Government Gazette

REPUBLIC OF SOUTH AFRICA

Regulation Gazette No. 7659

Vol. 455 Pretoria 2 May 2003 **No. 24785**

PART 1 OF 2

AIDS HELPLINE: 0800-0123-22 Prevention is the cure

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: .....

ADDRESS: .....

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

QUALIFICATIONS: .....

Signature Date

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.

3 PROCEDURES FOR REPORTING

3.1 GENERAL PRINCIPLES

3.1.1 Who to report to:

All reports required by these guidelines should be sent to the Authority at the addresses reflected in Appendix 1.

3.1.2 Route of Notification:

Reports may be sent by post, facsimile or electronically.

3.1.3 Follow-up reports:

After initial receipt of an adverse reaction report, a notice of acknowledgement will be sent to the applicant quoting the number assigned to the case report. Any follow-up correspondence from the applicant, relating to the same case report, should be cross-referenced to the assigned database number or to an appropriate unique number assigned by the applicant (relating specifically to the initial notification). **This is the only reliable way to minimise the duplication of reports submitted by applicants**.

3.1.4 Internal pharmacovigilance system:

(i) The applicant should ensure that it has in place an appropriate system for pharmacovigilance that will provide for the proper management of safety data for its medicines and to ensure that appropriate action can be taken when necessary. It is strongly recommended that the applicant has available, in South Africa a full-time qualified person(s) responsible for pharmacovigilance, both for pre- and post-marketing surveillance. This person(s) should have experience and training in all aspects of pharmacovigilance and, if not a health care professional, should have access to a medically qualified person.

(ii) The managing director of a pharmaceutical company must nominate a specific individual(s) responsible for pharmacovigilance activities. The NADEMC must be informed in writing who the person(s) will is that will assume responsibility for all matters pertaining to pharmacovigilance, including the person(s) contact details (postal and e-mail addresses and telephone and fax numbers).

(iii) Responsibilities of the applicant's pharmacovigilance officer should include:

- The establishment and maintenance of a system which ensures that information about all suspected adverse reactions, which are reported to the company or organisation, including to medical representatives and clinical research associates, is collected and collated so that it is accessible at a single point.
- Serving as a contact person for Council and, in particular, the NADEMