of meeting the acceptance criteria.

The minimum number of subjects should not be less than 12. If 12 subjects do not provide 80% power more subjects should be included.

A minimum of 20 subjects is required for modified release oral dosage forms.

The number of subjects required to provide an 80% power of meeting and passing the acceptance criteria for the 0,8 - 1,25 acceptable interval can be determined from Table 1 below (Reference 1).

Table 1 Sample sizes to attain a power of 70%, 80% and 90% in the case of the multiplicative model: á = 5 %, θ_1=0.8, θ_2=1.25 and various CVs.

CV	Power	μ_T/μ_R							
(%)	(%)	0.85	0.90	0.95	1.00	1.05	1.10	1.15	1.20
5.0	70	10	6	4	4	4	4	6	16
7.5		16	6	6	4	6	6	10	34
10.0		28	10	6	6	6	8	16	58
12.5		42	14	8	8	8	12	24	90
15.0		60	18	10	10	10	16	32	128
17.5		80	22	12	12	12	20	44	172
20.0		102	30	16	14	16	26	56	224
22.5		128	36	20	16	20	30	70	282
25.0		158	44	24	20	22	38	84	344
27.5		190	52	28	24	26	44	102	414
30.0		224	60	32	28	32	52	120	490
5.0	80	12	6	4	4	4	6	8	22
7.5		22	8	6	6	6	8	12	44
10.0		36	12	8	6	8	10	20	76
12.5		54	16	10	8	10	14	30	118
15.0		78	22	12	10	12	20	42	168
17.5		104	30	16	14	16	26	56	226
20.0		134	38	20	16	18	32	72	294
22.5		168	46	24	20	24	40	90	368
25.0		206	56	28	24	28	48	110	452
27.5		248	68	34	28	34	58	132	544
30.0		292	80	40	32	38	68	156	642
5.0	90	14	6	4	4	4	6	8	28
7.5		28	10	6	6	6	8	16	60
10.0		48	14	8	8	8	14	26	104
12.5		74	22	12	10	12	18	40	162
15.0		106	30	16	12	16	26	58	232
17.5		142	40	20	16	20	34	76	312
20.0		186	50	26	20	24	44	100	406
22.5		232	64	32	24	30	54	124	510
25.0		284	78	38	28	36	66	152	626
27.5		342	92	44	34	44	78	182	752
30.0		404	108	52	40	52	92	214	888

Note: Less than 12 subjects should not be used even if the above table indicates that a power of 80% can be attained with less than 12 subjects.

To determine the number of subjects required, proceed as follows:

i. Determine the CV% of the appropriate BA/BE parameter for the drug under investigation from published literature or an appropriate pilot study.

ii. Choose an appropriate mean test/ reference ratio that is envisaged for the BA/BE parameter (μ_T / μ_R). Ideally this value will be 1.00, however, in practice this is seldom the case so the choice of this ratio is at the discretion of the Sponsor/Applicant.

iii. Determine from the table the number of subjects required for the appropriate CV%, Power and μ_T / μ_R.

For example, if the drug under investigation has an AUC CV of 20% and if a μ_T/μ_R of 0.95 or 1.05 is selected, then a minimum of 20 and 18 subjects respectively will be required for a power of 80%.

Alternatively, the sample size can be calculated using appropriate power equations, which must be presented in the protocol.

Add-ons will be permitted but the number of subjects in the add-on should not exceed the initial number of subjects in the study, unless fully justified. The applicant must show that the data are homogeneous using appropriate statistical tests. The provision for add-ons must be made in the protocol *a priori*.

3.2.2 Selection of Subjects

The subject population for bioequivalence studies should be selected with the aim to minimise variability and permit detection of differences between pharmaceutical products. Therefore, the studies should normally be performed with healthy volunteers.

The inclusion/exclusion criteria should be clearly stated in the protocol.

In general, subjects should exhibit the following characteristics:

i. **Sex:** Subjects may be selected from either sex, however, the risk to women of childbearing potential should be considered on an individual basis.

ii. **Age**: Between 18 and 55 years of age.

iii. **Mass**: Have a body mass within the normal range according to accepted normal values for the Body Mass Index (BMI=weight in Kg divided by height in meters squared i.e. Kg /m^2) or within 15% of ideal body mass e.g. Metropolitan Height and Weight Tables which can be found in the following reference: Statistical Bulletin (Metropolitan Life Foundation) Vol 64, No 1, Jan-Jun 1983, or any other such recognised reference.

iv. **Informed Consent**: All subjects participating in the study must be capable of giving informed consent.

v. **Medical Screening**: Subjects should be screened for suitability by means of clinical laboratory tests, an extensive review of medical history, and a comprehensive medical examination. Depending on the drug's therapeutic class and safety profile special medical investigations may have to be carried out before, during and after the completion of the study.

vi. **Smoking/Drug and Alcohol Abuse**: Subjects should preferably be non-smokers and without a history of alcohol or drug abuse. If moderate smokers are included (less than 10 cigarettes per day) they should be identified as such and the possible influences of their inclusion on the study results should be discussed in the protocol.

3.2.3 Inclusion of Patients

If the active substance under investigation is known to have adverse effects and the pharmacological effects or risks are considered unacceptable for healthy volunteers it may be necessary, under suitable precautions and supervision, to use patients instead. In this case the applicant should justify the use of patients instead of healthy volunteers.

3.2.4 Genetic Phenotyping

Phenotyping and/or genotyping of subjects can be considered for exploratory bioavailability studies. It may also be considered in crossover studies (e.g. bioequivalence, dose proportionality, food interaction studies etc.) for safety or pharmacokinetic reasons.

If a drug is known to be subject to major genetic polymorphism, studies could be performed in cohorts of subjects of known phenotype or genotype for the polymorphism in question.

3.3 Standardisation of the Study Conditions

The test conditions should be standardised in order to minimise the variability of all factors involved, except that of the products being tested. Therefore standardisation of the diet, fluid intake and exercise is recommended.

i. **Dosing**: The time of day for ingestion of doses should be specified.

ii. **Fluid Intake at Dosing**: As fluid intake may profoundly influence the gastric transit of orally administered dosage forms, the volume of fluid administered at the time of dosing should be constant (e.g. 200 ml).

iii. **Food and Fluid Intake**: In fasted studies the period of fasting prior to dosing should be standardised and supervised. All meals and fluids taken after dosing should also be standardised in regard to composition and time of administration and in accordance with any specific requirements for each study.

iv. **Concommitant Medication**: Subjects should not take other medicines during a suitable period before and during the study and should abstain from food and drinks, which may interact with circulatory, gastrointestinal, liver or renal function (e.g. alcoholic or xanthine-containing beverages or certain fruit juices).

v. **Posture and Physical Activity**: As the bioavailability of an active moiety from a dosage form can be dependent upon gastrointestinal transit times and regional blood flows, posture and physical activity may need to be standardised.

3.4 Sample Collection and Sampling Times

Under normal circumstances, blood should be the biological fluid sampled to measure the concentrations of the drug. In most cases the drug may be measured in serum or plasma, however, in some cases, whole blood may be more appropriate for analysis.

When blood is collected:

i. The duration of blood sampling in a study should be sufficient to account for at least 80% of the known AUC to infinity (AUC_{∞}). This period is approximately three terminal half-lives of the drug.

ii. For most drugs 12 to 18 samples including a pre-dose sample should be collected per subject per dose.

iii. Sample collection should be spaced such that the maximum concentration of drug in blood (C_{max}) and the terminal elimination rate constant (K_{el}) can be estimated.

iv. At least three to four samples should be obtained during the terminal log-linear phase to estimate K_{el} by linear regression analysis.

v. The actual clock time when samples are collected as well as the elapsed time relative to drug administration should be recorded.

If drug concentrations in blood are too low to be detected and a substantial amount (> 40%) of the drug is eliminated unchanged in the urine, then urine may serve as the biological fluid to be sampled.

When urine is collected:

i. The volume of each sample must be measured immediately after collection and included in the report.

ii. Urine should be collected over an extended period and generally no less than seven times the terminal elimination half-life so that the amount excreted to infinity ($Ae_{\square}$) can be estimated.

iii. Sufficient samples must be obtained to permit an estimate of the rate and extent of renal excretion. For a 24-hour study, sampling times of 0 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 hours are usually appropriate.

3.5 Characteristics to be Investigated

3.5.1 Blood/Plasma/Serum Concentration *versus* Time Profiles

In most cases evaluation of bioavailability and bioequivalence will be based upon measured concentrations of the parent compound (i.e. the API) where the shape of and the area under the plasma concentration *versus* time curves are generally used to assess the rate and extent of absorption.

In some situations, however, measurements of an active or inactive metabolite may be necessary instead of the parent compound.

i. If the concentration of the active substance is too low to be accurately measured in the biological matrix.

ii. If there is a major difficulty with the analytical method.

iii. If the parent compound is unstable in the biological matrix.

iv. If the half-life of the parent compound is too short thus giving rise to significant variability.

Justification for not measuring the parent compound must be submitted by the applicant and bioequivalence determinations based on metabolites should be justified in each case.

Sampling points should be chosen so that the plasma concentration *versus* time profiles can be defined adequately so as to allow accurate estimation of relevant parameters.

The following bioavailability parameters are to be estimated:

i. AUC_t, AUC_∞, C_{max}, t_{max} for plasma concentration *versus* time profiles.

ii. AUC_τ, C_{max}, C_{min}, fluctuation (%PTF) and swing (%Swing) for studies conducted at steady state.

iii. Any other justifiable characteristics (cf. Appendix I).

iv. The method of estimating AUC-values should be specified.

3.5.2 Urinary Excretion Profiles

In the case of API's predominantly excreted renally, the use of urine excretion data may be advantageous in determining the extent of drug input. However, justification must also be given when this data is used to estimate the rate of absorption.

Sampling points should be chosen so that the cumulative urinary excretion profiles can be defined adequately so as to allow accurate estimation of relevant parameters.

The following bioavailability parameters are to be estimated:

i. Ae_t, Ae_∞ as appropriate for urinary excretion studies.

ii. Any other justifiable characteristics (cf. Appendix I).

iii. The method of estimating AUC-values should be specified.

3.5.3 Pharmacodynamic Studies

If pharmacodynamic parameters/effects are used as bioequivalence criteria, justification for their use must be submitted by the applicant. Bioequivalence determinations based on these measurements should be justified in each case. In addition:

i. A dose response relationship should be demonstrated.

ii. Sufficient measurements should be taken to provide an appropriate pharmacodynamic response profile.

iii. The complete effect curve should remain below the maximum physiological response.

iv. All pharmacodynamic measurements/methods must be validated with respect to specificity, accuracy and reproducibility.

3.6 Chemical Analysis

The bioanalytical part of bioequivalence trials should be conducted according to the applicable principles of Good Laboratory Practice (GLP) and cGMP.

Bioanalytical methods used to determine the active moiety and/or its metabolic product(s) in plasma, serum, blood or urine or any other suitable matrix must be well characterised, fully validated and documented to yield reliable results that can be satisfactorily interpreted.

The main objective of method validation is to demonstrate the reliability of a particular method for the quantitative determination of an analyte(s) in a specific biological matrix. Validation should therefore address the following characteristics of the assay (Reference 2):

i. Stability of stock solutions.

ii. Stability of the analyte(s) in the biological matrix under processing conditions and during the entire period of storage.

iii. Specificity.

iv. Accuracy.

v. Precision.

vi. Limits of detection and quantitation.

vii. Response function.

viii. Robustness and ruggedness.

A calibration curve should be generated for each analyte in each analytical run and it should be used to calculate the concentration of the analyte in the unknown samples in the run.

A number of separately prepared Quality Control samples should be analysed with processed test samples at intervals based on the total number of samples.

All procedures should be performed according to pre-established Standard Operating Procedures (SOPs).

All relevant procedures and formulae used to validate the bioanalytical method should be submitted and discussed.

Any modification of the bioanalytical method before and during analysis of study specimens may require adequate revalidation and all modifications should be reported and the scope of revalidation justified.

3.7 Reference Product

N.B. Products that are not registered in South Africa cannot be used as reference products in bioequivalence studies submitted in support of an application e.g. a product approved for marketing in another country(s) but not approved for marketing in South Africa cannot be used as a reference product.

3.7.1 Reference Products Registered and Marketed in South Africa

The reference product must be an innovator product registered with the Medicines Control Council (MCC) and must be procured in South Africa except that an "OLD MEDICINE" may be used as a reference product when no other such product has been registered and provided that it is available on the South African market. If more than one such product is available, then the product that is the market leader in South Africa should be used as the reference (e.g. IMS database).

3.7.2 Reference Products Registered but not Procured inside South Africa.

1. A foreign reference product can be used provided that the following evidence is submitted:

   i. The reference product has an identical formulation (the same in all respects) as the innovator product marketed in South Africa.

   ii. The reference product is manufactured by the same method as the innovator product marketed in South Africa.

   iii. The reference product is manufactured at the same site as the innovator product marketed in South Africa.

The intention of the above clause is to provide for the use of a reference product where that innovator product has been imported for use in South Africa.

2. As an interim measure, bioequivalence studies submitted where a foreign reference product has been used will require comparative dissolution profiles between the foreign product and the innovator product marketed in SA and must meet the f_2 requirements when tested in dissolution media of pH 1.2, 4.5 and 6.8, using an appropriate dissolution apparatus (see Guideline for Dissolution Testing).

   The intention of the above clause is to make provision for dossiers submitted prior to the implementation of this guideline.

3.7.3 Reference Products Registered in South Africa but not Marketed (Available) in South Africa

If a reference product is registered in SA but cannot be procured (i.e. is not available) in South Africa, then the reference product used can be obtained from outside South Africa provided that the product meets the following criteria:

i. The reference product must be a conventional, immediate-release oral dosage form.

ii. There is no documented evidence of bioavailability problems related to the active pharmaceutical ingredient(s) or the pharmaceutical product, or ingredients or products of similar chemical structure or formulations.

iii. It must be documented that the pharmaceutical product is authorised for marketing by the health authority of a country with drug registration requirements acceptable to the MCC. In such instances the registration requirements of the country where the reference product was approved must be submitted.

iv. It must be documented that the pharmaceutical product is marketed in the country of origin by the same innovator company or corporate entity which currently markets the same active pharmaceutical ingredient in the same dosage form in South Africa; or, that it is marketed in the country of origin through a licensing arrangement with the innovator company or corporate entity which currently markets the product in South Africa. The country of manufacture must be stated.

v. Copies of the labelling for the reference as well as the innovator product marketed in South Africa, together with Certificates of Analysis for both products, analysed using the specifications for description, assay, content uniformity and dissolution proposed in the submission for the multi-source product, must be provided.

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vi. The active pharmaceutical ingredient is uncomplicated i.e. it does not exhibit any of the following:

- A narrow therapeutic range or safety margin, e.g. it does not require careful dosage titration or patient monitoring.
- A steep dose / response relationship.
- A risk of serious undesired effects.
- Complicated or variable pharmacokinetics e.g.:
  - non linear pharmacokinetics
  - variable or incomplete absorption
  - an absorption window, i.e. site specific absorption
  - substantial first-pass metabolism (›40%)
  - an elimination half life of 24 hours or more

vii. The active pharmaceutical ingredient must not be a pro-drug.

viii. The dosage form:

- Contains a single API.
- Contains the same quantity of medicinal ingredient as the innovator product registered in South Africa.
- Is the same as the dosage form registered in South Africa with respect to colour, shape, size, weight, type of coating and other relevant attributes.

3.7.4 Reference Products for Combination Products

Combination products should in general, be assessed with respect to bioavailability and bioequivalence of individual active substances:

i. Either individually (in the case of a new combinations), or

ii. Using an existing combination as the reference.

iii. In the former instance, immediate release oral dosage forms containing a single API can be used as the reference. These reference products may include "OLD MEDICINES".

Bioequivalence testing of such products will be permitted only for those products approved by the MCC.

3.8 Study Products and Batch Size

3.8.1 Study Products

The following information on test and reference products must be submitted:

i. Assay of test and reference product.

ii. Comparative dissolution profiles of the test and the reference product.

iii. A CoA of the API used in the test product bio-batch as well as quality control data demonstrating compliance with the specifications.

In addition, the test and reference products must conform to the following:

i. Test and the reference product should not differ by more than 5% in assay.

ii. A sufficient number of retention samples of both test and reference products used in the bioequivalence study must be kept by the study sponsor for one year in excess of the accepted shelf life or two years after completion of the trial or until approval, whichever is longer, in order to allow re-testing if required by the MCC.

iii. A complete audit trail of procurement, storage, transport and other use of both the test and reference products must be recorded.

3.8.2 Batch Size

The bio-batch used in the bioequivalence study must satisfy the following requirements:

i. The bio-batch must be a minimum of 100 000 units or at least 10% of the production batch which ever is greater.

If the bio-batch is less than 100 000 the applicant must motivate and justify the use of a smaller batch.

ii. If the production batch is smaller than 100 000 units, a full production batch will be required.

iii. A high level of assurance must be provided that the product and process used in the production of the product will be feasible on an industrial scale. If the product is subjected to further scale-up, this should be validated appropriately.

3.9 Data Analysis

The primary concern of bioequivalence assessment is to quantify the difference in bioavailability between the test and reference products and to demonstrate that any clinically important difference is unlikely.

3.9.1 Statistical Analysis

The statistical method for testing relative bioavailability (i.e average bioequivalence) is based upon the 90% confidence interval for the ratio of the population means (Test/Reference) on the log-transformed scale, for the parameters under consideration.

Pharmacokinetic parameters derived from measures of concentration, e.g. AUC_t, AUC_∞, C_{max} should be analysed using ANOVA. Data for these parameters should be transformed prior to analysis using a logarithmic transformation.

If appropriate to the evaluation, the analysis technique for t_{max} should be non-parametric and should be applied to untransformed data.

In addition to the appropriate 90% confidence intervals, summary statistics such as geometric and arithmetic means, SD and %RSD as well as ranges for pharmacokinetic parameters (minimum and maximum) should be provided.

3.9.2 Acceptance Range for Pharmacokinetic Parameters

The pharmacokinetic parameters to be tested, the procedure for testing and the acceptance ranges should be stated beforehand in the protocol.

3.9.2.1 Single-Dose Studies

In single-dose studies designed to determine average bioequivalence, acceptance criteria for the main bioequivalence parameters are as follows:

i. AUC_t - ratio

The 90% confidence interval for the test/reference ratio should lie within the acceptance interval of 0.80-1.25 (80 – 125%) calculated using log transformed data.

In certain cases an alternative approach may be acceptable.

Justification for the use of alternative methods e.g. scaled average bioequivalence (ABE) based on sound scientific principles for the evaluation of the bioequivalence of highly variable drugs has been described in the literature (Reference 2 and 3). Use of alternative methods MUST be stated *a priori* in the protocol and cannot be added retrospectively.

ii. C_{max} - ratio

The 90% confidence interval for the test/reference ratio should lie within an acceptance interval of 75 – 133% calculated using log transformed data, except for narrow therapeutic range API's when an acceptance interval of 80 – 125% will apply.

In certain cases e.g. in the case of highly variable API's, a wider interval or other appropriate measures may be acceptable but must be stated *a priori* and justified in the protocol (See references 3 and 4).

3.9.2.2 Steady-State Studies

i. Immediate Release Dosage Forms

The acceptance criteria are the same as for single dose studies but using AUC_τ instead of AUC_t

ii. Controlled/Modified Release Dosage Forms

The acceptance criteria are as follows:

- AUC_τ - ratio

  The 90% confidence interval for the test/reference ratio should lie within the acceptance interval of 0.80-1.25 (80 – 125%) calculated using log transformed data.

- $C_{max\ (ss)}$ and $C_{min\ (ss)}$

  The 90% confidence interval for the test/reference ratio should lie within the acceptance interval of 0.75-1.33 (75 – 133%) calculated using log transformed data.

- %Swing and %PTF

  The 90% confidence interval for the test/reference ratio should lie within the acceptance interval of 0.80-1.25 (80 – 125%) calculated using log transformed data.

3.10 Reporting of Results

The report of a bioavailability or a bioequivalence study should give the complete documentation of its protocol, conduct and evaluation complying with GCP, GLP and cGMP.

3.10.1 Clinical Report

In addition to the protocol etc., the clinical section of the bioequivalence study report should include the following:

i. A statement indicating the independence of the ethics committee.

ii. Documented proof of ethical approval of the study.

iii. A complete list of the members of the ethics committee, their qualifications and affiliations.

iv. An independent monitor's report on the study.

v. Names and affiliations of the all investigator(s), the site of the study and the period of its execution.

vi. The names and batch numbers of the products being tested.

vii. The manufacturing sites (address of the manufacturer of both the reference and the test product).

viii. Expiry date of the reference product and the date of manufacture of the test product used in the study.

ix. Assay and comparative dissolution profiles for test and reference products.

x. CofA of the API used in the test product bio-batch.

xi. A signed statement confirming that the test product used in the bio-study is the same as the one that is submitted for registration.

xii. A summary of adverse events which must be accompanied by a discussion on the influence of these events on the outcome of the study.

xiii. A summary of protocol deviations (sampling and non-sampling) which must be accompanied by a discussion on the influence of these adverse events on the outcome of the study.

xiv. Subjects who drop out or are withdrawn from the study should be identified and their withdrawal fully documented and accounted for.

3.10.2 Analytical Report

The analytical section of the bioequivalence report should include the following which must be clearly presented:

i. The full analytical validation report.

ii. All individual subject concentration data.

iii. All individual plasma concentration *versus* time profiles presented on a linear/linear as well as log/linear scale (or, if appropriate, cumulative urinary excretion data presented on a linear/linear scale).

iv. Calibration data i.e. raw data and back-calculated concentrations for standards, as well as calibration curve parameters for the entire study.

v. Quality control samples for the entire study.

vi. Chromatograms from analytical runs for 20% of all subjects (or a minimum of 4 subjects) including chromatograms for the associated standards and quality control samples.

vii. Analytical data from subjects who dropped out of the study due to an adverse drug event should also be presented.

viii. A summary of protocol deviations which must be accompanied by a discussion on the influence of these deviations on the outcome of the study. Protocol deviations must be justified.

3.10.3 Pharmacokinetic and Statistical Report

The pharmacokinetic and statistical section of the bioequivalence report should include the following, which must be clearly presented:

i. All drug concentration *versus* time data from the bio-study. This data must be submitted in hard copy and also formatted on a diskette in a format compatible for processing by SAS software. Individual subject data should be in rows and arranged in columns which reflect the subject number, phase number, sequence, formulation and sample concentration *versus* time data (Appendix 2).

ii. The method(s) and programs used to derive the pharmacokinetic parameters from the raw data.

iii. A detailed ANOVA and/or non-parametric analysis, the point estimates and corresponding confidence intervals for each parameter of interest.

iv. Tabulated summaries of pharmacokinetic and statistical data.

v. The statistical report should contain sufficient detail to enable the statistical analysis to be repeated, e.g. individual demographic data, randomisation scheme, individual subject concentration vs. time data, values of pharmacokinetic parameters for each subject, descriptive statistics of pharmacokinetic parameters for each formulation and period.

vi. Drug concentration data of any subject withdrawn from the study due to an adverse drug event should also be submitted, but should not be included in the statistical analysis.

3.10.4 Quality Assurance

i. The study report should be accompanied by a signed QA statement confirming release of the document.

ii. A declaration must be made by the applicant to indicate whether the site(s) (clinical and analytical) where the study was performed was subjected to a pre-study audit to ascertain the status of GCP and GLP &/or cGMP conditions at the site(s). All audit certificates should clearly indicate the date of audit and the name(s), address(es) and qualifications of the auditor(s).

iii. The applicant should submit an independent monitor's report on the clinical portion of the study. This report should clearly indicate the date of monitoring and the name, address and qualifications of the monitor and should be included in the study report.

3.11 Expiry Dates of Biostudies

The bioavailability/ bioequivalence study must have been completed not longer than three years prior to the date of submission.

4 BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

4.1 Orally Administered Drug Products Intended for Systemic Action

4.1.1 Solutions

A bioequivalence waiver may be granted for oral solutions, elixirs, syrups or other solubilized forms containing the same active pharmaceutical ingredient(s) in the same concentration(s) as the South African reference product and containing no ingredient known to significantly affect absorption of the medicinal ingredient(s).

4.1.2 Suspensions

Bioequivalence for a suspension should be treated in the same way as for immediate release solid oral dosage forms.

4.1.3 Immediate Release Products – Tablets and Capsules

In general bioequivalence studies are required. *In vivo* BE studies should be accompanied by *in vivo* dissolution profiles on all strengths of each product. Waivers for *in vivo* bioavailability and bioequivalence studies for immediate release solid oral dosage forms based on comparative dissolution studies may be acceptable (see Guideline for Dissolution Testing).

4.1.4 Modified Release Products

Modified release products include delayed release products and extended (controlled) release products. In general bioequivalence studies are required. In addition to the studies required for immediate release products, a food-effect study is necessary. Multiple dose studies are generally not recommended.

4.1.5 Miscellaneous Oral Dosage Forms

Rapidly dissolving drug products, such as buccal and sublingual dosage forms, should be tested for *in vitro* dissolution and *in vivo* BA and/or BE. Chewable tablets should also be evaluated for *in vivo* BA and/or BE. Chewable tablets (as a whole) should be subject to *in vitro* dissolution because they might be swallowed by a patient without proper chewing. In general, *in vitro* dissolution test conditions for chewable tablets should be the same as for non-chewable tablets of the same active ingredient/moiety.

4.2 Orally Administered Drugs Intended for Local Action

Generally BE studies with clinical efficacy and safety endpoints and/or suitably designed and validated *in vitro* studies are required.

4.3 Parenteral Solutions

The applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently approved product.

In the case of other parenteral routes other than i/v., e.g. intramuscular or subcutaneous, if the test product is of the same type of solution (aqueous) as the reference product, contains the same concentration of the same active substance and the same or comparable excipients as the medicinal product currently approved, then bioequivalence testing is not required provided that the formulation does not contain an excipient(s) known to significantly affect absorption of the active ingredient(s).

For all other parenterals bioequivalence studies are required.

For intramuscular dosage forms monitoring is required until at least 80% of the AUC_{∞} has been covered.

4.4 Topically Administered Products

4.4.1 Locally Acting

Topical preparations containing corticosteroids intended for application to the skin and scalp, the human vasoconstrictor test (blanching test) is recommended

to prove bioequivalence. Validated visual and/or chromometer data will be necessary.

Topical formulations, other than a simple solution, with bacteriostatic, bactericidal, antiseptic and/or antifungal claims, clinical data (comparative clinical efficacy) will be required. Microbial growth inhibition zones will not be acceptable as proof of efficacy. Simple solutions however, may qualify for a waiver based on appropriate *in vitro* test methods.

Proof of release by membrane diffusion will not be accepted as proof of efficacy unless there has been data to show the correlation between release through a membrane and clinical efficacy data.

Whenever systemic exposure resulting from locally applied, locally acting medicinal products entails a risk of systemic adverse reactions, systemic exposure should be measured.

4.4.2 Systemically Acting

For locally applied products with systemic action e.g. transdermal products, a bioequivalence study is always required.

4.5 Products Intended for Other Routes of Administration

Products for local use (oral, nasal, inhalation, ocular, dermal, rectal, vaginal etc. administration.) intended to act without systemic absorption the approach to determine bioequivalence based on systemic measurements is not applicable and pharmacodynamic or comparative clinical studies are required. However, pharmacokinetic studies may be required as measures of safety.

4.6 Variations or Post Registration Amendments

For all post registration changes that require proof of efficacy the requirements of this guideline will be applicable.

5. WAIVERS OF *IN VIVO* BIOEQUIVALENCE STUDIES

Bio-waivers will be considered under the circumstances detailed below.

5.1 Immediate Release Products

5.1.1 Class 1 Drug Substances

When the drug product contains a Class 1 drug substance(s) (based on the Biopharmaceutics Classification System, BCS), and the inactive ingredients used in the dosage form do not significantly affect absorption of the active ingredients

a bio-waiver may be acceptable.

The drug substances must be highly soluble, highly permeable and the dosage form rapidly dissolving (see Guideline for Dissolution Testing).

The applicant must provide relevant information to prove that the drug substance falls within the Class 1 classification (Reference 5).

5.1.2 Different Strength Dosage Forms

When the drug product is the same dosage form but of a different strength and is proportionally similar (See Section 2.9) in its active and inactive ingredients, a bio-waiver may be acceptable.

In such cases the demonstration of bioequivalence *in vivo* of one or more of the lower strength/s may be waived based on dissolution tests (see Guideline for Dissolution Testing) and an *in vivo* study on the highest strength.

1. **For Multi-source pharmaceutical products**, conducting an *in vivo* study on a strength that is not the highest may be appropriate for reasons of safety. In this case a waiver may be considered for the higher strength when an *in vivo* BE study was performed on a lower strength of the same drug product provided that:

   i. Linear elimination kinetics has been shown over the therapeutic dose range.

   ii. The higher strength is proportionally similar to the lower strength.

2. **For New Chemical Entities** with questions on toxicity, bio-wavers for a higher strength will be determined to be appropriate based on:

   i. Clinical safety and/or efficacy studies including dose desirability of the higher strength, and

   ii. Linear elimination kinetics over the therapeutic dose range, and

   iii. The higher strength being proportionally similar to the lower strength, and

   iv. The same dissolution procedures being used for both strengths and similar dissolution results obtained.

Dissolution profiles are required for all strengths. The f_2 similarity factor should be used to compare dissolution profiles from different strengths of a product. An f_2 value ≥ 50 indicates a sufficiently similar dissolution profile such that further *in vivo* studies are not necessary. For an f_2 value <50, it may be necessary to conduct an *in vivo* study. The difference factor, f_1, must also be submitted but will not be used as an acceptance criterion (Reference 6).

Note: Details on the performance of dissolution studies are described in the Guideline for Dissolution Testing and not in the BA-BE guideline.

5.2 Modified Release Products

5.2.1 Beaded Capsules - Lower Strength

For extended release beaded capsules where the strength differs only in the number of beads containing the active ingredient, a single-dose, fasting BE study should be carried out on the highest strength. A bio-waiver for the lower strength based on dissolution studies can be requested.

Dissolution profiles in support of a bio-waiver should be generated for each strength using the recommended dissolution test methods described in the Guideline for Dissolution Testing.

5.2.2 Tablets – Lower strength

For extended release tablets when the drug product is:

i. In the same dosage form but in a different strength, and

ii. Is proportionally similar in its active and inactive ingredients, and

iii. Has the same drug release mechanism,

an *in vivo* BE determination of one or more lower strengths may be waived based on dissolution testing as previously described. Dissolution profiles should be generated on all the strengths of the test and the reference products.

For Section 5.2.1 and 5.2.2 above, the f_2 factor should be used to compare profiles from the different strengths of the product. An f_2 value of ≥ 50 can be used to confirm that further *in vivo* studies are not needed (see Guideline for Dissolution Testing).

6 References

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5. Guidance for Industry. Waiver of In vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), August 2000.

6. Mathematical Comparison of Dissolution Profiles. Pharm. Technol. 20:6 (1996) 64-74, J.W. Moore and H.H.Flanner.

APPENDIX 1 - Abbreviations and Symbols.

C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
$C_{max\ (ss)}$	maximum plasma concentration at steady-state
$C_{min\ (ss)}$	minimum plasma concentration at steady-state
C_{av}	average plasma concentration
t_{max}	time to C_{max}
AUC_t	area under the plasma/serum/blood concentration-time curve from time zero to time t where t is the last time point with measurable concentration.
AUC_∞	area under the plasma/serum/blood concentration-time curve from time zero to time infinity
AUC_τ	AUC during a dosage interval at steady state
MRT	mean residence time
Ae_t	cumulative urinary excretion from drug administration until time t
Ae_∞	Amount of unchanged drug excreted in the urine at infinite time (7-10 half lives).
$t_{1/2}$	elimination half-life
%PTF	$(C_{max\ (ss)} - C_{min\ (ss)}) / C_{av}.100$
%Swing	$(C_{max\ (ss)} - C_{min\ (ss)}) / C_{min}.100$

APPENDIX 2 - Example of Bio-Study Data Formatted for SAS.
Note: Data should preferably be saved in .sas files but can also be saved in free-format ASCII DOS TEXT files.

Subj. #	Seq.	Period	Form	t1	t2	t3	t4	t5	t6	t7	t8	t9	t10
t11	t12	t13	t14	t15	t16	t17	t18	t18	t20	t21			
01	AB	1	A	0.000	n.nnn	nn.nnn	nn.nnn	nn.nnn	nnn.nnn	nnn.nnn	nn.nnn	nn.nnn	nn.nnn
nn.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn	n.nnn	n.nnn	n.nnn	n.nnn			
01	AB	2	B	0.000	n.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn
nn.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn	n.nnn	n.nnn	n.nnn	n.nnn	n.nnn	n.nnn			
02	BA	1	B	0.000	n.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn
nn.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn	n.nnn	n.nnn	n.nnn	n.nnn			
02	BA	2	A	0.000	n.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn
nn.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn	nn.nnn	n.nnn	n.nnn	n.nnn	n.nnn			

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

ADDENDUM 4

STABILITY STUDIES

This document has been prepared to serve as a recommendation to applicants wishing to submit applications for registration of medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request for any additional information to establish the safety, quality and efficacy of a medicine and may make amendments in keeping with the knowledge which is current at the time of consideration of data accompanying applications for registration of medicines. Alternative approaches may be used but these must be scientifically and technically justified. The MCC is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy. It is important for applicants to adhere to the administrative requirements to avoid delays in the processing of applications.
This guideline will come into effect from 1 October 2004.
Guidelines and application forms are available from the office of the Registrar of Medicines.

REGISTRAR OF MEDICINES
MS M.P. MATSOSO
DATE: 29/4/2003

STABILITY STUDIES

The Tripartite guideline, which has been developed within the Expert Working Group (Quality) of the International Conference on Harmonization (ICH), provides a general indication on the requirements for stability testing. It primarily addresses the information required in applications for registration for new chemical entities and associated medicinal products. This guideline is adopted with only minor modifications. It contains aspects relating to testing conditions, numbers of batches to be tested and the requirements regarding follow-up stability data and applicants are advised to study this guideline carefully.

Applicants are reminded that the Tripartite guideline has now been included in the USP23 (<1196>) and latest updates appear on the ICH website.

Applicants are also referred to the following guidelines on the ICH website:
1. Stability Data Package for Registration in Climatic Zones III and IV (Q1F)
2. Photostability Testing (Q1B)

Appendices 1 and 2 attached to this guideline comprise -
APPENDIX 1 - GLOSSARY AND INFORMATION
APPENDIX 2 - APPROPRIATE TESTS

Index to Guideline contents

STABILITY

1 STABILITY TRIAL DESIGN

There shall be a written testing program designed to assess stability characteristics of dosage forms. The results of such stability testing shall be used in determining appropriate storage conditions and retest or expiry dates.

The design of the study should consider the methodology for determining the stability of the active substance and dosage forms. The following factors must be considered in designing a stability trial:

1.1 ACTIVE PHARMACEUTICAL INGREDIENT

1.1.1 New Chemical Entity

1.1.1.i General

Information on the stability of the active substance is an integral part of the systematic approach to stability evaluation.

The actual studies to be carried out will depend on the nature of the active substance, but may include the effect of elevated temperatures or low temperatures, susceptibility to moisture, oxidation and the effect of light. The effect of pH and high oxygen atmosphere may be important for aqueous solutions or suspensions of the active substance.

1.1.1.ii Stress Testing

Stress testing helps to determine the intrinsic stability of the molecule by establishing degradation pathways in order to identify the likely degradation products and to validate the stability indicating power of the analytical procedures used.

1.1.1.iii Formal Studies

STABILITY

Primary stability studies are intended to show that the active substance will remain within specification during the retest period if stored under recommended storage conditions.

1.1.1.iv Selection of Batches

Stability information from accelerated and long-term testing is to be provided on at least three batches. The long-term testing should cover a minimum of 12 months duration on at least three batches at the time of submission of the application for registration.

The batches manufactured to a minimum of pilot plant scale should be by the same synthesis route and use a method of manufacture and procedure that simulates the final process to be used on a manufacturing scale.

The overall quality of the batches of active substance placed on stability should be representative of both the quality of the material used in pre-clinical and clinical studies and the quality of material to be made on a manufacturing scale.

In the event of more than one manufacturer being used it must be confirmed that the same method of synthesis is used or extensive comparative data submitted including all aspects of quality, safety and efficacy.

Supporting information may be provided using stability data on batches of active substance made on a laboratory scale.

The first three production batches of active substance manufactured post approval, if not submitted in the original application for registration, should be placed on long-term stability studies using the same stability protocol as in the approved application for registration.

1.1.1.v Test Procedure and Test Criteria

The testing should cover those features susceptible to change during storage and likely to influence quality, safety and/or efficacy. Stability information should cover as necessary the physical, chemical and microbiological test characteristics. Validated stability-indicating testing methods must be applied. The need for the extent of replication will depend on the results of validation studies.

1.1.1.vi Specifications

Limits of acceptability should be derived from the profile of the material as used in the preclinical and clinical batches. It will need to include individual and total upper limits for impurities and degradation products, the justification for which should be influenced by the levels observed in material used in preclinical studies and clinical trials.

1.1.1.vii Storage Conditions

The length of the studies and the storage conditions should be sufficient to cover storage, shipment, and subsequent use. Application of the same storage conditions as applied to the drug product will facilitate comparative review and assessment. Other storage conditions are allowable if justified. In particular, temperature sensitive active substances should be stored under an alternative, lower temperature condition which will then become the designated long-term testing storage temperature. The six months accelerated testing should then be carried out at a temperature at least 15 °C above this designated long-term storage temperature (together with appropriate relative humidity conditions for that temperature). The designated long-term testing conditions will be reflected in the labelling and retest date.

STABILITY

	Conditions	Minimum time period at submission
Long-term testing	25 +- 2 °C/60 +- 5%RH	12 months
Accelerated	40 +- 2 °C/75 +- 5%RH	6 months

Where "significant change" occurs during six months storage under conditions of accelerated testing at 40 °C +- 2 °C/75%RH +- 5%, additional testing at an intermediate condition (such as 30 ° C +- 2 ° C/65% +- 5%RH) should be conducted for active substances to be used in dosage forms tested long term at 25 °C/60%RH and this information included in the application for registration. The initial application should include minimum of 6 months' data from a 12month study.

STABILITY

"Significant change" at 40 °C/75%RH or 30 °C/60%RH. is defined as failure to meet the specification.

The long-term testing will be continued for a sufficient period of time beyond 12 months to cover all appropriate retest periods, and the further accumulated data can be submitted to the Council during the assessment period of the application. The data (from accelerated testing or from testing at an intermediate condition) may be used to evaluate the impact of short-term excursions outside the label storage conditions such as may occur during shipping.

Long-term stability studies can also be performed at 30°C/65% RH, but then there are no intermediate conditions (Zone IV)

1.1.1.viii Testing Frequency

Frequency of testing should be sufficient to establish the stability characteristics of the active substance. Testing under the defined long-term conditions will normally be every three months over the first year, every six months over the second year and then annually.

1.1.1.ix Packaging/Containers

The containers to be used in the long-term, real-time stability evaluation should be the same as or simulate the actual packaging used for storage and distribution.

1.1.1.x Evaluation

The design of the stability study is to establish, based on testing a minimum of three batches of the active substance and evaluating the stability information (covering as necessary the physical, chemical, and microbiological test characteristics), a retest period applicable to all future batches of the bulk active substance manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification until the retest date.

An acceptable approach for quantitative characteristics that are expected to decrease with time is to determine the time at which the 95% one-sided confidence limit for the mean degradation curve intersects the acceptable lower specification limit. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate, and this can be done by first applying appropriate statistical tests (for example, p values for level of significance of rejection of more than 0,25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall retest period may depend on the minimum time a batch may be expected to remain within acceptable and justified limits.

The nature of any degradation relationship will determine the need for transformation of the data for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

The data may show so little degradation and so little variability that it is apparent from looking at the data that the requested retest period will be granted. Under the circumstances, it is normally

unnecessary to go through the formal statistical analysis but merely to provide a full justification for the omission.

Limited extrapolation of the real time data beyond the observed range to extend the retest period at approval time, particularly where the accelerated data supports this, may be undertaken. However, this assumes that the same degradation relationship will continue to apply beyond the observed data, and hence the use of extrapolation must be justified in each application in terms of what is known about the mechanism of degradation, the goodness of fit of any mathematical model, batch size, existence of supportive data, etc.

Any evaluation should cover not only the assay but the levels of degradation products and other appropriate attributes.

When degradation products are identified in significant amounts or suspected of toxicity, a concerned effort has to be made to collect the following additional information about the substance concerned:

- chemical structure
- cross-reference to any available information about biological effect and significance at the concentrations likely to be encountered
- procedure for isolation and purification
- mechanism of formation, including order of reaction
- physical and chemical properties
- specifications and directions for testing their presence at the levels of concentrations expected to be present, and
- indication of pharmacological activity, or inactivity or toxicity profile.

Where the route of degradation is not known, suitable screening chromatographic or other tests may be required.

Official compendia or other tests designed to identify impurities in the active substance used in the formulation may not necessarily be suitable for investigation into degradation products.

When it has been considered necessary to perform toxicity studies these results should be presented.

Consideration should be given to the stereo-chemical and polymorphic integrity of active substances.

Stability information gained should enable the applicant to institute a routine system whereby re-analysis to validate the conformance to specification of the active substance is done in order that the stability of the dosage form concerned is assured.

1.1.1.xi Statements/Labelling

A storage temperature should be based on the stability evaluation of the active substance. Where applicable, specific requirements should be stated, particularly for active substances that cannot tolerate freezing. The use of terms such as "ambient conditions" or "room temperature" is unacceptable.

A retest period should be derived from the stability information.

1.1.2 Well-known Chemical Entities (established active substances)

Literature data on decomposition process and degradability are generally available and must be included in the submission.

If degradation pathways/products are unknown, references to support such conclusions must be included or experimental data submitted. Reference to pharmacopoeias will not satisfy this requirement.

1.2 DOSAGE FORMS

1.2.1 Products containing New Chemical Entities

1.2.1.i General

The design of the stability program for the finished product should be based on the knowledge of the behaviour and properties of the active substance and the experience gained from clinical trial formulation studies and from stability studies on the active substance. The likely changes on storage and the rationale for the selection of product variables to include in the testing program should be stated.

1.2.1.ii Selection of Batches

Stability information from accelerated and long-term testing is to be provided on three batches of the same formulation and dosage form in the containers and closure proposed for marketing. Two of the three batches should be at least pilot scale. The third batch may be smaller (e.g., 25 000 to 50 000 tablets or capsules for solid oral dosage forms).

The long-term testing should cover at least 12 months duration at the time of submission. The manufacturing process to be used should meaningfully simulate that which would be applied to large- scale batches for marketing. The process should provide product of the same quality intended for marketing, and meeting the same quality specification as to be applied to release of material. Where possible, batches of the finished product should be manufactured using identifiably different batches of active substance.

Where an application includes different sources of active substances that are not physically and/or chemically equivalent and/or where the difference in physical and/or chemical specifications may adversely affect the stability of the product, stability studies should be performed on the final product manufactured from each active substance.

Data on laboratory scale batches is not acceptable as primary stability information. Data on associated formulations or packaging may be submitted as supportive information, provided that the difference in the formulations is clearly stated. The first three production batches manufactured post approval, if not submitted in the original application for registration should be

placed on accelerated and long-term stability studies using the same stability protocols as in the approved application for registration.

1.2.1.iii Test Procedures and Test Criteria

The testing should cover those features susceptible to change during storage and likely to influence quality, safety and/or efficacy. Analytical test procedures should be fully validated, and assays should be stability-indicating. .

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Where the "in-use" form of the product differs markedly from the manufactured and packaged form (for example, where the product is required to be reconstituted, diluted or mixed prior to use), data to establish the stability of the "in-use" form of the product should be supplied. "In-use" stability studies may also be required for certain sensitive products where the opening and closing of the containers may have an effect. This also applies to "in-use" multidose vials.

Where the manufacturer claims the product may be diluted with a range of solutions prior to use, for example, products that require dilution prior to parenteral infusion, stability data to establish compatibility with and stability in each solution should be submitted. Data on compatibility with the range of materials, such as are used for the intravenous infusion containers and the administration sets recommended for use should be submitted.

Where the dosage form is to be reconstituted at the time of dispensing, its labelling should bear supportive expiration information and storage conditions for both the reconstituted and unreconstituted dosage forms.

The range of testing should cover not only chemical and biological stability but also loss of preservative (where relevant), physical properties and characteristics, organoleptic properties and, where required, microbiological attributes.

Preservative efficacy testing and assays on stored samples should be carried out to determine the content and efficacy of antimicrobial preservatives.

Stability should be established for the whole period of intended use under the conditions reflected in the printed packaging components (Annexure 1).

1.2.1.iv Specifications

The stability studies must include testing of those attributes of the product that are susceptible to change during storage and that are likely to influence quality, safety and efficacy.

Limits of acceptance should relate to the release limits (where applicable), to be derived from consideration of all the available stability information. The shelf life specification could allow acceptable and justifiable deviations from the release specification based on the stability evaluation and the changes observed on storage. It will need to include specific upper limits for degradation products, the justification for which should be influenced by the levels observed in material used in pre-clinical studies and clinical trials. The justification for limits proposed for certain other tests such as particle size and/or dissolution rate will require inference to the results observed for batch(es) used in bioavailability and/or clinical studies. Any differences between the

release and shelf life specifications for antimicrobial preservatives should be supported by preservative efficacy testing.

1.2.1.v Storage Test Conditions

The length of the studies and the storage conditions should be sufficient to cover storage, shipment, and subsequent use (e.g., reconstitution or dilution as recommended in the labelling).

See table below for accelerated and long-term storage conditions and minimum times. An assurance that long-term testing will continue to cover the expected shelf-life should be provided. Other storage conditions are allowable if justified. Heat sensitive drug products should be stored under an alternative lower temperature condition which will eventually become the designated long-term storage temperature. Special consideration may have to be given to products that change physically or even chemically at lower storage conditions, e.g. suspensions or emulsions which may sediment or cream, oils and semi-solid preparations, which may show an increased viscosity.

The clarity of solutions and the physical stability of semi-solid preparations and emulsions should be determined over a wide temperature range. Where a lower temperature condition is used, the six months accelerated testing should be carried out at a temperature at least 15 ° C above its designated storage temperature (together with appropriate relative humidity conditions for that temperature). For example, for a product to be stored long term under refrigerated conditions, accelerated testing should be conducted at 25 +- 2 °C/60%RH +- 5%RH. The designated long-term testing conditions will be reflected in the labelling and expiration date.

Storage under conditions of high relative humidities applies particularly to solid dosage forms. For products such as solutions, suspensions, etc., contained in packs designed to provide a permanent barrier to water loss, specific storage under conditions of high relative humidity is not necessary, but the same range of temperatures should be applied. Low relative humidity (e.g., 10 - 20% RH) can adversely affect products packed in semi-permeable containers (e.g., solutions in plastic bags, nose drops in small plastic containers, etc.,) and consideration should be given to appropriate testing under such conditions.

For solutions with a high sugar content (greater than 60 %) or where the solubility of the active is low (less than 5 mg per 100 ml) or its content is close to saturation, stability data at low temperatures (2 to 8 ° C) must be conducted for at least 14 days.

	Conditions	Minimum time period at submission
Long-term testing	25 +- 2 °C / 60 +- 5%RH	12 months
Accelerated	40 +- 2 °C / 75 +- 5%RH	6 months

Where "significant change" occurs due to accelerated testing additional testing at an intermediate condition, e.g., 30°C +- 2 °C / 65%RH +- 5%RH should be conducted. "Significant change" at accelerated condition is defined as:
- A 5% potency loss from the initial assay value of a batch;
- Any specified degradant exceeding its specification limit;
- The product exceeding its pH limits;

- Dissolution exceeding the specification limits for 12 capsules or tablets;
- Failure to meet specifications for appearance and physical properties, e.g., colour, phase separation, resuspendability, delivery per actuation, caking, hardness, etc.

Should significant change occur at 40 °C/75%RH then the initial application for registration should include a minimum of 6 months' data from an ongoing one-year study at 30°C/65%RH, the same significant change criteria shall apply.

The long-term testing will be continued for a sufficient time beyond 12 months to cover shelf-life at appropriate test periods.

Long-term stability studies can also be performed at 30°C/65% RH, but then there are no intermediate conditions (Zone IV)

1.2.1.vi Testing Frequency

Frequency of testing should be sufficient to establish the stability characteristics of the drug product. Testing will normally be every three months over the first year, every six months over the second year, and then annually throughout the proposed shelf-life.

The use of matrixing or bracketing can be applied if justified (See Glossary).

1.2.1.vii Packaging Material

The testing should be carried out in the final packaging proposed for marketing. Additional testing of unprotected drug product can form a useful part of the stress testing and pack evaluation, as can studies carried out in other related packaging materials in supporting the definitive packs).

Where package container sealant integrity is to be assessed, higher than 75% relative humidity may be appropriate to stress its adhesive properties at 30 to 40°C e.g., blister units and strip packages. Alternatively, sealant integrity can be performed through physical testing of the pack itself

The loss of moisture can be important for liquid formulations, semisolid and certain solid dosage forms packed in moisture permeable containers and studies at low relative humidity and high temperature for a limited period of time may be appropriate for these products.

For most dosage forms stability data need only be obtained for the container-closure system to be marketed, provided that all container-closure systems are of identical composition and seal integrity and a brief justification is included stating the reasons for the container size chosen e.g. larger air volume, or largest surface contact etc.

If the product is to be marketed in more than one type of container and the applicant proves that resistance to variables such as moisture permeation, oxygen permeation, light diffusion etc., is demonstrated to be equal to or better than existing container closure systems, additional stability testing would usually not be required for solid dosage forms before such changes in packaging can be supplemented.

STABILITY

Physician's samples should be included in the stability studies if their container-closure system is different from the marketing container unless equivalence or superiority of the packaging material can be demonstrated.

In instances where the product will be marketed packaged in a "moisture permeable" material (e.g., polyethylene, polypropylene, polyvinyl chloride, etc.), the stability of the product should be determined under conditions of high humidity and elevated temperature.

Stability may be conducted in the least protective container-closure system if the superiority of the other containers can be proven. These data must be included in Part G .

The time that the product is stored in the bulk container, prior to packing into the final immediate container, constitutes part of the approved shelf-life, that is, the date of expiry remains a function of the date of manufacture, not the date of packaging. Stability data must be submitted for bulk products that are stored for a period of time prior to packaging into the final immediate containers e.g., for 25% or more of the approved shelf-life.

1.2.1.viii Evaluation

A systematic approach should be adopted in the presentation and evaluation of the stability information which should cover as necessary physical, chemical, biological and microbiological quality characteristics, including particular properties of the dosage form (for example dissolution rate for oral solid dosage forms).

The design of the stability study is to establish, based on testing a minimum of three batches of the drug product, a shelf-life and label storage instructions applicable to all future batches of the dosage form manufactured and packed under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification until the expiration date.

An acceptable approach for quantitative characteristics that are expected to decrease with time is to determine the time at which the 95% one-sided confidence limit for the mean degradation curve intersects the acceptable lower specification limit. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate, and this can be done by first applying appropriate statistical tests (for example, p values for level of significance of rejection of more than 0,25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall shelf-life may depend on the minimum time a batch may be expected to remain within acceptable and justified limits.

The nature of the degradation relationship will determine the need for transformation of the data for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Where the data shows so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the formal statistical analysis but only to provide a justification for the omission.

STABILITY

Limited extrapolation of the real time data beyond the observed range to extend expiration dating at approval time, particularly where the accelerated data supports this, may be undertaken. However, this assumes that the same degradation relationship will continue to apply beyond the observed data, and hence the use of extrapolation must be justified in each application in terms of what is known about the mechanisms of degradation, the goodness of fit of any mathematical model, batch size, existence of supportive data, etc.

Any evaluation should consider not only the assay, but the levels of degradation products and appropriate attributes. Where appropriate, attention should be paid to reviewing the adequacy of the mass balance, different stability, and degradation performance.

The stability of the drug products after reconstituting or diluting according to labelling, should be addressed to provide appropriate and supportive information.

In the case of reconstituted products for oral use, the reconstituted product must be tested for at least the recommended storage period at 25 °C even if the recommended storage temperature is 2-8 °C.

1.2.1.ix Statements/Labelling

The storage temperature should be based on the stability evaluation of the drug product. Where applicable, specific requirements should be stated particularly for drug products that cannot tolerate freezing.

The use of terms such as "ambient conditions" or "room temperature" is unacceptable.

There should be a direct linkage between the label statement and the demonstrated stability characteristics of the drug product.

The use of a temperature range, for example 15 - 25 °C, is not acceptable, unless adequate motivation for the lower temperature is submitted. The recommendation, "Store below 25 °C. Do not refrigerate" could be considered.

1.2.2 PRODUCTS CONTAINING WELL-KNOWN CHEMICAL ENTITIES (GENERICS)

1.2.2.i Selection of Batches

Stability information from accelerated and long-term testing is to be provided on at least two batches of the same formulation and dosage form in the containers and closure proposed for marketing. One of the two batches should be at least pilot scale. The second batch may be smaller (e.g.,
25 000 to 50 000 tablets or capsules for solid oral dosage forms). The long-term testing should cover at least 9 months duration at the time of submission. The manufacturing process to be used should meaningfully simulate that which would be applied to large scale batches for marketing. The process should provide product of the same quality intended for marketing, and meeting the same quality specification as to be applied to release of material.

1.2.2.ii Storage Test Conditions

STABILITY

	Conditions	Minimum time period at Submission
Long-term testing	25 +- 2 °C / 60 +- 5%RH	9 months
Accelerated	40 +- 2 °C / 75 +- 5%RH	3 months

The above criteria will be used for allocation of a tentative shelf-life of 24 months.
Stability data over the full shelf-life period must submitted for confirmation. ~~3~~ to confirm the tentative ~~At least 9 months' data must be submitted before a shelf-life can be considered.~~

Long-term stability studies can also be performed at 30°C/65% RH, but then there are no intermediate conditions (Zone IV)

The first two production batches manufactured post approval, if not submitted in the original application for registration, should be placed on long-term stability using the same stability protocols as in the approved application for registration.

If the accelerated data submitted in the original application were derived from batches other than production batches, accelerated data on at least one production batch must be generated.

Heat-sensitive drug products should be stored under an alternative lower temperature condition which will eventually become the designated long-term storage temperature. Where a lower temperature condition is used, the 3 months accelerated testing should be carried out at a temperature at least 15 °C above its designated long-term storage temperature (together with appropriate relative humidity conditions for that temperature).

Note:
Other general points discussed under "Products containing new chemical entities" are also relevant to generics.

2. PRESENTATION OF STABILITY DATA

a) The criteria for acceptance of each parameter (minimum and maximum values) relating to stability must be stated.
b) Overages in the formulation of batches included in the stability investigation should be clearly stated.
c) The actual analytical results obtained at the commencement (zero time) and at nominated time intervals throughout the trial (for example 0, 3, 6, 9, 12, 18, 24, 30, 36 months which can if necessary be adapted to suit the product) must be provided in a tabulated form. For products predicted to degrade rapidly more frequent sampling is necessary.
d).The container-closure system used must be clearly indicated, e.g., the type, nature, grade and colour of the material of the container and closure must be stated, composition of strip packaging, blister packaging and liners and size of the container(s) or pack-size must be clearly stated.
e) Storage conditions must be clearly defined in respect of temperature, light, humidity, opening and closing of container, whether stored upright or inverted, whether a desiccant is included in the container and presence of foam/cotton wool.

f) The name and strength of product, dosage form, batch size, batch number, name of manufacturer, source of active substance, dates of manufacture and initial testing must be stated.
g) If more than one assay result is available for any particular time interval, all results should be quoted including the Mean and Standard Deviation (where possible).
h) The actual result obtained for an assay at the beginning of the stability trial should be recorded and compared with subsequent values.
i) Initial assay results should be expressed as the quantity of active substance per unit dosage form in terms of micrograms, milligrams or grams. Assay results for subsequent checkpoints should be given in the same way and in terms of percentage of initial assay.
j) Quantitative results must be reflected wherever relevant in which case the expression "complies" does not suffice.
k) All results obtained should be discussed and conclusions drawn from the stability studies be given. A shelf-life must be concluded from the results. Explanations should be given where necessary e.g., anomalous or unusual results, change in assay method. Results should be processed utilizing current statistical methods and any assumption made should be statistically tested at the 90 - 95 % confidence level.
l) Stability-indicating method refers to the specific analytical method and does not absolve the applicant from submitting reasons why the assay methods are assumed to be stability-indicating.
m) An assurance that long-term testing will continue to cover the shelf-life period must be given in Part 2G (written undertaking at the time of submission of the application). Applicants are reminded of the recommendation under Testing frequency that products should be tested at least annually after the second year.

3. PREDICTION OF SHELF-LIFE FROM STABILITY DATA

a) At least nine months' data derived from the product stored at the maximum recommended storage conditions and three months under conditions of stress for generic products must be available at the time of submission , for consideration of a tentative shelf-life of 24 months. For products containing new entities, the data accumulated over a sufficient period of time, beyond the initial 12 months, to cover appropriate retest periods must be available.
b) Generally a tentative shelf-life shall only be assigned provided that the stability investigation of the product as above has been satisfactorily completed.
c) Applicants are reminded that a tentative shelf-life is often established on condition that the applicant has committed himself by an undertaking to continue and complete the required studies and to submit the results as they become available.

4. FOLLOW-UP STABILITY DATA

a) The tentative shelf-life must be substantiated by stability data derived from at least two production batches, stored at the maximum recommended storage conditions for the full period of shelf-life for generics. If the accelerated data submitted previously were derived from batches other than production batches, three months' accelerated data on at least one of the production batches are required.
b) For products containing new entities, the tentative shelf-life must be substantiated by stability data derived from at least three production batches. If the accelerated data submitted previously were derived from batches other than production batches, six months' accelerated data on the three production batches are required.
c) The maximum recommended storage conditions, integrity of container used and formulation will determine the temperatures and humidity conditions to be included in the stress-testing program.

d) Stability trials involving the product stored at the maximum recommended temperature must be continued for the full period to validate the tentative shelf-life.
e) An approved shelf-life may be extended through submission of additional data accumulated on production batches covering the full period applied for. Applicants should note, however, that the shelf-life may not be extended until the data have been evaluated and approved.

5. CALCULATION OF EXPIRY DATE

The expiry date is calculated from the date of manufacture. If the production batch contains reprocessed material the expiry date is calculated from the date of manufacture of the oldest reprocessed batch and it should be verified that the batch will meet the final product specification for the full period of the shelf-life allocated.

6. STORAGE IN BULK

The applicant must consider the suitability of the container used for in-process storage and transportation of bulk product in terms of compatibility, moisture permeation and closure seal ability.

7. EXTENSION OF SHELF-LIFE

For an extension of shelf-life real time data obtained according to the program on at least two production batches for the full period required must be submitted for generics and on at least three batches for new entities.

Note:
In order to facilitate evaluation, the application for an extension of shelf-life should include all the stability data in support of the shelf-life extension (including previously submitted data for the relevant batches).
Reference only to previously submitted data is not acceptable.

8. STABILITY REQUIREMENTS FOR POST REGISTRATION AMENDMENTS

Procedures and submission of data relating to changes in formulation, site and method of manufacture and packaging, that may influence the shelf-life quality of a product are outlined in the Guideline for Minor and Major Amendments.

APPENDIX 1

GLOSSARY AND INFORMATION

The following terms have been in general use, and the following definitions are provided to facilitate interpretation of the guideline.

Accelerated testing

STABILITY

Studies designed to increase the rate of chemical degradation or physical change of an active substance or product by using exaggerated storage conditions as part of the formal, definitive, storage program. These data, in addition to long-term stability studies, may also be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the impact of short-term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes.

Active substance; Active Pharmaceutical Ingredient; Drug Substance; Medicinal Substance

The unformulated active substance which may be subsequently formulated with excipients to produce the product.

Bracketing

The design of a stability schedule so that at any time point only the samples on the extremes, for example of container size and/or dosage strengths, are tested. The design assumes that the stability of the intermediate condition samples are represented by those at the extremes. Where a range of dosage strengths is to be tested, bracketing designs may be particularly applicable if the strengths are very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Where a range of sizes of immediate containers is to be evaluated, bracketing designs may be applicable if the material of composition of the container and the type of closure are the same throughout the range.

Climatic Zones

The concept of dividing the world into four zones based on defining the prevalent annual climatic conditions. Fluctuations in climatic conditions throughout South Africa prohibit the characterization of this country by any one of the four identified zones and the conditions of storage likely to be encountered in South Africa must be considered in designing the stability trial.

Dosage Form; Preparation

A pharmaceutical product type, for example tablet, capsule, solution, cream, etc. that contains an active ingredient generally, but not necessarily, in association with excipients.

Product; Finished Product
The dosage form in the final immediate packaging intended for marketing.

Excipient

Anything other than the active substance in the dosage form.

Expiry/Expiration Date

The date placed on the container/labels of a product designating the time during which a batch of the product is expected to remain within the approved shelf-life specification if stored under defined conditions, and after which it must not be used.

Formal (Systematic) Studies

Formal studies are those undertaken according to a pre-approval stability protocol which embraces the principles of these guidelines.

Long-Term (Real Time) Testing

Stability evaluation of the physical, chemical, biological, and microbiological characteristics of a product and an active substance, covering the expected duration of the shelf life and retest period, that are claimed in the application for registration and will appear on the labelling.

Mass Balance; Material Balance

The process of adding together the assay value and levels of degradation products to see how closely these add up to 100 per cent of the initial value, with due consideration of the margin of analytical precision. This concept is a useful scientific guide for evaluating data, but it is not achievable in all circumstances. The focus may instead be on assuring the specificity of the assay, the completeness of the investigation of routes of degradation, and the use, if necessary, of identified degradants as indicators of the extent of degradation via particular mechanisms.

Matrixing

The statistical design of a stability schedule so that only a fraction of the total number of samples is tested at any specified sampling point. At a subsequent sampling point, different sets of samples of the total number would be tested. The design assumes that the stability of the samples tested represents the stability of all samples. The differences in the samples for the same product should be identified as, for example, covering different batches, different strengths, different sizes of the same container and closure and possibly, in some cases, different container/closure systems.
Matrixing can cover reduced testing when more than one variable is being evaluated. Thus the design of the matrix will be dictated by the factors needing to be covered and evaluated. This potential complexity precludes inclusion of specific details and examples, and it may be desirable to discuss design in advance with the Council, where it is possible. In every case it is essential that all batches are tested initially and at the end of the long-term testing.

Mean Kinetic Temperature

When establishing the mean value of the temperature, the formula of J D Haynes* can be used to calculate the mean kinetic temperature. It is higher than the arithmetic mean temperature and takes into account the Arrhenius equation from which Haynes* derived his formula. *. Pharm. Sci. J 60, 927-929, 1971.

New Chemical Entity; New Molecular Entity; New Active Substance

A substance that has not previously been registered as a new active substance with the Council.

Pilot Plant Scale

STABILITY

The manufacture of either active substance or product by a procedure fully representative of and simulating that to be used on a full manufacturing scale. For oral solid dosage forms this is generally taken to be at a minimum scale of one-tenth that of full production or 100 000 tablets or capsules, whichever is the larger.

Primary Stability Data

Data on the active substance stored in the proposed packaging under storage conditions that support the proposed retest date. Data on the product stored in the proposed container-closure for marketing under storage conditions that support the proposed shelf-life.

Retest Date

The date when samples of the active substance should be re-examined to ensure that material is still suitable for use.

Retest Period

The period of time during which the active substance can be considered to remain within the specification and therefore acceptable for use in the manufacture of a given drug product, provided that it has been stored under the defined conditions after this period, the batch should be retested for compliance to its specification and then used immediately.

Shelf-life; Expiration Dating Period

The time interval that a product is expected to remain within the approved shelf-life specifications provided that it is stored under the conditions defined on the label in the proposed containers and closure.

The shelf-life is used to establish the expiry date of individual batches. It is the length of time required for:

a) the least stable active ingredient to degrade to the specified, motivated and approved or proposed fraction of the labeled quantity
b) some element of pharmaceutical elegance to drop to an unacceptable level, or
c) an arbitrary minimum of 2 years, unless otherwise determined by Council.

The shelf-life could also reflect the length of time required for:

d) a measurable increase in toxicity as shown by either animal experiments or clinical adverse reaction reports, or,
e). a measurable loss in reported clinical effectiveness(even though analytical methods show little or no reduction in apparent concentration).

– Release Specification

The combination of physical, chemical, biological, and microbiological test requirements that determine a product is suitable for release at the time of its manufacture.

- Shelf Life Specification

STABILITY

The combination of physical, chemical, biological and microbiological test requirements that an active substance must meet up to at its retest date or a product must meet throughout its shelflife.

Stability-Indicating Assay Methodology

Analytical method(s) that will quantitatively differentiate between the active ingredient and all known degradation products and/or related impurities.

Stability

The capacity of an active ingredient or dosage form to remain within specifications established to assure its identity, purity, strength and critical physico-chemical characteristics.

Storage Conditions

An acceptable variation in temperature and relative humidity of storage facilities. The equipment must be capable of controlling temperature to a range of +- 2 °C and Relative Humidity to +- 5%RH. The real temperatures and humidities should be monitored during stability storage. Short-term spikes due to opening of doors of the storage facility are accepted as unavoidable.
The effect of variations during equipment failure should be addressed by the applicant and reported if judged to impact stability results. Exceptions that exceed these ranges (i.e., 2 °C and/or 5%RH) for more than 24 hours should be described in the study report and their impact assessed.

Strength

A quantitative measure of active ingredient, as well as other ingredients requiring quantitation.

Stress Testing (Active Pharmaceutical Ingredient)

These studies are undertaken to elucidate intrinsic stability characteristics of the API. Such testing is part of the development strategy which is normally carried out under more severe conditions than that used for accelerated tests. Stress testing is conducted to provide data on forced decomposition products and decomposition mechanisms for the active substance. The severe conditions that may be encountered during distribution can be covered by stress testing of definitive batches of the active substance. These studies should establish the inherent stability characteristics of the molecule, such as the degradation pathways, and lead to identification of degradation products and hence support the suitability of the proposed analytical procedures. The detailed nature of the studies will depend on the individual active substance and type of drug product.

This testing is likely to be carried out on a single batch of material and to include the effect of temperature in
10 °C increments above the accelerated temperature test condition (e.g., 50°C, 60°C, etc.) humidity where appropriate (e.g., 75% or greater); oxidation and photolysis on the
active substance plus its susceptibility to hydrolysis across a wide range of pH values when in solution and suspension. Results from these studies will form an integral part of the information provided to the Council.

Photostability testing should be an integral part of stress testing.

STABILITY

It is recognized that some degradation pathways can be complex and that under forced conditions decomposition products may be observed which are unlikely to be formed under accelerated or long-term testing. This information may be useful in developing and validating suitable analytical methods, but it may not always be necessary to examine specifically for all degradation products, if it has been demonstrated that in practice these are not formed.

Stress Testing (Finished Product)

Studies undertaken to assess the effect of severe conditions on a product.

Light testing should be an integral part of stress testing (see above).

Special test conditions for specific products (e.g., metered dose inhalations and creams and emulsions) may require additional stress studies.

Supporting Stability Data

Data other that primary stability data, such as stability data on early synthetic route batches of active substance, small scale batches of materials, investigational formulations not proposed for marketing, related formulations, product presented in containers and/or closures other than those proposed for marketing, information regarding test results on containers, and other scientific rationale that support the analytical procedures, the proposed retest period or shelf life and storage conditions.

Tentative Shelf-life

A provisional shelf-life determined by projecting results from less than full term data (such as "accelerated studies") and storage under maximum recommended conditions for a period motivated by the applicant using the dosage form to be marketed in the proposed container-closure system.

APPENDIX 2

APROPRIATE TESTS

Both physical and chemical characteristics of the product should be monitored during storage. The possibility of interaction between the components of a fixed-combination product should be considered. Where a pharmaceutical interaction appears possible, the applicant should either submit data to establish that an interaction does not occur, or that it is clearly recognized and defined. Where significant interaction with the pack is likely, the effects on the product and on the pack (e.g., due to leaching of extractables, or due to absorption of constituents), should be evaluated and the results reported. The following tests must always be included for all dosage forms:

- Appearance
- Assay of all actives
- Degradation, if relevant

Assay

Detailed records of all analytical methods used in the stability studies should be kept along with validation data.

Published methods of analysis for which validations are also published as well as compendia methods of analysis should be kept, with partial validation data only demonstrating suitability of the in-house equipment and personnel. If a change in procedure is necessary during the stability trial, data should be generated and kept and processed in such a way as to prove that no statistically significant difference exists between the results of the older method versus the newer method.

The stability-indicating methodology should be validated by the applicant (and the accuracy, precision and reproducibility established) and analytical procedures described in sufficient detail to permit validation.

Degradation products

Chromatographic or other analytical methods designed to determine the content of degradation products should be submitted with the assay results even where an assay procedure specific for the active ingredient has been used.

Physical properties

In addition to assay for content of active ingredient and degradation products, it is necessary to ensure that physical properties of the product are unimpaired after storage. Consideration should be given to the stereo-chemical integrity of the product. The additional tests will vary with the formulation in question, but important attributes of various dosage forms may include the following:

a) Tablets
Disintegration time, dissolution rate (multi-point profiles for each active if it is a multi component product), moisture content, appearance, hardness, friability, colour and odour.

Solubility time and appearance of solution for soluble tablets, dispersion time, fineness of dispersion, dissolution rate (unless the active ingredient is in solution after dispersion) for dispersible tablets.

b) Capsules
Moisture content, colour and appearance (capsule shell and contents), brittleness, disintegration time (when dissolution rate is not applicable) and dissolution rate (multipoint profile).

In conducting stability trials for solid dosage forms and other products with compendia dissolution requirements, and which have a history of bioavailability problems, dissolution rates should be determined and multi-point profiles presented in tabulated form as a function of percentage of labelled claim dissolved to time.

c) Emulsions and suspensions
Appearance (such as colour and phase separation), odour, pH and viscosity,
resuspendability, particle size, sterility for ophthalmic preparations, preserving ability, preservative content.

d) Solutions
Appearance, pH, viscosity and density, (where relevant), solubility time (reconstitution and appearance thereof), and sterility preserving ability and preservative content (where relevant).

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Tests should be performed to ensure compatibility between the container-closure system and the product and the results included in the submission.

Test methods to determine particle size should not employ extensive dilution of particles or any other manipulation which could affect the real particle size existing in the dosage form. The applicability of the particle size dependent variable, such as sedimentation should also be considered.

After storage, samples of suspensions should be prepared for assay in accordance with the recommended labelling under "Directions for use".

e) Powders, granules (including those for reconstitution)
Moisture, resuspendability/reconstitution time and appearance of reconstituted product, microbial limits. The reconstituted product must be tested according to a solution or suspension.

f) Metered Dose Inhalation aerosols
Uniformity of delivered dose, number of metered doses, particle size (suspensions), spray pattern, microbial limits, deposition of emitted dose.

Because the container contents are under pressure, filled containers must be checked for loss in mass over the expiration dating period. For suspensions, aggregate (or solvate) formation may lead to clogged valves, or the delivery of a pharmacologically inactive dose. Corrosion of the metering valve or deterioration may adversely affect the delivery of the correct amount of active ingredient.

g) Ointments and creams
Homogeneity, pH, rheological properties, particle size and mass loss (plastic containers). Preserving ability if preservative present. Preserving ability for all topical preparations containing corticosteroids.

h) Parenterals
Small volume parenterals include an extremely wide range of preparations and container-closure types. Each should be included in the stability study. Evaluation of these products should include at least the following: pH particulate matter, pyrogens (containers larger than 15 ml), syringeability of non-aqueous products.

If a validated system exists, sterility will generally not be required to be included in the stability program. Initial sterility should be recorded on stability reports.

Tests should be performed to ensure the compatibility between the container-closure and the product and the results submitted. Aspects to be investigated on the closure include possible pigmentation, resealing following multiple penetration and force for needle to penetrate.
For Large Volume Parenterals the smallest container-closure size should be studied, provided that all container-closure systems are identical in composition and seal integrity.

A brief justification should be included stating the reasons for the container size chosen e.g., largest air volume or largest surface contact etc. Additional tests - globule size (where applicable), volume(plastic containers), moisture permeability (where applicable) and extractables (plastic containers). Tests should be performed to ensure the compatibility between the container-closure and the product. These data must be submitted.

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i) Suppositories
Melting range point, breaking strength and disintegration. The effect of aging may also be observed from hardening of the suppository base, therefore, control and stability testing should include disintegration time at 37 degrees C. Accelerated studies should be conducted at 2 - 3 degrees C below the melting point of the suppositories. In such cases, the product labelled to be administered by addition to another product (e.g., parenterals, aerosols) should be studied for stability and compatibility in admixture.

j) Admixtures
For any product intended for use as an additive to another product, the possibility of incompatibilities exists.

A suggested protocol should provide for tests to be conducted at zero-, 6-, 8-, 24- hour intervals. These should include:
- Assay of active ingredient and any other ingredient for which a limit is set in the final product specification;
- pH (especially for unbuffered LVPs), colour, clarity (particulate matter);
- interaction with the container;
- identification of precipitant/sediment (although the presence of any precipitant is already non-conforming)

k) Intra-uterine Devices (IUD)
Tensile strength of the withdrawal string and integrity of the package, i.e., seal strength of the pouch, sterility of the device. If the device contains a reservoir from which active ingredient diffuses through a controlled release membrane, it should be tested for total active content, degradation products and in vitro release rate of the active ingredient in
addition to the above tests. Vaginal devices such as doughnut shaped silastic or other polymeric matrix containing an active ingredient uniformly dispersed throughout the matrix must be checked for in vitro release rate of the active ingredient and extraneous extractable substances to establish stability and compatibility of the active with the matrix.

l) Tran dermal patches
Release rate, seal integrity, mass variation, adhesive properties.

Content of Antimicrobial Preservatives

Dosage forms containing preservatives to control microbial contamination should have the preservative content monitored initially (zero time) and at reasonable intervals throughout the projected expiration dating period of the product. This may be accomplished by performing microbial challenge tests (e.g., Antimicrobial Preservative Effectiveness Test of the USP or BP which is applicable to unopened containers) and by performing chemical assays for the preservative. When the minimum quantity of preservative to achieve effective microbial control has been determined for solutions, chemical assays for the full period of the shelf-life may be adequate, provided that the results of tests demonstrating the preservative effectiveness are submitted for evaluation. It is particularly important to consider the adequacy of the preservative system under conditions of use for multidose vials. When less than full term data are submitted for registration purposes, or for a major change in formulation, preliminary results for preservative effectiveness are a minimum storage period of nine months should be included for

STABILITY

those products for which the effect of aging on preservative effectiveness needs to be demonstrated e.g., suspensions, creams etc.

Those products requiring control of the microbial quality that do not contain preservatives, should be tested initially (at zero time) and at the termination of study or at the end of the projected expiration dating period according to the final product specification (Part 2F), for bio burden (e.g., Microbial limits Tests of the USP or BP, which includes a limit for total microbial count and for absence of Staphylococcus aureus, Escerichia coli, Pseudomonas aeruginosa and Salmonella species. In addition, it is recommended that topical preparations be controlled for the absence of
Pseudomonas cepacia, Aspergillus niger and Candida albicans as well as any other topical pathogens that may be identified as potentially harmful. Simulated use tests on topical preparations packed in jars and on ophthalmics are desirable.

Effects of Opening and Closing Containers

Investigation into "in-use" stability may be important for certain sensitive products. Where applicable, the opening and closing of containers may follow a recommended dosage direction included in Part 1A to the MRF application form.

Desiccants

Duration of satisfactory performance of desiccants should be related to the shelf-life/expiry date.

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

ADDENDUM 3

POST-IMPORTATION IDENTIFICATION AND TESTING OF MEDICINES

This document has been prepared to serve as a recommendation to applicants wishing to submit applications for registration of medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request for any additional information to establish the safety, quality and efficacy of a medicine and may make amendments in keeping with the knowledge which is current at the time of consideration of data accompanying applications for registration of medicines. Alternative approaches may be used but these must be scientifically and technically justified. The MCC is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy. It is important for applicants to adhere to the administrative requirements to avoid delays in the processing of applications.

Guidelines and application forms are available from the office of the Registrar of Medicines.

REGISTRAR OF MEDICINES
MS M.P. MATSOSO
DATE: 29/4/2003

POST-IMPORTATION IDENTIFICATION AND TESTING OF MEDICINES

1. Imported medicines must be identified chemically, assayed through a stability-indicating method, and other relevant tests as may be required, conducted before release, to prove that the product integrity has not been prejudiced during transport from sources in other countries.

(a) Exemption from these requirements will be considered in the following circumstances:

(b) When very small quantities are imported for "selected" patients, or groups of patients.

(c) If the identification and assay cannot be performed in South Africa the applicant must submit full justification and motivation, as the return of samples to overseas testing laboratories or manufacturers is not acceptable. The MCC may direct that a laboratory recommended by it perform the tests.

(d) Any other reason deemed by the applicant as being of such nature as to qualify for consideration for this exemption.

2. Any exemption approved will be valid for three years, provided that all the requirements are complied with during the period of validity. Initially, post importation testing must be done and subsequently at specific intervals.

3. When requesting exemption the following must be submitted:

ii. A suitable motivation for the request, that is, a suitable projection as to the annual usage of the relevant project, and/or detail of the identification and assay method which cannot be performed locally.

iii. Validation of transport, that is, evidence that the conditions during transport are continuously monitored by temperature and, where relevant, humidity recorders.

A tabulated summary indicating the method of transport utilized and the conditions during transport as indicated below must be submitted. A minimum of five printouts are required, giving an account of the same product or, five different products, provided that the products require the same storage conditions, and provided that the products are dispatched from the same site but by different shipments.

iv. A copy of the accelerated stability data of the formulation being applied for, packed in the final container as specified in Part 2D (to determine if the humidity must be monitored).

v. A copy of Part 2B as per the MRF 1 Form.

POST-IMPORTATION ID/TESTING

vi. An indication as to whether the request is for bulk products or for the product packed in the final container.

vii. A certificate of GMP compliance not older than 2 years, issued by competent regulatory authority or in terms of the WHO certification scheme.

viii. A copy of the proposed master release document in accordance with Part 2F reflecting the specifications pertaining to the product in question (example attached).

- The type of recorder used in transit
- Specify that the received certificate of analysis is valid, is complete (reflects the actual results of the tests performed) and reflects compliance with the registration requirements.
- Visual identification of the product and dosage form
- A consignment reference e.g. GRN (goods received notice) or invoice, etc. (Batch numbers on the invoice must concur with the batch numbers of the products).
- Confirmation of the integrity of the containers, seals, and labels. Each aspect must be specified and controlled to ensure that no damaged articles are accepted.

4. Furthermore, the following must be ensured:
   a) The transport conditions (temperature and humidity, where relevant) of each shipment are recorded by a suitable device which provides a printout that will form a permanent record of the specific shipment and is filed with the batch release documents
   b) An SOP, specifying the details of inclusion of the recorders, must be available for inspection. The procedure must include amongst others, the number of recorders, position of placement, date of activation and inactivation (on leaving the place of dispatch i.e. factory, and on receipt by the applicant i.e. warehouse) and evaluation of the printout with the reference to the stability data.
   c) The monitor must be validated and the validation data must be available for inspection.
   d) Please note that exemption is applicable only if each future shipment is monitored and subsequently evaluated for compliance with the stability profile.
   e) The submission must include the necessary supportive stability data. If previously submitted, a statement to this effect will suffice.
   f) The transport monitoring method, or transport conditions must be specified in the master release document. Applicants should note that any shipment received, not complying with these transport specifications, does not qualify for the exemption. These shipments must be assayed and identified as if exemption was not granted in the first instance.

POST-IMPORTATION ID/TESTING

N.B. The Medicines Control Council reserves the right to withdraw the exemption, should the applicant give cause.
Applicants who have obtained permission for exemption previously from the MCC for their products must re-apply for exemption.

NAME OF PRODUCT:
REGISTRATION NUMBER:
DOSAGE FORM:
APPROVED STORAGE CONDITION:
QC FUNCTION TO BE AUTHORISED (point (v) below):
ASSURANCE: TEMPERATURE RECORDED IN EACH SHIPMENT

Name of Product	Batch Number	Maximum and minimum temperature recorded	Maximum humidity recorded (Where relevant)	Duration of transport (Date commenced and date terminated)	Mode of Transport	Signature of MD/responsible pharmacist who verified the printouts

POST-IMPORTATION ID/TESTING

MASTER RELEASE DOCUMENT

Product name and code	
Batch number	
Approved storage conditions	
Final product specification reference number	
Receiving notice number (GRN)	
Date of dispatch and of receipt	
Quantity dispatched	
Number of containers received	

Test	**Specification**	**Result**	**Signature**
Temperature printout (storage conditions)	Present, attached, conforms to stability profile submitted		
Certificate of Analysis	Present, valid (batch specific), conforms to MBR1, complete		
Visual Identification	e.g. Product description, labelling, container, batch number, expiry date		
Shipping containers' condition	Clean, undamaged	Number approved, Number rejected	
Shipping container label	Untampered		
Shipping container seal	Present, intact		

Position/ Function

Signature	Date

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

ADDENDUM 2

VALIDATION PROTOCOLS AND VALIDATION REPORTS

This document has been prepared to serve as a recommendation to applicants wishing to submit applications for registration of medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request for any additional information to establish the safety, quality and efficacy of a medicine and may make amendments in keeping with the knowledge which is current at the time of consideration of data accompanying applications for registration of medicines. Alternative approaches may be used but these must be scientifically and technically justified. The MCC is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy. It is important for applicants to adhere to the administrative requirements to avoid delays in the processing of applications.

Guidelines and application forms are available from the office of the Registrar of Medicines.

REGISTRAR OF MEDICINES
MS M.P. MATSOSO
DATE: 29/4/2003

VALIDATION PROTOCOLS AND VALIDATION REPORTS

This guideline intends to communicate to Industry, the policy and requirements in respect of validation protocols and validation reports to be submitted to the Medicines Control Council.

1 IMPORTANT REFERENCES:

Chapter 9 of the SA Guide to Good Manufacturing Practice (1996 edition)
Circulars
United States Pharmacopoeia (USP)
British Pharmaceutical Codex (BPC)
FDA Guidelines on Validation

2 GENERAL COUNCIL POLICY:

The standard to be used to assess compliance with current Good Manufacturing Practice, would be the South African Guide to Good Manufacturing Practice (SAGMP) (latest edition).

"that the Guide to Good Pharmaceutical Manufacturing Practice as amended, which was prepared jointly by the secretariat and the PMA, be considered as the standard determined by Council as referred to in the specific condition for registration of a medicine, namely that the applicant shall ensure that the medicine is manufactured and controlled in accordance with Good Manufacturing Practice as determined by Council."

3 WHAT VALIDATION IS:

3.1 The SA Guide to GMP defines "validate" as follows:

"VALIDATE...

To provide documented evidence that an item of equipment, process, system or method is in a state of control (i.e. that all assignable causes of variation have been eliminated) and is able to consistently deliver specified results."

3.2 Validation is an integral part of current good manufacturing practice; it is, therefore, also an element of the quality assurance programme associated with a particular product or process.

3.3 There should be levels where validation and qualification should be performed, and the level should determine the intensity of these products. It should be least for liquid preparations (solutions) and most for parenteral medicines. For solid

dosage forms, it should depend on the criticality of the product as far as the patient is concerned.

4 WHEN VALIDATION SHOULD BE DONE:

4.1 Validation should be considered in the following situations:

- totally new processes
- new equipment
- processes and equipment which have been altered to suit changing priorities
- processes where the end product test if poor and an unreliable indicator of product quality

4.2 When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to consistently yield a product of the required quality.

4.3 In this phase the extent to which deviations from the chosen processing parameters can influence product quality should also be evaluated. In general the final batch size should not be more than ten times the batch size of the representative development batches.

4.4 The validation in the production unit mainly comprises the determination and evaluation of the process parameters of the facilities applied for the scale-up to final batch size. The control of all critical process parameters, the results of the in-process controls, final controls and stability tests should prove the suitability of the important individual steps of a procedure.

4.5 At least three batches (including at least two production batches in the final batch size) should be validated, to show consistency. Worst case situations should be considered.

4.6 When certain processes or products have been validated during the development stage, it is not always necessary to re-validate the whole process or product if similar equipment is used or similar products have been produced, provided that the final product conforms to the in-process control and final product specifications.

4.7 There should be a clear distinction between in-process controls and validation. In-process tests are performed each time on a batch-to-batch basis using specifications and methods devised during the development phase. The objective is to monitor the process continuously.

5 WHAT VALIDATION INVOLVES:

Validation involves the accumulation of documentary evidence relating to a process, item of equipment, or facility. This is achieved by means of validation protocol which should exist for every product and which details the tests to be carried out, the frequency of testing, and the results anticipated (acceptance criteria).

6 THE VALIDATION PROTOCOL (VP)

The Validation protocol should clearly describe the procedure to be followed for performing validation. The protocol should include at least:

- the objectives of validation and qualification study,
- site of the study,
- the responsible personnel,
- description of equipment to be used (including calibration before and after validation),
- SOP's to be followed,
- standards and criteria for the relevant products and processes,
- the type of validation,
- time/frequency should be stipulated,
- processes and/or parameters to be validated (e.g. mixing times, drying temperatures, particle size, drying times, physical characteristics, content uniformity etc.) should be clearly identified.

7 THE VALIDATION REPORT (VR)

7.1 A written report should be available after completion of the validation. The results should be evaluated, analysed and compared with acceptance criteria. All results should meet the criteria of acceptance and satisfy the stated objective. If necessary, further studies should be performed. If found acceptable, the report should be approved and authorised (signed and dated).

7.2 The report should include at least:

- the title and objective of the study,
- refer to the protocol,
- detail of material,
- equipment,
- programmes and cycles used
- details of procedures and test methods
- results (compared with the acceptance criteria).

- recommendations on the limits and criteria to be applied to all future production batches (which could form part of the basis of a batch manufacturing document).

8 RE-VALIDATION:

a). As a rule re-validation is required under the following circumstances:

- change of formulae, procedures or quality of raw materials
- change of equipment, installation of new equipment, major revisions to machinery or apparatus and breakdowns
- major changes to process parameters
- changes to facilities and installations which influence the process
- on appearance of negative quality trends
- on appearance of new findings based on current knowledge, e.g. sterilisation where

the frequency of checking is dependent on sophistication of in-process methodology

NOTE: The extent of re-validation will depend on the nature and significance of the changes.

9 GENERAL NOTES

9.1 The following aspects could be considered during the validation of specific dosage forms.

9.2 Validation of tableting: In the case of an oral tablet manufactured by granulation and compression, the critical process parameters may include (but not be limited to):

- blending time for the powder
- particle size distribution of the active
- granulating time and speed
- amount of granulating fluid-binder concentration
- drying time - final moisture content
- granule particle size distribution
- granule active content and homogeneity
- blending time of external phase
- tablet hardness with respect to water content, friability, disintegration, and dissolution
- lubrication level with respect tablet hardness, disintegration, dissolution and die-ejection force
- tablet mass and thickness control uniformity of content

If the tablet is film coated, the following additional parameters may require validation:

- spray rate of coating solution
- inlet and outlet air temperatures
- coating mass of polymer with respect to table appearance, friability, disintegration, and dissolution

10 REQUIREMENTS

10.1 Each applicant should have a Validation Master Plan (VMP) (See SA Guide to GMP, Chapter 9)

10.2 Each product must have a Validation Protocol (VP), (where validation is required, i.e. for *inter alia* solid dosage forms, certain suspensions, sterile products etc or where major changes in formulation or manufacturing method is envisaged).

10.3 There should be a Validation Report (VR) following the completed validation.

10.4 Validation Protocols and Validation Reports should be available for inspection purposes by the inspectorate.

The following is applicable:

10.4.1 New Applications for registration:
A VP must be included in Part 2E. (The VR should only be submitted when requested by the inspectorate).

10.4.2 Applications for change in applicant/manufacturer/packer/laboratory
A VP must be submitted with each application for a change in manufacturer or laboratory, or change in applicant where it also involves a change in manufacturer.

[If the validation had already been done, it should be indicated as such in the application. A VR should only be submitted when requested by the inspectorate.]

10.5 Applications will not be accepted if the Validation Protocol should be found to be incomplete.

10.6 Applicants should note that the submission of the VP or VR does not imply that the VP or VR had been approved by the council or secretariat.

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

ADDENDUM 1

ALCOHOL CONTENT

This document has been prepared to serve as a recommendation to applicants wishing to submit applications for registration of medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request for any additional information to establish the safety, quality and efficacy of a medicine and may make amendments in keeping with the knowledge which is current at the time of consideration of data accompanying applications for registration of medicines. Alternative approaches may be used but these must be scientifically and technically justified. The MCC is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy. It is important for applicants to adhere to the administrative requirements to avoid delays in the processing of applications.

Guidelines and application forms are available from the office of the Registrar of Medicines.

REGISTRAR OF MEDICINES
MS M.P. MATSOSO
DATE: 29/4/2003

ALCOHOL CONTENT FOR MEDICINES INTENEDED FOR ORAL ADMINISTRATION

a) The following maximum concentration limits will be allowed for ethyl alcohol as inactive ingredient:

0,5 % (v/v) ethyl alcohol for children under 6 years of age
5,0 % (v/v) ethyl alcohol for children 6-12 years of age
10,0 % (v/v) ethyl alcohol for adults and adolescents over 12 years of age.

b) Minute dose preparations are exempted from this requirement.

c) For products where higher concentration of alcohol are required, (e.g. plant extracts or where solubility or preservation might be problematic), exemption from ethanol concentration limits will be considered individually, provided that justification and motivation is submitted together with proof that the proposed dosage will not result in blood alcohol levels of 25 mg/dl or higher. (Table 1 is attached for reference purposes only).

d) In all instances, the alcohol content of a mixture must be stated prominently on the immediate container label, the outer label (carton), as well as in the package insert and patient information leaflet.

e) All medicines (registered products, "Old medicines" and new applications) must comply with the alcohol levels stated in this policy.

TABLE 1.#

Volume (Millilietres) of Ethanol Preparation Predicted to Produce a Blood Ethanol Concentration of 25mg/100ml* (100ml=1dl)

% Ethanol (v/v) in Product	**Age (Weight)**					
	2yr (12kg)	4yr (16kg)	6yr (21kg)	8yr (27kg)	10yr (32kg)	12yr (38kg)
2,5	91	122	160	205	243	289
5,0	46	61	80	103	122	144
7,5	30	41	53	68	81	96
10,0	23	30	40	51	61	72
12,5	18	24	32	41	49	58
20,0	11	15	20	26	30	36
25,0	9	12	16	21	24	29

ALCOHOL CONTENT

* Values were calculated from data contained in McCoy et al, 1979, by use of the formula: dose (in milligrams) = plasma concentration (Cp) x volume distributed (Vd) and assuming that absorption is complete. For example, the calculation to obtain the value of 40 ml for a 6-year-old ingesting a product containing 10% alcohol would be made as follows: Cp = 250 mg/L and Vd = 0.6 L/kg x 21 kg; therefore, dose = 250 mg/L x (0.6L/kg x 21kg) = 3.150 mg. Because for absolute ethanol (specific gravity 0.789), 1 g = 1.27 ml, 31.5 g = 40 ml; thus, for 10% ethanol, the calculated volume is 40 ml.

TABLE 1 is an abstract from an article on "Ethanol in Liquid preparations intended for Children", by the American Academy of Pediatrics, published in PEDIATRICS, Vol. 73 no.3 March 1984, page 406.

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

CLINICAL REQUIREMENTS

This document has been prepared to serve as a recommendation to applicants wishing to submit applications for registration of medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request for any additional information to establish the safety, quality and efficacy of a medicine and may make amendments in keeping with the knowledge which is current at the time of consideration of data accompanying applications for registration of medicines. Alternative approaches may be used but these must be scientifically and technically justified. The MCC is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy. It is important for applicants to adhere to the administrative requirements to avoid delays in the processing of applications.

These guidelines should be read in conjunction with Regulations 5, 22, 24, 25, 42 and 43 of the Medicines and Related Substances Act No. 101 of 1965.

Guidelines and application forms are available from the office of the Registrar of Medicines.

REGISTRAR OF MEDICINES
MS M.P. MATSOSO
DATE: 29/4/2003
Version MCC2003/1

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CLINICAL REQUIREMENTS

CLINICAL REQUIREMENTS

1. INTRODUCTION

This guideline serves to help applicants with the correct way of presenting a package insert for evaluation on application for registration of a medicine. Applicants are requested to follow the format stipulated in the guideline, in conjunction with provisions set out under Regulation 9 of the Act 90 of 1997 (hereafter referred to as the Act).

The professional package insert is regarded as the document that ensures the safe and effective use of the medicine under most circumstances. It presents a scientific, objective account of the medicines' uses and limitation as established by the supporting evidence. Ensure that all statements are adequately cross-referenced (See **Addendum I**). No promotional material may be included. Promotional statements and comparisons to other agents, indicative of any potential advantage over competitors will not be allowed.

After registration, the professional package insert may not be altered without the approval of the Medicines Control Council. In the case of safety-related matters the Council should be informed immediately, with submission of an approved professional package insert, a proposed amended package insert and the evidence/motivation for the change. (refer to PART 5.3 – Application for the Amendment to a package insert).

2. GENERAL:

2.1 Package inserts must be typed in a double-spaced text with a minimum legibility of 6-point Helvetica typeface in black ink on white cartridge paper or the equivalent thereof. The package insert text must be in at least English (British English) and any other official language.

2.2 Cross-referencing of the package insert shall be by leaving a broad margin on the right hand side of the page where every statement is clearly referenced.

2.3 Every statement shall be verified by a reference for purposes of evaluation. The exact page/s shall be stated and, if possible, the column and line number. Note, however, that no references shall appear on the finalized printed package insert. If an entire section is quoted from one source, it will be acceptable to indicate the one reference at the end of the relevant section.

2.4 The printing quality of the package insert must be clear to enable duplication, for inclusion into various documents, during the evaluation and registration process. The spelling and grammar in the package insert text, and typographical errors must be checked by the applicant before submission to the Medicines Control Council. Failure to do so shall result in a delay of the registration process.

2.5 Electronic submissions will be preferred.

3. PART 1A – PROFESSIONAL PACKAGE INSERT MULTI-SOURCE MEDICINES

3.1 HEADINGS AND PARTICULARS IN A PACKAGE INSERT

Applicants shall take note of which sources to be used as a reference for the different headings specified in Regulation 9 of Act 90 of 1997. Applicants also to note that in-house package insert templates shall be used as a reference during the evaluation process of therapeutically equivalent, interchangeable multi-source medicines, (Schedule of definitions (2) of Regulation 9 of Act 90 of 1997), and as contemplated under sub-regulation 1 (s)(iv) of Act 90.

3.2 SCHEDULING STATUS

Applicants shall note the scheduling status of medicines as determined from time to time by the Minister, and as published in the Government Gazette. The correct term for unscheduled medicines is "Not Scheduled".

3.3 PROPRIETARY NAME AND DOSAGE FORM

Shall be in accordance with the first page of the MRF 1.

3.4 COMPOSITION

An approved name of all active ingredients in accordance with Part 2 shall be listed.
The quantity thereof per dosage unit, per suitable mass, per volume, or per unit of the medicine shall be indicated.
The approved name and quantity of any preservative shall be listed and expressed as a percentage. The content of ethyl alcohol, where such quantity exceeds 2% shall be indicated.

Any ingredient which may cause an allergic reaction, or which may be harmful to certain individuals e.g. tartrazine, must be indicated as such, in accordance with Regulation 9 of the Act.

3.5 PHARMACOLOGICAL CLASSIFICATION

Shall be in accordance with Regulation 25 of the Act.

3.6 PHARMACOLOGICAL ACTION INCLUDING PHARMACOKINETICS

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data.

CLINICAL REQUIREMENTS

3.7 INDICATIONS

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data.

3.8 CONTRA-INDICATIONS

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data.

3.9 WARNINGS

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data.

3.10. INTERACTIONS

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data.

3.11 PREGNANCY AND LACTATION

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data.

3.12. DOSAGE AND DIRECTIONS FOR USE

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data.

3.13. SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data.

3.14. KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data.

3.15. IDENTIFICATION

In accordance with Part 2F.

3.16. PRESENTATION

In accordance with Part 2D.

3.17. STORAGE INSTRUCTIONS

In accordance with Part 2G.

The statement "Store all medicines out of reach of children." must be stated.

3.18. REGISTRATION NUMBER

Allocated by the Medicines Control Council.

3.19. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE

The name and business address of the holder of the certificate of registration, or the holder of the parallel importer license, whichever is applicable, shall be listed under this section of the package insert.

3.20. DATE OF PUBLICATION OF THE PACKAGE INSERT

This date shall be the date of the Medicines Control Council Resolution. The date shall only change when the package insert is amended extensively and is re-evaluated by Council.

Note: Any deviations from the requirements as described in these guidelines will require approval by the Council prior to implementation.

4. PART 1A - PROFESSIONAL PACKAGE INSERT NEW CHEMICAL ENTITIES

4.1 HEADINGS AND PARTICULARS IN A PACKAGE INSERT

The package insert shall follow the same format as laid out in the guidelines for interchangeable multi-source medicines above, in conjunction with Regulation 9 of the Act. The difference being that the primary source of reference for headings 5 to 13 below shall be the clinical study data in the SBRA, or the AMRP, whichever is applicable to that particular application.

CLINICAL REQUIREMENTS

4.2. SCHEDULING STATUS

Applicants to note that the scheduling status of medicines shall be determined from time to time by the Minister.

4.3. PROPRIETARY NAME AND DOSAGE FORM

Shall be in accordance with the first page of the MRF 1.

4.4. COMPOSITION

An approved name of all active ingredients in accordance with Part 2B(i) shall be listed.
The quantity thereof per dosage unit, per suitable mass, per volume, or per unit of the medicine shall be indicated.
The approved name and quantity of any preservative shall be listed and expressed as a percentage. The content of ethyl alcohol, where such quantity exceeds 2% shall be indicated.
Any ingredient which may cause an allergic reaction, or which may be harmful to certain individuals e.g. tartrazine, must be indicated as such, in accordance with Regulation 9 of the Act.

4.5. PHARMACOLOGICAL CLASSIFICATION

Shall be in accordance with Regulation 25 of the Act.

4.6. PHARMACOLOGICAL ACTION

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

4.7. INDICATIONS

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

4.8. CONTRA-INDICATIONS

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

4.9. WARNINGS

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

4.10. INTERACTIONS

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

4.11. PREGNANCY AND LACTATION

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

4.12. DOSAGE AND DIRECTIONS FOR USE

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

4.13. SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

The side effects that belong together shall be grouped together either in one paragraph or under one sub-heading, e.g. gastro-intestinal, skin, hematological etc., as per the System Organ Class Classification System of either WHOART or MeDRA.
Side effects that occur more frequently as well as the more serious type of side effects shall be listed at the beginning of the paragraph. The terms "more frequent" or "less frequent" may be used.

In the case of multi-component formulations, the side effects shall be listed separately for each active ingredient.

Special precautions shall be grouped together in a separate sub-section or paragraph. They should also be listed in order of importance.

4.14. KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

For treatment of over-dosage it is usually acceptable to state, "Treatment is symptomatic and supportive". There are exceptions where a standard text is required e.g. paracetamol, codeine, beta-blockers. Applicants should update themselves with the relevant Circulars on a regular basis.

4.15. IDENTIFICATION

In accordance with Part 2F.

4.16. PRESENTATION

In accordance with Part 2D.

4.17. STORAGE INSTRUCTIONS

In accordance with Part 2G.

The statement "Store all medicines out of reach of children." must be stated.

4.18. REGISTRATION NUMBER

Allocated by the Medicines Control Council.

4.19. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTFICATE

The name and business address of the holder of the certificate of registration, or the holder of the parallel importer license, whichever is applicable, shall be listed under this section of the package insert.

4.20. DATE OF PUBLICATION OF THE PACKAGE INSERT

This date shall be the date of the Council Resolution. The date shall only change when the package insert is amended extensively and is re-evaluated by Council.
Note: Any deviations from the requirements as described in these guidelines will require approval by the Council prior to implementation.

5. PART 1 B -PATIENT INFORMATION LEAFLET

5.1 INTRODUCTION:

This guideline serves to help applicants with the correct way of presenting a patient information leaflet for evaluation on application for registration of a medicine. Applicants are requested to follow the format stipulated in the guideline, in conjunction with provisions set out under Regulation 10 of the Act 90 of 1997 (hereafter referred to as the Act).

5.2 GENERAL:

5.2.1 Patient information leaflet shall be typed in a double-spaced text with a minimum legibility of 6-point Helvetica typeface in black ink on white cartridge paper or the equivalent thereof. The package insert text must be in at least English (British English) and any other official language.

5.2.2 Cross-referencing of the patient information leaflet shall be by leaving a broad margin on the right hand side of the page where every statement is clearly referenced.

5.2.3 Every statement shall be verified by a reference for purposes of evaluation. The exact page/s shall be stated and, if possible, the column and line number. Note, however, that no references shall appear on the finalized printed patient information leaflet. If an entire section is quoted from one source, it will be acceptable to indicate the one reference at the end of the relevant section.

5.2.4 The printing quality of the patient information leaflet must be clear to enable duplication, for inclusion into various documents, during the evaluation and registration process. The spelling and grammar in the patient information leaflet text, and typographical errors must be checked by the applicant before submission to the Medicines Control Council. Failure to do so shall result in a delay of the registration process.

5.2.5 Electronic submissions will be preferred.

5.3 HEADINGS AND PARTICULARS IN A PATIENT INFORMATION LEAFLET

The patient information leaflet must be written in easily understandable English, be consistent with the professional package insert and in accordance with the regulation 10, in terms of the legibility, language and format. (Refer to Addendum I for Lay terms).

Each immediate container should have a patient information leaflet and should reflect the following:

5.3.1 SCHEDULING STATUS

That is the scheduling status of the medicine as in the professional package insert.

5.3.2 PROPRIETARY NAME AND DOSAGE FORM

Shall be in accordance with the first page of MRF 1. When umbrella / brand" names are used, the applicants would be responsible to include precautionary statements of usage of these products simultaneously so as to inform patients of the correct usage and potential safety concerns. Example, if a range of products under the same umbrella name contains

paracetamol; it should not be used in conjunction with another products in the range also containing paracetamol.

6 WHAT THIS MEDICINE CONTAINS

The composition of the medicine, that is -

(i) the approved name of each active ingredient and the quantity thereof contained in a dosage unit or per suitable mass or volume or unit of the medicine;

(ii) all inactive ingredients must be listed qualitatively;

7 WHAT THIS MEDICINE IS USED FOR

The registered indications for use of the medicine as accepted by the Council in the professional package insert;

(e) **BEFORE TAKING THIS MEDICINE** – the following information should be included

- contra-indications
- precautions
- warnings e.g. warnings concerning sedative properties of the medicine, warnings concerning the risks involved with sudden withdrawal of the medicine etc must be included here
- interactions
- General statement to be included in this section:
  "If you are taking medicines on a regular basis, concomitant use of the medicine may cause undesirable interactions. Please consult your doctor, pharmacist or other health care professional for advice."
  "If you are pregnant or breast feeding your baby while taking this medicine please consult your doctor, pharmacist or other health care professional for advice."
  (THIS STATEMENT SHOULD BE BOXED AND BOLDED)

(f) HOW TO TAKE THIS MEDICINE

The recommended dosage must be included here. (Any special information, which the patient may require for the proper and safe use of the medicine, should be provided)

Information on what to do in specific circumstances, for example in the case of a missed dose, an unexpected reaction or in the case of an overdose should be included. **"Do not share medicines prescribed for you with others."** must be stated. As well as, **"In the event of over-dosage, consult your doctor or pharmacist. If neither is available, rush the patient to the nearest hospital or poison control centre".**

(g) SIDE-EFFECTS

(i) This section should be in layman's terms for the consumer to understand -

CLINICAL REQUIREMENTS

(a) Side-effects associated with the use of the particular medicine – listing the more frequent side-effects first.

(b) Side-effects that can be easily recognised by the patient.

(ii) The following general statement should be stated:
"Not all side-effects reported for this medicine are included in this leaflet. Should your general health worsen while taking this medicine, please consult your doctor, pharmacist or other health care professional for advice."

(h) **STORAGE AND DISPOSAL INFORMATION -**

Should contain information on how to store the medicine properly and how to dispose of unused medicine, such as by returning such medicines to the pharmacy. The following statement must be stated:
"Store all medicines out of reach of children."

(i) **PRESENTATION**

The number, volume or mass per package unit must be mentioned. A description of the packaging material (i.e. bottle, blister, etc.) should be included.

(j) **IDENTIFICATION OF THE MEDICINE**

A complete description of the physical appearance of the medicine.

(k) REGISTRATION NUMBER/ REFERENCE NUMBER

The number as allocated by the Medicines Control Council.
This date shall be the date of the Council Resolution. The date shall only change when the patient

(l) **THE NAME AND THE BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE**

The name and business address of the holder of the certificate of registration, or the holder of the parallel importer license, whichever is applicable, shall be listed under this section of the patient information leaflet.

(m) **THE DATE OF PUBLICATION OF THE PATIENT INFORMATION LEAFLET**

The information leaflet is amended extensively and is re-evaluated by Council.

Note: Any deviations from the requirements as described in these guidelines will require approval by the Council prior to implementation.

Note:
The responsibility for ensuring that the patient information leaflet is in line with the regulations, including assurance that the patient information leaflet corresponds with the information in the professional package insert will essentially rest with the applicant.

6. PART 1 C- LABEL

An example of the facsimile of the label must be included here. Requirements e.g. font size as stipulated in the Regulations should be adhered to.

The following inclusions are permitted:

"For state use only – Not for sale" – for tender items

"Professional sample" – samples for professionals

Note: Any deviations from the requirements as described in these guidelines will require approval by the Council in terms of Section 36 of the Act, prior to implementation.

7. PART 1 D - FOREIGN REGISTRATION

7.1 A list of countries including SADC countries in which an application has been lodged and the status of such applications shall be furnished. Countries that are members of the PER Scheme, other EU countries and the USA should specifically be identified. Approvals (with indications), deferrals, withdrawals and rejections should be stated. If the medicine has already been registered in any of the countries mentioned above, a copy of the registration certificate and the approved package insert (data sheet) as well as the conditions of registration, should be provided.

7.2 It should be stated whether data packages submitted in the countries in 7.1 are essentially similar to those submitted to the Medicines Control Council, including the proposed indications.

7.3 The Medicines Control Council should also be notified of any rejections, withdrawals or approvals of applications in the EU commission (mutual recognition process), Australia Canada, the Netherlands, Sweden, UK and USA during the evaluation period. Where the rejections or withdrawals relate to safety matters details in each case should be provided.

8. PART 4 - PRE-CLINICAL STUDIES

8.1 Guidelines are constantly evolving as a result of scientific developments and harmonisation of the requirements of the major overseas regulatory authorities. The Medicines Control Council endeavors to keep abreast of such developments and keep its application requirements and evaluation policies in line with "best international practice".

8.2 Legislation to be read in conjunction with these guidelines is:

CLINICAL REQUIREMENTS

- The Act
- Application form - PART 4
- Regulations

8.3 *For Biological Medicines the applicant must include details (published or unpublished) of the results of any trials or experiments carried out in man or in the animal target species, or carried out in other animals, that establish and confirm the safety of the medicine, with particular reference to the dosage and directions for use.*

8.4 For medicines other than biological medicines

In PART 4 the applicant needs to address the Pharmacology and Toxicology of the medicine;

8.4.1 Pharmacology:

8.4.1.1 Pharmacodynamics:

i) The primary effects of the medicine, with results in different animal species (ED_{50} values if possible) must be addressed.

ii) Comparison of the effects of the product with that of reference products is valuable information.

iii) Where relevant, the pharmacology of significant metabolites must be investigated.

iv) Other pharmacodynamic effects, especially those that might be of significance for adverse effects of the medicine, should be studied and described.

v) Interaction studies, where relevant, should be included.

8.4.1.2 Pharmacokinetics:

i) To assist in the interpretation of toxicological studies, it is important to compare the exposure of the animals used in the toxicity testing with that anticipated in patients given the proposed therapeutic dose regimen.

ii) PART 4 should, therefore, include comparative pharmacokinetics data, which includes C_{max} (after a single dose and at steady state) and AUC data for the parent drug and major/active metabolite(s), where relevant, in human and all species used in the toxicity, carcinogenicity and reproduction studies.

iii) These data should preferably be obtained from the toxicity studies.

iv) Other information (for example, $t_{½}$ and clearance), may be of value where important differences have been shown between animals and man.

8.4.2 Toxicology:

i) A summary or expert report must be submitted for each animal species studied, including sex, number of animals, dosage, route of administration, duration of study and toxic manifestations.

CLINICAL REQUIREMENTS

ii) Important points pertaining to preclinical toxicity to consider and address are:

- Dose-response relationship
- Time-response relationship
- Species specificity
- Target organ specificity
- Reversibility / irreversibility of toxic effects.

iii) Medicines that show specific toxicological effects, such as immunotoxicity, hepatotoxicity or neurotoxicity, should be investigated further, taking into account the points under ii)

iv) New medicines, which belong to classes that are known to produce a particular toxic effect, should be tested appropriately.

v) The possible mechanism(s) underlying the changes observed in toxicity studies need to be investigated and addressed.

vi) Due to the local climatic conditions the phototoxic potential of a medicine should be considered.

vii) The points to address in the reproduction studies are: fertility, embryonal toxicity, teratogenicity, peri- and postnatal effects.

8.5 The details of results from tests shall depend on the state of scientific knowledge at the time when the application is lodged. Any interim and final results of ongoing studies must be submitted as soon as these data become available.

8.6 A new route of administration or an increased daily dose of known excipients may result in the need for additional pharmaco-toxicological data.

9. PART 5 - CLINICAL STUDIES

9.1 Guidelines are constantly evolving as a result of scientific developments and harmonisation of the requirements of the major overseas regulatory authorities (USA, UK, Sweden, EU, Canada, Netherlands, Australia). The Medicines Control Council endeavors to keep abreast of such developments and keep its application requirements and evaluation policies in line with "best international practice" as per introduction. Please refer the Medicines Control Council Clinical trials guidelines.

9.2 Legislation to be read in conjunction with these guidelines are:

- Act
- Application form - PART 5.
- Regulation.

9.3 The clinical data must be presented in such manner that allows for easy cross-referencing to the index, other studies and the professional package insert. [Applicants wishing to submit data in electronic form should discuss the requirements with the Registrar of the Medicines Control Council].

9.4 Data presented in support of the safety and efficacy of the medicine must be derived from clinical trials conducted in compliance with

internationally accepted GCP guidelines. The studies must be properly designed and conducted and must be of acceptable statistical power. Where relevant, results published in peer reviewed scientific journals should be submitted.

9.5 Clinical trials should be conducted with the formula as applied for. Where studies have been conducted with different formulations, comparative equivalence studies need to be submitted to enable extrapolation to the formula intended for the market.

9.6 Normally individual patient data from clinical trials need not be included in an application dossier (except in the case of bioequivalence studies where the individual plasma/serum concentrations and derived pharmacokinetic data are to be supplied). Tabulated individual patient data may be included in the application if the applicant considers it appropriate.

9.7 Studies designed to demonstrate the pharmacodynamics of a medicine should address the effect of the medicine, duration of effect, dose-response and tolerance. Additional action on the central nervous system, respiration, circulation, blood chemistry, liver and kidney function, etc., should be considered at the proposed therapeutic dose(s).

9.8 Pharmacokinetics studies should be conducted with the formula as applied for. All relevant pharmacokinetics data shall be given, such as amount and rate of absorption after various routes of administration, plasma concentration, half-lives, drug clearance, drug metabolism as well as the routes and rates of excretion.

The pharmacokinetics studies are to be carried out with both single dose and multiple doses to steady state within the recommended dosage range.

Where applicable the plasma concentration(s) producing pharmacological and/or therapeutic effects, as well as adverse effects should be presented.

Possible dose-dependent pharmacokinetics needs to be addressed.

9.9 The trial design of the relevant clinical studies should be such that the safety and efficacy of the medicine can be established in comparison to either placebo and/or a registered medicine in UK, USA, Sweden. Netherlands, Canada, Australia and EU. The description of the studies must include patient population size and diagnosis, in- and exclusion criteria, test and comparator drug dosage regimens and duration of therapy, parameters assessed for efficacy and safety, including results of special investigations. Detailed statistical results must be presented. It should be noted that the randomised, double blind, placebo and/or active controlled trial design remains the gold standard for establishing the efficacy and safety of medicines.

9.10 The dosage of the active comparator (refer to Section 4.10 Bio-equivalence of a new multi-source medicines) must be in line with that approved for the specific indication.

9.11 The patient drop-outs must be addressed, including the time of and reason(s) for withdrawal.

9.12 To enable evaluation of safety of the medicine it should be noted that the long-term safety, particularly for medicines proposed for chronic use, needs to be addressed.

9.13 While a product is being evaluated, applicants should notify MCC of:

i) any approvals, rejections or withdrawals of applications in other countries and

ii) any serious adverse effects observed for the first time, or at a frequency, which has become a concern.

9.14 During the evaluation period, if new significant data becomes available that is contrary to the use of the medicines, applicants must notify Council. With this notification the applicant should state it's intention.

10. STANDARD PACKAGE INSERT INFROMATION FOR CERTAIN CATEGORIES/INGREDIENTS:

Unless the applicant can provide convincing evidence to the contrary, package inserts should contain the following, although the wording need not be identical. Standard information to be included in the professional package insert;

10.1 GENERAL DROWSINESS WARNING FOR ANTIHISTAMINES (OLD GENERATION)

This medicine may lead to drowsiness and impaired concentration that may be aggravated by simultaneous intake of alcohol or other central nervous system depressants. Patients should be warned against taking care of vehicles or machinery or performing potentially hazardous tasks where loss of concentration may lead to accidents.

10.2 GENERAL DROWSINESS WARNING FOR ANTIHISTAMINES (NEW GENERATION)

This medicine lacks significant sedative effects.

10.3 NON-CONTENT CLAIM : "CONTAINS NO ASPIRIN"

The use of the words "contains no Aspirin" may not appear on the package insert or in the advertising of non-aspirin containing medicines. In terms of regulation 9(3) the wording may still appear on the immediate label of the medicine provided that the type size is not bigger than the type size in which the active ingredients appear.

10.4 DEPENDENCE PRODUCING POTENTIAL OF MEDICINES

Warnings concerning the dependence-producing potential of certain substances may be made known to the professionals.

10.5 IMPORTANT PATIENT INFORMATION TO BE INCLUDED IN ALL PACKAGE INSERTS OF MEDICINES INTENDED FOR MALARIA PROPHYLAXIS

The following patient warnings must be included in all package inserts of products intended for malaria prophylaxis:

Because no form of prophylaxis is fully effective, the prevention of mosquito bites should form the mainstay of malaria prophylaxis. The following preventative measures to prevent mosquito bites should be taken:

i) endemic areas should preferably be visited during the dry season or in years when rainfall is low;
ii) high risk patients should avoid malaria areas altogether.
High risk persons include:
-babies and young children less than 5 years of age;
-pregnant women; -immuno-compromised individuals such as those on long-term steroids, cancer patients and those on chemotherapy, AIDS patients and those who have had their spleens removed;
iii) not going outside between dusk and dawn, when mosquitoes are most active;
iv) applying insect repellant to exposed skin and clothing;
v) wearing long sleeves and trousers at night;
vi) using mosquito nets, screens, coils or pads

A warning that should flu-like symptoms present the patient must inform the doctor that he has been to a malarious area.

10.6 USE OF MEDICINES DURING PREGNANCY AND LACTATION

In cases where the safety of a medicine with regard to its use in pregnancy and lactation has not been established, the following warning must be included in the package inserts for those medicines
"The safety of this preparation in pregnant women has not been established."

10.7 PACKAGE INSERTS / SLOGANS

Advertising (slogans) in package inserts is not permissible.

10.8 PACKAGE INSERT REQUIREMENTS : WATER FOR INJECTION

General exemption from package insert requirements in respect of sales packs of water for injection will be considered provided that the following warning appears on at least the outer label in prominent type:

"Water for injection must not be administered alone"

10.9 PRODUCTS CONTAINING ACE-INHIBITORS

The following boxed warnings must be included:

"Should a woman become pregnant while receiving an ACE-inhibitor, the treatment must be stopped promptly and switched to a different medicine."

"Should a woman contemplate pregnancy, the doctor should consider alternative medication."

CLINICAL REQUIREMENTS

The following warnings must be included:
"ACE-inhibitors pass through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydramnios as well as hypotension, oliguria and anuria in newborns have been reported after administration of ACE-inhibitors in the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur."

10.10 ANTIBIOTICS INDICATED FOR THE TREATMENT OF BETA-HAEMOLYTIC STREPTOCOCCAL INFECTIONS

The following statement must be included under the heading DOSAGE AND DIRECTIONS FOR USE:

"In the treatment of beta-haemolytic streptococcal infections, a therapeutic dose must be administered for at least 10 days".

10.11 REYE'S SYNDROME WARNING FOR MEDICINES CONTAINING ASPIRIN

The following warning be included in all package inserts for aspirin containing products:

"WARNING: ASPIRIN HAS BEEN IMPLICATED IN REYE'S SYNDROME, A RARE BUT SERIOUS ILLNESS, IN CHILDREN AND TEENAGERS WITH CHICKENPOX AND INFLUENZA. A DOCTOR SHOULD BE CONSULTED BEFORE ASPIRIN IS USED IN SUCH PATIENTS."

10.12 BENZALKONIUMCHLORIDE-PRESERVED OPHTHALMOLOGICAL PREPARATIONS:

The concentration of benzalkonium chloride should not exceed 0,01% and should not be used in preparations intended for soft contact lens solutions.

The following warnings should be included in the package insert:
"As the possibility of adverse effects on the corneal permeability and the danger of disruption op the corneal epithelium with prolonged or repeated usage of benzalkonium chloride preserved ophthalmological preparations cannot be excluded, regular ophthalmological examination is required.
Caution should be exercised in the use of benzalkonium chloride preserved topical medication over an extended period in patients with extensive ocular surface disease."

10.13 PACKAGE INSERTS FOR BENZODIAZEPINE

Unless the applicant can provide convincing evidence to the contrary package inserts for benzodiazepine should contain the following, although the wording need not be identical:

Under "Side-effects and special precautions"

CLINICAL REQUIREMENTS

The side-effects most commonly encountered are drowsiness and over sedation. Drowsiness is more common in elderly and debilitated patients and in patients receiving high doses. Less common are depression of mood and affect, disorientation or confusion, lethargy and ataxia.

Paradoxical reactions such as acute hyper excitable states with rage may occur. If these occur, the medicine should be discontinued.

There is a potential for abuse. Withdrawal symptoms (including convulsions) have occurred following abrupt cessation especially in patients receiving large doses for prolonged periods.

Injections:
Respiratory depression due to a depressant effect on the respiratory centre and cardiovascular collapse may occur following intravenous and intramuscular administration.

Special Precautions:
Particular caution should be exercised with the elderly and debilitated - who are at particular risk of over sedation respiratory depression and ataxia. (The initial oral dosage should be reduced in these patients);

- patients with pulmonary disease and limited pulmonary reserve;
- patients suffering from impairment or renal or hepatic function;
- patients suffering from anxiety accompanied by an underlying depressive disorder;
- patients receiving barbiturates or other central nervous system depressants. There is an additive risk of central nervous system depression when these medicines are taken together;
- patients should be cautioned regarding the additive effect of alcohol;

the medicine should be used judiciously during pregnancy and preferably avoided. Given during labour it crosses the placenta and may cause the floppy-infant syndrome characterised by central respiratory depression, hypothermia and poor sucking. It should not be administered to lactating mothers.

Patients should be advised, particularly at the initiation of therapy, not to drive a motor vehicle, climb dangerous heights or operate dangerous machinery. In these situations, impaired decision making could lead to accidents.

Overdosage:
Manifestations of overdosage include somnolence, confusion, coma, respiratory and cardiovascular depression and hypotension.

10.14 BENZODIAZEPINE OR BENZODIAZEPINE-LIKE COMPOUNDS

Product name to be inserted in [ ]

Indications

CLINICAL REQUIREMENTS

[ ] is only indicated when the disorder is severe, disabling or subjecting the individual to extreme stress.

Dosage and directions for use:
Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded.

For products with anxiety approved as indication:
Treatment should be as short as possible. The patient should be reassessed regularly and the need for continued treatment should be evaluated, especially in case the patient is symptom-free. The overall duration of treatment generally should not be more than 8-12 weeks, including a tapering off process. In certain cases extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status.
For products with insomnia approved as an indication:
Treatment should be as short as possible. Generally the duration of treatment varies from a few days to two weeks, with a maximum, of four weeks including the tapering-off process. In certain cases extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status.

Side-effects and special precautions:

[ ] is not recommended for the primary treatment of psychotic illness. [ ] should not be used alone to treat depression or anxiety with depression as suicide may be precipitated in such patients. [ ] should be used with extreme caution in patients with a history of alcohol or drug abuse.

Dependence
There is a potential for abuse and the development of physical and psychological dependence, especially with prolonged use and high doses. The risk of dependence is also greater in patients with a history of alcohol or drug abuse. Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability.
In severe cases the following symptoms may occur: de-realisation, depersonalisation, hyperacusis, numbness and tingling of extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Rebound effects
A transient syndrome whereby the symptoms that led to treatment with [ ] recur in an enhanced form may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.

Duration of treatment
The duration of treatment should be as short as possible (see Dosage), but should not exceed 4 weeks for insomnia and eight to twelve weeks in case of anxiety, (**) including the tapering-off process. Extension beyond these periods should

not take place without re-evaluation of the situation. It may be useful to inform the patient when treatment is started that it will be of limited duration, and to explain precisely how the dosage will be progressively decreased. Moreover, it is important that the patient be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur while the product is being discontinued.

(**) Note that the duration must be adapted according to approved indications for each individual product.

10.15 BETA-2 AGONISTS

INDICATION

"Treatment of reversible airway obstruction in asthma, chronic bronchitis and emphysema and prevention of bronchospasm in exercised-induced asthma."

Under "SIDE EFFECTS AND SPECIAL PRECAUTIONS"

Hypokalaemia may occur.
Overdosage may cause cardiac effects.
High dosages may increase the risk of serious side-effects, including cardiac dysrhythmias. This risk is further aggravated if administered concomitantly with other medicines that cause hypokalaemia and cardiac dysrhythmias or in the presence of hypoxia and acidosis.
The maximum dose should not be exceeded.

Under "DOSAGE AND DIRECTIONS FOR USE":

Do not exceed the recommended dose.

10.16 STANDARDIZED PACKAGE INSERTS FOR BETA-BLOCKING AGENTS

Unless the applicant can provide convincing evidence to the contrary, package inserts for beta-blocking agents should contain the following, although the wording need not be identical:

Under "Side-effects and special precautions"

a) Bronchoconstriction may occur in patients suffering from asthma, bronchitis and other chronic pulmonary diseases
b) Congestive cardiac failure and marked bradycardia may occur
c) A variety of neuropsychiatric disorders may occur, ranging from vague fatigue and nightmares to overt psychosis
d) the following may occur: exacerbation of peripheral vascular disease, or the development of Raynaud's phenomenon (due to unopposed arteriolar alpha-sympathetic activation), sexual impotence, hypoglycaemia, skeletal muscle weakness and gastrio-intestinal disturbances. Severe peripheral vascular disease and even peripheral gangrene may be precipitated.

CLINICAL REQUIREMENTS

e) Adverse reactions are more common in patients with renal decompensation, and in patients who receive the drug intravenously.
f) It is dangerous to administer this medicine concomitantly with the following medicines: hypoglycaemic agents, phenothiazines and various antiarrhythmic gents.

NB: - Such drug-drug interactions can have life-threatening consequences.

SPECIAL NOTE: - digitalisation of patients receiving long-term beta-blocker therapy may be necessary if congestive cardiac failure is likely to develop. This combination can be considered despite the potentiation of negative chronotropic effect of the two medicines. Careful control of dosages and of the individual patient's response (and notably pulse rate) is essential in this situation.

g) Abrupt discontinuation of therapy may cause exacerbation of angina pectoris in patients suffering from ischaemic heart disease. Discontinuation of therapy should be gradual, and patients should be advised to limit the extent of their physical activity during the period that the medicine is being discontinued.
h) Administration to pregnant mothers shortly before giving birth, or during labour may result in the newborn infants being born hypotonic, collapsed and hypoglycaemic.
i) Patients with phaeochromocytoma usually require treatment with an alpha-adrenergic blocker.

Under "Contra-Indications":

a) Particular caution should be exercised with patients suffering from the following: asthma, bronchitis, chronic respiratory diseases, second and third-degree heart block and bradycardia (less than 50 beats per minute), peripheral vascular diseases and Raynaud's phenomenon.

b) The normal dose should be reduced in elderly patients, or in patients suffering from renal dysfunction.

c) In the perioperative period it is generally unwise to reduce the dosage to which the patient is accustomed, as there may be danger of aggravation of angina pectoris or hypertension. A patient's normal tachycardic response to hypovolaemia or blood loss may be obscured during or after surgery. Particular caution should be taken in this regard.

Under "Known symptoms of overdosage and particulars of its treatment"

Overdosage may produce bradycardia and severe hypotension. Bronchospasm and heart failure may be produced in certain individuals.

Cases of mild overdose should be observed for at least 4 hours, as apnoea and cardiovascular collapse may appear suddenly.

Gastric lavage should be performed within 4 hours of suspected overdose. Repeated activated charcoal is necessary in severe overdose.

Atropine may be used to treat severe bradycardia. If the response is inadequate, glucagon may be give intravenously. Alternatively, dobutamine or isoprenaline may be required to reverse beta-blockade.

CLINICAL REQUIREMENTS

Intravenous cardiac pacing may be required for severe bradycardia. Bronchospasm should be treated with IV aminophylline or inhaled or IV beta-agonist eg. salbutamol.

10.17 WARNINGS FOR INCLUSION IN BETA-BLOCKER AND CLONIDINE PACKAGE INSERTS

The following warnings must be included in all beta-blocker and clonidine package inserts.

"Caution should be exercised when transferring a patient from clonidine. The withdrawal of clonidine may result in the release of large amounts of catecholamines that may give rise to a hypertensive crisis. If beta-blockers are administered in these circumstances, the unopposed alpha receptor stimulation may potentiate this effect";

"If a beta-blocker and clonidine are given concurrently, the clonidine should not be discontinued until several days after the withdrawal of the beta-blocker as severe rebound hypertension may occur".

10.18 BETA-LACTAM ANTIBIOTICS

The following statement must be included in the package inserts of all beta-lactam and fluoroquinolone antibiotics containing an indication or claim for Pseudomonas aeruginosa under the heading

INDICATIONS:

"In the treatment of infections caused by Pseudomonas aeruginosa, an aminoglycoside must be administered concomitantly".

10.19 BISMUTH CONTAINING MEDICINES

The package inserts for bismuth containing preparations must include a warning regarding the possibility of neurotoxicity with prolonged or excessive use.

10.20 PACKAGE INSERTS FOR CLOFIBRATE CONTAINING

Package inserts for all clofibrate-containing medicines must reflect:

Under "Indications"

Before starting treatment with clofibrate, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control over diabetes mellitus, etc.

If after considering the possible benefits in relation to the risks, it is decided to use clofibrate it is indicated in types II(B), III, IV and V hyperlipoproteinaemias (Frederickson and Levy Classification)

FREDERICKSON TYPE	LIPOPROTEIN ELEVATION	CLINICAL REQUIREMENTS MAJOR LIPID ELEVATION
I (very rare)	chylomicra	Triglycerides
II (a)	(LDL)	Cholesterol
II (b)	pre - + (VLDL + RDL)	Cholesterol + Triglycerides
III (rare)	abnormal (LDL)	Cholesterol + Triglycerides
IV	pre (VLDL)	Triglycerides
V (rare)	chylomicra + pre (VLDL)	Triglycerides + cholesterol

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has detrimental, beneficial or no effects on morbidity or mortality due to atherosclerosis or coronary heart disease.

Clofibrate therapy should be discontinued if a significant lowering in serum lipids is not obtained.

Under "Side-effects and special precautions"
Due to its action on cholesterol metabolism, clofibrate may increase the lithogenicity of bile and there is an increased frequency of gallstones.

A possible association between treatment with clofibrate and gastro-intestinal malignancies exists.

10.21 CONTRAST MEDIA - WATER SOLUBLE - BOXED WARNING

Fatal reactions have been associated with the administration of water-soluble contrast media. It is therefore of utmost importance that a course of action be carefully planned in advance for the immediate treatment of serious reactions, and that adequate and appropriate facilities and personnel be readily available in case of a severe reaction. Patients should be observed for a possible severe reaction during and for at least 30 - 60 minutes after administration of [proprietary name]. Patients with known or suspected hypersensitivity to iodated contrast media must be closely observed.

10.22 EXEMPTION FROM PACKAGE INSERT REQUIREMENTS IN RESPECT OF CONTACT LENS SOLUTIONS.

THIS EXEMPTION SPECIFICALLY DOES NOT APPLY TO ARTIFICIAL TEAR SOLUTION.

CLINICAL REQUIREMENTS

Contact lens solutions are exempted from package insert requirements in respect of contact lens solutions provided that: -

i) the relevant immediate container labels and cartons (if any) contain the necessary information that would normally be required on the package insert;
ii) such labels are fully bilingual;
iii) no advertising matter of reference to other products be included on such labels and
iv) the draft labels be submitted to this office for prior approval.

10.23 WARNING FOR INCLUSION IN POTENT TOPICAL CORTICOSTEROID PACKAGE INSERTS

The following warning must be included in all potent topical corticosteroid package inserts:
"Potent topical corticosteroid preparations (name) should not be applied to any skin crease areas"

10.24 PRODUCTS FOR TOPICAL USE CONTAINING CORTICOSTEROIDS

Package insert for all topical corticosteroid must reflect the following:

Under "CONTRA-INDICATIONS":
"Corticosteroids have been shown to be teratogenic in animals following dermal application. As these agents are absorbed percutaneously, teratogenicity following topical application cannot be excluded. Therefore (name of product) should not be used during pregnancy."

10.25 CO-TRIMOXAZOLE

All package inserts of products containing co-trimoxazole or long-acting sulphonamides must include a warning with regard to the occurrence of erythema multiforme, toxic dermal necrolysis and allergic vasculitis.

10.26 DICYCLOMINE IN INFANTS

The indication "infantile colic" and dosage schedule for children under six months of age be not included and a warning against its use in "infantile colic" be included.

Applicants submit evidence of, as well as a motivation for the dosage, dosage intervals, efficacy and safety of the administration to children older than six months and;

10.27 PACKAGE INSERTS FOR DISOPYRAMIDE PREPARATIONS

Under "Side-effects and Special Precautions"

CLINICAL REQUIREMENTS

The administrations of disopyramide may precipitate cardiac failure when administered to patients with congestive failure who have been stabilised.

Under "Contra-indications"

The administration of disopyramide is contra-indicated in patients with congestive cardiac failure, irrespective of whether the patient is digitalised or not

10.28 FLUOROQUINOLONE ANTIBIOTICS

Refer to Beta-lactam antibiotics

10.29 BOXED WARNING FOR GLIBENCLAMIDE & GLICLAZIDE

A reduction in dosage may be necessary in patients with renal dysfunction.

10.30 IODINE AND IODIDE CONTAINING MEDICINES

Synthetic thyroid hormone preparations are exempted from the following requirements.

On the LABELS as well as the package inserts of all medicines containing more than 0,60 mg iodine/ionic iodide per daily dose, the following warning must appear:

" NOT TO BE USED DURING PREGNANCY OR BY LACTATING MOTHERS"

On the package inserts of ALL iodine containing preparations, there must be a warning:

" NOT TO BE USED BY PERSONS WHO ARE ALLERGIC TO IODINE"

10.31 PACKAGE INSERTS FOR METOCLOPRAMIDE PREPARATIONS

Kindly note that this warning must appear on ALL package inserts

"WARNING

The use of metoclopramide throughout the duration of pregnancy is considered unsafe as teratogenicity has been demonstrated in animal studies."

10.32 WARNING TO BE INCLUDED IN THE PACKAGE INSERTS OF ALL PRODUCTS CONTAINING METRONIDAZOLE

The following warning must be included in the package inserts of all products containing metronidazole:

"Pseudomembranous colitis has been reported following the use of metronidazole".

10.33 NON STEROIDAL ANTI-INFLAMMATORY AGENTS

The following warning regarding the use of non-steroidal anti-inflammatory agents in pregnancy must be included in all package insert of non-steroidal anti-inflammatory agents:

"Regular use of NSAIDs during the third trimester of pregnancy may result in premature closure of the foetal ductus arteriosus in utero and possibly in persistent pulmonary hypertension of the newborn. The onset of labour may be delayed and its duration increased."

In addition to the above, the following special precaution should be included: "In view of the product's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients."

10.34 PACKAGE INSERT WARNING FOR OESTROGEN-CONTAINING PRODUCTS

With the exclusion of oestrogen-containing oral contraceptives, all other oestrogen-containing medicines shall have package inserts bearing the following warnings:

"Not for use during pregnancy. Vaginal adenosis and vaginal and cervical adenocarcinoma has been noted in post pubertal girls whose mothers were treated for threatened abortion with large doses of stilboestrol or related oestrogenic substances during their pregnancies."

"An increased incidence of endometrial uterine carcinoma, related to the continuous use of oestrogens in the post menopausal period, has been reported."

Products intended solely for post-menopausal use may have in their package inserts, instead of the aforementioned warning, the warning:

"NOT FOR USE DURING PREGNANCY"

All combination oral contraceptive products containing oestrogen shall have package inserts reflecting:

Under "SIDE EFFECTS AND SPECIAL PRECAUTIONS":

Oral contraceptive failure may occur with concomitant antibiotic therapy. For maximal protection, additional non-hormonal contraception is recommended for the duration of antibiotic therapy and for seven days afterwards. Those on long-term antibiotic therapy need only take extra precautions for the first two weeks of antibiotic therapy.

Spotting and breakthrough bleeding are possible signs of diminished contraceptive effectiveness.

CLINICAL REQUIREMENTS

10.35 PHENYLBUTAZONE & OXYPHENBUTAZONE

The indications and period of use for phenylbutazone and oxyphenbutazone preparations must be restricted to "acute exacerbations of ankylosing spondylitis" and a maximum period of use of 7 days;

Warnings (to be in prominent type and boxed) - the following must be included:

"Because of potentially serious and occasionally fatal adverse effects, use should be restricted to a maximum of 7 days and the maximum recommended dosage should not be exceeded".

"Caution against repeated short-term use is advised, due to the possible danger of sensitisation";

"Haematological disorders are potentially fatal";

For parenteral dosage forms the dosage be limited to a maximum 600 mg per day;
Combination products containing phenylbutazone and oxyphenbutazone is not allowed

10.36 POTASSIUM SUPPLEMENTATION

The following statement must be included in package inserts of medicines containing potassium for the purpose of potassium supplementation (under the heading pharmacological Action):

"This medicine contains potassium .... (salt to be named). It has not been proven that this dosage will necessarily prevent a significant potassium loss or correct an existing deficiency of potassium".

10.37 LONG-ACTING SULPHONAMIDES

Refer to co-trimoxazole

10.38 TAMOXIFEN

The following safety information must be included in the package inserts of all tamoxifen containing products:

WARNINGS:
"Endometrial changes
An increased incidence of endometrial changes, including hyperplasia, polyps and cancer has been reported in association with tamoxifen treatment. Any patients receiving or having previously received tamoxifen, who report vaginal bleeding should be promptly investigated".

CLINICAL REQUIREMENTS

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:
"Tamoxifen was shown to be genotoxic in some in-vivo genotoxicity tests in rodents. Gonadal tumours in mice, and liver tumours in rats receiving tamoxifen were reported in long-term studies. The clinical relevance of these findings has not been established.

10.39 TARTRAZINE (FD & C YELLOW NO 5) – WARNING IN THE PACKAGE INSERT

It is required that the following warning be included under the heading of "WARNING" in the package insert of medicines which contain "Tartrazine" –

"This product contains FD & C Yellow No 5 (Tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of tartrazine sensitivity in the general population is currently thought to be low it is frequently seen in patients who also have aspirin sensitivity."

10.40 TOPICAL TRETINOINS - STATEMENT ON PREGNANCY AND LACTATION.

Oral tretinoin has been shown to be teratogenic in a wide variety of animals.

Limited animal data urge caution in the use of preparations containing tretinoin during the first trimester of pregnancy.

In the case of eventual pregnancy the patient should inform her doctor.
Therefore, it may be concluded that cutaneous administration of tretinoin to pregnant women should not pose a significant hazard, although, as with all medicines, its use should be avoided during pregnancy unless the benefits outweigh any potential risk to the foetus.

It is not known whether tretinoin is excreted in animal or human milk. Because many medicines are excreted in human milk, caution should be exercised when applying topical tretinoin to nursing women. In this event the product should not be used on the chest.

10.41 TRICYCLIC ANTIDEPRESSANTS:

ACCEPTABLE CLAIMS

Serious depressive conditions such as major depressive illness, reactive depression and secondary depression. The following reflects what is defined under the various disorders:
Major depressive illness:
endogenous depression, unipolar depression, bipolar depression (manic-depressive psychosis), masked depression;
Reactive depression:
neurotic depression;
Secondary depression:

depression associated with alcoholism, schizophrenia, and Parkinsonism, depression associated with personality disorder, depression caused by medicines and senility with depression.

The claims for enuresis and other states which may benefit from the administration of tricyclic antidepressants such as phobic anxiety disturbances, obsessive compulsive disturbances and chronic pain, may be considered but will require the submission of substantiating data.

10.42 STANDARDIZED PACKAGE INSERTS FOR TRICYCLIC ANTIDEPRESSANTS

Unless the applicant can provide convincing evidence to the contrary, package inserts for tricyclic antidepressants should contain the following, although the wording need not be identical:

Under "Side-effects and special precautions"
Peripheral anticholinergic side effects: notably dry mouth, constipation, urinary retention and pupillary dilatation with blurred vision and changes in visual accommodation. When anticholinergic effects are severe, the medicine should be discontinued or reduced.

Drowsiness or excessive sedation in certain patients. On the other hand disorientation and agitation, insomnia and restlessness can also occur with normal doses. The risks of central nervous system depression are greater when administered together with other central nervous system depressants, e.g. alcohol, barbiturates.

NOTE: Elderly patients are more prone to all these effects, and therapy should be initiated at lower than standard doses in the elderly.

Special Precautions:

a) At the time of initiation of therapy, patients should be advised not to drive a motor vehicle, climb dangerous heights or operate dangerous machinery, for at least several days. In these situations impaired decision making could lead to accidents.

b) Caution should be observed with patients suffering from a depressive phase of manic depressive psychosis, as occasionally hypomania or mania can be precipitated in such patients. Withdraw the drug if the depression turns into a manic phase.

c) In elderly male patients suffering from prostatism urinary retention may be precipitated.

d) In patients suffering from cardiac disease, special caution should be observed because of the occasional problems of tachycardia, dysrhythmias orthostatic hypotension and other unwanted effects on blood pressure, aggravation of conduction disturbances and electrocardiographic abnormalities. Regular cardiological and electrocardiagraphic examination is advised.

CLINICAL REQUIREMENTS

e) Epilepsy may be aggravated.

f) The medicine should not usually be given to patients receiving other central nervous system depressants, e.g. barbiturates, and to patients receiving monoamine oxidase inhibitors only after a suitable interval (the drugs may be given together if the dosages are carefully controlled, preferably in hospital). The pressor effects of the direct-acting sympathomimetic agents, adrenaline and noradrenaline, are enhanced, and the use of local anaesthetics containing these vasoconstrictors should be avoided as hypertensive reactions may occur. The simultaneous administration of anticholinergic agents may be dangerous. The hypotensive effect of certain antihypertensive agents may be reduced.

g) Narrow-angle glaucoma may be aggravated.

h) Withdraw the drug if allergic skin reactions appear.

Under "Contra-Indications":
The acute phase of myocardial infarction. Administration is not advised during the first trimester of pregnancy, unless there are compelling reasons for its use.

Under "Overdosage":
Overdosage and poisoning may be characterised by central nervous system depression or excitation, severe anticholinergic effects and cardiotoxicity. The following symptoms and signs are characteristic of acute overdosage: drowsiness, restlessness, ataxia, stupor, coma, pyrexia, palpitations, tachycardia, cardiac arrhythmias, hypotension and in severe cases, respiratory depression. Epileptiform seizures may occur. Mixed poisoning with other central nervous system depressants is not uncommon.

Special warning:
This medicine should at all times be kept out of the reach of children, as even small doses may be fatal to them.

10.43 STATEMENT ON EOSINOPHILIA MYALGIA SYNDROME TO BE INCLUDED IN PACKAGE INSERTS OF L-TRYPTOPHAN CONTAINING PRODUCTS

The following statement must be included under the heading "WARNINGS" in the package inserts of the products containing L-Tryptophan.

"In the USA the Eosinophilia Myalgia Syndrome has been associated with the intake of L-Tryptophan."

10.44 CODEINE WARNING

The following warning must appear on the immediate container label, the outer label (if applicable) and the package insert of all CODEINE-containing products.

CLINICAL REQUIREMENTS

"Exceeding the prescribed dose, together with prolonged and continuous use of this medication may lead to dependency and addiction.

PHARMACEUTICA & ANALYTICAL REQUIREMENTS

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

PHARMACEUTICAL AND ANALYTICAL REQUIREMENTS

This document has been prepared to serve as a recommendation to applicants wishing to submit applications for registration of medicines. It represents the Medicines Control Council's current thinking on pharmaceutical and analytical aspects of medicines. It is not intended as an exclusive approach. The Council reserves the right to request for additional information to establish the safety, quality and efficacy of any medicine for which an application is submitted for registration. Alternative approaches may be used but these must be scientifically and technically justified. The MCC is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy and, in doing so, reserves the right to make amendments in keeping with the knowledge which is current at the time of consideration of data accompanying applications for registration of medicines.
These guidelines should be read in conjunction with Regulations 2, 8, 9, 22, 24, 42, 43, 44 and 48.

REGISTRAR OF MEDICINES
MS M.P. MATSOSO
DATE: 29/4/2003

Version MCC2003/1

PHARMACEUTICAL & ANALYTICAL REQUIREMENTS

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PHARMACEUTICAL & ANALYTICAL REQUIREMENTS

1. INTRODUCTION

The technical requirements for pharmaceutical and analytical information are divided into ten parts in the application form. The parts are as follows:

Part 2A – Active Pharmaceutical Ingredient.

Part 2B – Formulation.

Part 2C – Specifications and control procedures for active and inactive ingredients.

Part 2D – Containers and Packaging materials.

Part 2E – Manufacturing procedure.

Part 2F – Finished Product Pharmaceutical medicines.
Final filling lot and diluent Biological medicines

Part 2G – Stability studies.

Part 2H – Pharmaceutical Development.

Part 2I – Expertise and premises used for manufacture of biological medicines.

Part 3 – Bioequivalence studies as proof of efficacy.

The above Parts must be read together with the following documents:

ADDENDA TO THE GUIDELINES

ADDENDUM 1: Alcohol Content
ADDENDUM 2: Validation Protocols and Validation Reports
ADDENDUM 3: Post-importation Identification and Testing of medicines
ADDENDUM 4: Stability Studies
ADDENDUM 5: Bioequivalence Studies as Proof of Efficacy
ADDENDUM 6: Dissolution Studies

2. PHARMACEUTICAL AND ANALYTICAL REQUIREMENTS

2.1 PART 2A - ACTIVE PHARMACEUTICAL INGREDIENT

2.1.1 The International Nonproprietary Name (INN), or approved name, or chemical description of the active pharmaceutical ingredient(s) must be stated including the structural formula, the empirical formula and the molecular mass.

2.1.2 The solubility of each active pharmaceutical ingredient must be stated in terms of a unit part of the substance per number of parts of the solvent, or in unit mass of substance in a given volume of solvent, at a specific temperature. The solvents must include water and the solvent(s) relevant to the formulation.

2.1.3 The storage requirements for the active pharmaceutical ingredient and the retesting period must be stated

2.1.4 The name and physical address of each manufacturer of the API being applied for must be stated. No API from any source other than the approved source(s) may be used.

2.1.5 The Active Pharmaceutical Ingredient File (APIF) or open part of the DMF must be submitted and should include the following information:

- The name and physical address of the manufacturer (including any intermediate manufacturer)
- The INN or approved name of the relevant API
- The chemical name and chemical structure of the API
- A description of the pathway of synthesis using a flow chart which includes the starting materials, reagents, solvents, conditions, processes, duration of treatments, intermediates formed and any other relevant aspects. Note that specifications and control procedures for substances used in this process are not generally required. (The specific processes under any intermediate manufacturer must be identified)
- Evidence of occurrence of isomers and polymorphism, where applicable
- Structure elucidation for NCEs
- A description of impurities and a clear distinction between actual and possible impurities
- A description of possible degradation products
- The physical and chemical properties of the API
- The detailed methods used for identification and assay, including chromatograms wherever relevant
- CoA results relating to at least two full-scale batches manufactured not more than 2 years prior to date of submission
- Results of stability studies performed on the API obtained by the above method of synthesis. The conditions under which degradation products are formed. A validated stability-indicating assay method must be used in these studies, and must be described in full. Supporting chromatograms wherever relevant must be included.

PHARMACEUTICAL & ANALYTICAL REQUIREMENTS

2.1.6 Alternatively, if available, an EU certificate of suitability (CEP) can be submitted. Ensure that the CEP is accompanied by report A and any appendices mentioned in the CEP. If a CEP is submitted, detailed methods for the identification and assay of the API is not required in the APIF, and only an outline of the method of synthesis will suffice. Impurities and residual solvents listed in the CEP must be included in the API specifications (Part 2C).

2.1.7 Certificates of analyses (CoAs)

Valid CoAs* of two batches of the API, purchased and received by the manufacturer of the final product must be submitted. Any test not included in the valid CoA as specified in Part 2C must be performed by or on behalf of the manufacturer of the final product. A valid CoA must be on the letterhead of the manufacturer of the API.

2.1.8 When more than one manufacturer is being applied for or when different methods of synthesis are used in the manufacture of API, the following must be submitted:

a) An Active Pharmaceutical Ingredient File (APIF) for each manufacturer Note that if an identical method of synthesis is used by each manufacturer, or by each site of the same parent company, a statement to this effect will suffice.

b) Communication pointing out the differences in the methods used, where applicable, and the differences with regard to the impurity profiles and residual solvents. The specifications for the API must make provision for these impurities and residual solvents

c) Valid CoAs* issued by each manufacturer or site and the analytical reports issued by or on behalf of the manufacturer of the final product. For new sources the valid CoA* is required.

d) Comparative critical tests e.g. identification, assay, solubility and/or dissolution, particle size distribution, polymorphism, optical rotation, residual solvents and impurity profiles, performed on samples from each source to demonstrate physical and chemical equivalence, must be performed by the same laboratory (either the laboratory of the manufacturer or an independent laboratory). The same analytical methods and equipment must be used for these tests. These results must be presented in tabulated format.

*Valid as defined in the cGMP

2.1.9 Stability data on new chemical entity APIs must be generated according to the stability guidelines.

2.1.10 For biological medicines, specifications of raw materials used in the primary production lot are required:

a) In the case of a biological medicine of microbial origin, history and preparation of the seed lot must be described with specific reference to the tests that are carried out on such a seed lot to establish and maintain the integrity thereof.

b) Particulars of the composition of all culture media used in the preparation and testing of a biological medicine must be given.

c) Particulars must be given of the other biological source material from which a biological medicine (e.g. blood fractions) is extracted, including the origin of culture or blood.

d) Specifications must be at the level of the latest editions of recognised pharmacopoeial reference books and any deviations must be disclosed and fully substantiated.

e) Reference only to the recognized pharmacopoeial reference books shall be acceptable where the specifications correspond to the reference.

2.1.11 For biological medicines full details of tests carried out on the raw materials must be provided. (Refer to WHO guidelines on Biologicals).

2.2 PART 2B - FORMULATION

2.2.1 The formula must show the INN or approved names and/or chemical names of all APIs and approved names of excipients (inactive ingredients) including those that do not remain in the final product after manufacturing.

2.2.2 The name and the amount of the API must correspond to the name and quantity stated under Composition in the package insert.

2.2.3 A product may contain more than one API provided that

a) each API makes a contribution to the claimed indications;

b) the effect of combining the APIs in one product does not decrease the safety, stability or efficacy of the product; and

c) the product provides rational concurrent therapy for a significant proportion of the target population. e.g. tuberculostatic combinations.

2.2.4 Each raw material must be listed together with its quantity per dosage unit. This would include the vehicle(s), solvent(s) or base(s). In the absence of an approved name (INN) or chemical name, a chemical description or characterization of the substance must be given. Special technical characteristics of the excipient, where applicable, must be indicated. The technical grade of excipients, where relevant, must be indicated.

2.2.5 The purpose of each inactive ingredient or excipient must be stated briefly. If the excipient is used for multiple purposes in the formulation, each purpose must be mentioned.

2.2.6 For inactive ingredients, such as coating formulations, or excipients that are chemically modified, the chemical composition and the quantity of each component must be specified.

2.2.7 Any overages for the API must be stated separately and the justification for them must be given. The label claim quantity must be stated and the excess quantity indicated as the actual quantity or as a percentage. For example, 500 mg + 5 mg (=1%) overage*

*Use the asterisk to indicate the justification for the overage.

2.2.8 Where a potency adjustment for the API has to be made, a statement to the effect that the actual quantity of the active will depend on the potency, and the excipient(s) that will be used to adjust the bulk quantity must be identified, as well as the manner in which the

adjustment will be made. Potency calculations and formulae, where applicable, must be included and must also be shown in PART 2E **(Manufacturing Procedures)**.

2.2.9 Permitted flavouring and colouring agents (that comply with the **The Foodstuffs, Cosmetics and Disinfectants Act, Act 54 of 1972**), because of their complexity in many instances, may be described in terms of their main constituents only, provided that appropriate chemical identification and characterisation for them is given in the relevant section. The Colour Index Numbers (Foodstuffs, cosmetics and disinfectants Act, 1972 Reg. Food Colourants) of colourants must be included in the formula. The use of dyes, printing ink, coating materials, flavourants and organic solvents is subject to the same safety and quality requirements that apply to medicinal substances.

2.2.10 The content of alcohol, if included in medicines for oral administration, must comply with the requirements of Supplementary Guideline SG 1.

2.2.11 Where the vehicle is added up to the required volume or mass of the product, the actual or estimate quantity of that vehicle may be stated. However, expressions such as "add up to" and "q.s." are acceptable. Solutions added to adjust the pH must be described in terms of composition and strength (normality, molarity, etc.), but it is not necessary to state the actual quantity added as none may be added or only minute quantities may be needed.

2.2.12 For capsules, the fill mass, as well as the capsules size, composition and mass must be indicated.

2.2.13 In the case of coated dosage forms, the theoretical mass of the core, coating material, as well as the total mass of the dosage form/unit must be indicated

2.2.14 For biological medicines the details of any solution supplied by the manufacturer for the reconstitution before use of a dried biological medicine that is offered for sale in a dried form shall be supplied

2.2.15 oxicity levels per dosage unit must be indicated for all solvents and for other ingredients when required by Council. Levels must be indicated as per USP DI or Martindale, or The Complete Drug Reference, etc.

2.3 PART 2 C - SPECIFICATIONS AND CONTROL PROCEDURES FOR ACTIVE AND INACTIVE INGREDIENTS

2.3.1 Specifications and the limits of all active and inactive ingredients must be listed and adherence to pharmacopoeial requirements (BP, USP and EP), where applicable, is recommended. Any deviation from such specifications and limits must be fully substantiated. Use of any other pharmacopoeia must be justified and acceptable to the Council. In the latter case, copies of the relevant monographs must be included. More than one pharmacopoeia may be used for the active or inactive ingredients provided that each individual reference is used fully and not partially or selectively. For example, USP may be used for starch, and BP for lactose.

2.3.2 Any in-house specifications that are at a lower quality standard than that of an approved pharmacopoeia must be fully motivated, subject to approval by the Council.

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2.3.3 Additional specifications for isomers, polymorphs, as well as impurities, particle size distribution, residual solvents, etc., where relevant, must be submitted for all APIs

2.3.4 Control procedures for all active and inactive ingredients must be fully described. When pharmacopoeial methods are used, copies of those procedures must be submitted.

2.3.5 Specification limits and the control procedures for particle size of APIs which have a solubility of less than 1 part in 200 parts water, and for those which the Council may request, must be submitted. Particle size must be stated in SI units (μm). Exemption from this requirement may be granted if the API is administered as, a clear solution.

2.3.6 Colourants and flavourants must comply with either one of the following:

a) at least a specification limit and control procedure regarding chemical identification and a statement that the flavourants comply with the general requirements and that the colourants comply with the purity criteria of Act 54 of 1972 **(The Foodstuffs, Cosmetics and Disinfectants Act, Act 54 of 1972)**.

b) at least a specification limit and control procedure regarding chemical identification and a statement that it complies with the directives of the EU or the register of the FDA.

2.3.7 The following minimum requirement must be confirmed:

a) Identification and assay of the API will be performed irrespective of the possession of a certificate of analysis from the manufacturer.

b) Identification of the inactive ingredient will be performed irrespective of the possession of a certificate of analysis from the supplier; and that

c) Any tests not included in a valid* certificate of analysis will be performed.

*valid as defined by c GMP

2.3.8 Inactive ingredients for which a conclusive identification test is not described, all those parameters which are specific to the identification of those raw materials must be listed and the tests performed irrespective of the possession of a Certificate of Analysis from the supplier.

2.3.9 Microbial limits and control procedures for all natural raw materials of organic origin, must be included.

2.3.10 Frequency of testing of water, if applicable, shall be included. Water must be tested at least once a week for microbiological contaminants, and daily or just before use for conductivity, pH and total organic carbon if applicable.

2.3.11 All raw material of bovine origin must be certified BSE/TSE free and talc, asbestos-free

2.3.12 *For biological medicines:*

a) Specifications for the primary production lot used in the manufacture of the final filling lot of a biological medicine and specifications for all raw materials for the diluent must be listed.

b) Tests of a biological source material must include tests to confirm the identification, safety and potency of the primary production or bulk lot used in the manufacture of the final filling lot.

c) Parameters and criteria of acceptance to confirm the identification, safety and potency of the product must be provided.

2.4 PART 2D - CONTAINERS AND PACKAGING MATERIALS

2.4.1 Full details of the immediate container specifications and limits, including the nature of material, dimensions and sketches where applicable, as well as those of applicators and administration sets, the closure system, wadding and any other component in direct contact with the product, where applicable, and a description of the control procedures must be supplied.

2.4.2 A brief description of the outer container, if any, must also be given. At least the nature of the material must be mentioned e.g. Outer cardboard carton.

2.4.3 The type of container described here must correspond to that described in the package insert under "Presentation" and in the stability studies.

2.4.4 If the product is packed in bulk containers, the type of material of the container must be stated

2.4.5 All pack sizes must be described in the submission.

2.5 PART 2E - MANUFACTURING PROCEDURES

2.5.1 An Inspection Flow Diagram must be included.

2.5.2 The batch manufacturing formula and the batch size(s) must be included. Where more than one batch size is indicated, the batch formula of all batch sizes must be given.

2.5.3 A copy of Batch/Master manufacturing document for a real batch must be submitted. In addition, either a comprehensive flow diagram or a description of the manufacturing procedures detailing the various stages of manufacturing must be submitted. Indicate the type and size of equipment (including sieve sizes in μm), duration of treatment, temperature, light and humidity conditions, machine settings (e.g. rotation speed or rpm) etc. The frequency of all inprocess control tests (analytical, microbiological, and physical) must be shown in the flow diagram or specified in the description.

2.5.4 A copy of the Batch/Master Packaging document or a comprehensive description of the packaging procedures, detailing the various stages of packaging and labeling must be submitted. The type of equipment used in the packaging process must be indicated. The in-process tests and control procedures carried out during the packaging process must be included.

2.5.5 A process validation protocol must be submitted and, subsequent to this, a validation report when available (see Addendum 2: Validation Protocols and Validation Reports)

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2.6 PART 2F – FINISHED PRODUCT

2.6.1 Final product specifications and limits must be listed for in-process controls, final product controls (batch release), stability controls and the manipulated final product (if applicable).

2.6.2 The description of the final product must correlate with the description given under "Identification" in the package insert.

2.6.3 Content uniformity must be specified and a control procedure must be submitted if the quantity of the API is less than 2 mg or less than 2% mass per mass of the total mass of the dosage unit (e.g. tablet, capsule, suspensions, etc.), unless otherwise requested by Council. The active content assay need not be performed separately in the case where Uniformity of Content has already been performed for batch release purposes.

2.6.4 For quality control and batch release purposes, final product specifications for all solid oral dosage forms and suspensions shall include a requirement for dissolution of API(s) unless otherwise requested by Council.

2.6.5 Disintegration time, where relevant, for example for chew tablets, matrix tablets and soft gelatin capsules will be determined as a lot release requirement on all batches on which dissolution is not determined as a criterion for lot release as well as for stability. Disintegration time can be used as a lot release requirement for preparations containing multivitamins and minerals, unless a dissolution requirement for a specific product is included in the USP, in which case dissolution must be done as a lot release requirement.

2.6.6 See Appendix 2 of Stability guideline (Addendum 4, for minimum suggested specifications required for each dosage form.

2.6.7 For imported products, at least the identification and assay of the API content must be performed by an approved laboratory (FPRC) after importation. This is intended to verify that the product has not been affected adversely during the transfer process. Exemption from this requirement may be applied for according to the Guide on Post-importation Identification and Testing of Medicines (See Addendum 3).

2.6.8 The final non-analytical release criteria must include the verification of the appearance of the dosage form, the container, the package insert, the label, the batch number, the expiry date of the product, the certificate of analysis and the batch release documents (Final Product Release Responsibility or FPRR functions).

2.6.9 All control procedures other than those from a recognized pharmacopoeia must be described in full. Copies of pharmacopoeial procedures, when referenced, must also be submitted.

2.6.10 A complete analysis report or certificate of analysis for one batch (pilot or production not older than 2 years) of the finished product must be submitted with the application.

2.6.11 The full validation data of the assay method of the API related to batch release must be submitted. Chromatograms confirming the separation of the active from the degradation products, if relevant, must be included (See Addendum 4: Stability studies).

It must be demonstrated that the assay method is stability indicating, i.e. it must distinguish between the APIs and the degradation products.

If the assay method used to determine the API content is not stability indicating, then it cannot be used for assaying after importation.

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If the assay method (chromatographic) is taken from one of the latest recognized pharmacopoeias, then other partial validation data, e.g. system suitability and specificity must be submitted.

If different assay method/s are used for stability testing, then a full description of the method and the validation thereof must be submitted.

Supportive Chromatograms for the validation must be submitted.

2.6.12 All other quantitative assay methods (for preservatives, degradation products, antioxidants, dissolution assay, etc) must be validated and the validation data included.

2.6.13 For a product from a non-biological origin which has endotoxin levels, the validation data as required by the USP / BP/ EP must be submitted.

2.6.14 If the endotoxin levels are not determined according to the method in a recognised pharmacopoeia, the validation data must be submitted for evaluation.

2.6.15 For medicines imported into the country see Addendum 3.

2.7 PART 2G – STABILITY DATA: FINISHED PRODUCT

2.7.1 All applications for registration of a medicine must be submitted with stability data in accordance with the minimum requirements stated in Addendum 4: Stability studies.

2.7.2 The stability program must be described in detail and must include the following information:

(a) Conditions (temperature, humidity)

(b) Time points for testing e.g. 3 months, 6 months etc.

(c) Specifications to be determined

(d) How often the stability testing will be performed on future batches (should be in accordance with cGMP guidelines.)

2.7.3 Stability data must be presented in a tabulated format and must include the following:

i. Batch No. (Confirm that the formula is the same as the one applied for)

ii. Date of manufacture.

iii. Date of commencement of stability study

iv. Name of manufacturer.

v. Source of API (manufacturer not the supplier).

vi. Indicate whether production/pilot/experimental batch.

Vii. Container (Confirm that the container is the same as the one applied for).

viii. Storage conditions (must be controlled according to guidelines).

ix. Specifications and limits.

x. Stability results.

xi. Discussion and conclusion of shelf life for each type of container must be provided.

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2.8 PART 2H - PHARMACEUTICAL DEVELOPMENT

2.8.1 Any change or differences in the formulation during the development history must be indicated clearly.

2.8.2 A separate Pharmaceutical Expert Report (of not be more than 25 pages of A4 paper) must be submitted with each application and must include at least the following:

a) **Active Pharmaceutical Ingredient(s):**

- Comment on the synthesis of the API(s);
- Discuss all physico-chemical properties, e.g. solubility, water content, particle size, crystal properties, polymorphs, chirality, stability etc. Reference may be made to the APIF.

b) **Formulation:**

- Motivate and explain the function of the inactive ingredients;
- Indicate the safety/toxicity profile of the inactive ingredients;
- State any interactions likely to occur or that may occur under given circumstances;
- Motivate/explain all overages;
- Discuss relevant physico-chemical parameters separately, e.g., dissolution and choice of medium, pH, etc.
- Include pre-formulation studies and motivate.
- Novel formulations and excipients must be discussed /explained.

c) **Production/Manufacture:**

- Describe how the manufacturing method was derived;
- Describe how in-process controls and validation plans were developed.

d) **Stability:**

- Discuss the stability of the final product formulation and the parameters used during stability and to confirm quality for lot release;
- Discuss the containers used during stability studies;
- Discuss dissolution;
- Conclusion on stability and shelf-life allocation.

e) **Conclusion in Expert Report**

f) **Name, signature, date of signature and CV of responsible person.**

a) A reference list used in the compilation of the report.

2.9 PART 2I – EXPERTISE AND PREMISES USED FOR BIOLOGICAL MEDICINES - DETAILS RELATING TO THE PREMISES ON WHICH PRIMARY PRODUCTION OF BIOLOGICAL MEDICINES IS UNDERTAKEN AND TO THE STAFF INVOLVED IN THE PRODUCTION AND TESTING OF THE PRODUCT

2.9.1 A description of the premises where preparation of the primary production or bulk batch are carried out, names, qualifications, field and experience of the persons involved in preparation of the primary production and the final lot and details of the facility where the imported final filling lot is stored must be recorded.

2.9.2 A floor plan of the premises must be included.

2.9.3 If the premises are used for other purposes such details must be supplied.

2.9.4 Conditions under which the product is stored must be described.

3. PART 3 - BIOEQUIVALENCE STUDIES AS PROOF OF EFFICACY

3.1 Where clinical evidence in support of efficacy has not been submitted, studies and data to demonstrate the pharmaceutical and/or biological availability of the product must be included.

3.2 The applicant may request partial or total exemption from these requirements if efficacy and safety are intended to be established by means of clinical data (or for other reasons determined by the Council): Provided that clinical trials have been conducted with the same formulation as the one being applied for.

3.3 For details on requirements for bioequivalence refer to Addendum 5: Bioequivalence Studies as Proof of Efficacy as well as Addendum 6: Dissolution Studies.

3.4 The following must be included:

a) The purpose of the study must be stated.

b) Full details of the reference products used as the standard for reference purposes (including the applicant, proprietary name, lot number, expiry date, etc.) must be supplied. The reference products used must be motivated and will be subject to approval by the Council.

c) Details of the method used must be given.

d) Full data must be submitted. (including all individual patient data)

e) A discussion and the conclusion drawn from the data must be submitted

f) If pharmaceutical availability or equivalence data is submitted, the studies must be carried out according to the guidelines determined by the Council, and the data must be submitted in the format determined by the Council.

g) The applicant must state whether there are any *in vivo-in vitro* correlation from the data obtained by the method used.

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h) The applicant must confirm that the data submitted have been obtained with the formulation being applied for.

i) Bioequivalence studies must be carried out for all antibiotics and bioavailability for antimicrobial preparations (such as for tuberculosis) unless otherwise determined by the Council.

j) The applicant must motivate and justify why the study and the results obtained should be acceptable.

k) When bio-equivalence studies are submitted in support of efficacy of the formulation, the Application control document for bioequivalence studies included under FORMS must accompany the data.

REFERENCES

1. **ICH Guidelines (Q1A, Q1B and Q1F)**

2. **WHO Guidelins on biologicals**

3. **Stability Data Package for Registration in Climatic Zones III and IV (Q1F)**

4. **Photostability Testing (Q1B)**

LIST OF ABBREVIATIONS

API	**Active Pharmaceutical Ingredient**
APIF	**Active Pharmaceutical Ingredient File**
BSE	**Bovine Spongiform Encephalitis**
BP	**British Pharmacopoeia**
CGMP	**Current Good Manufacturing Practices**
CoA	**Certificate of Analysis**
CV	**Curriculum Vitae**
DMF	**Drug Master File**
EP	**European Pharmacopoeia**
EU	**European Union**
FDA	**Food and Drug Administration (USA)**
FPRC	**Final Product Release Control**
FPRR	**Final Product Release Responsibility**
GMP	**Good Manufacturing Practices**
INN	**International Nonproprietary Name**
MCC	**Medicines Control Council**
NCE	**New Chemical Entity**
NTI	**Narrow Therapeutic Index**
TSE	**Transmissable Spongiform Envcephalopathy**
USP	**United States Pharmacopoeia**
USP DI	**United Stated Pharmacopoeia Drug Index**
WHO	**World Health Organisation**

PHARMACEUTICAL & ANALYTICAL REQUIREMENTS

TERMINOLOGY

Active pharmaceutical ingredient
A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a therapeutically active ingredient

Finished product
A product that has undergone all stages of production, including packaging in its final container and labelling

Inactive ingredient
A substance or compound that is used in the manufacture of a pharmaceutical product and does not contribute to the therapeutic effect of the product, but is intended to enhance the consistency, appearance, integrity, stability, release characteristics, or other features of the product.

Manufacture (manufacturing)
All operations of purchase of materials and products, production, quality control, release, storage, shipment of finished product and related controls

Medicine
As defined in section 1 of the Medicines and Related Substances Act 1965, (Act No. 101 of 1965)

Medicinal product
See pharmaceutical product

Pharmaceutical product
Any preparation for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient

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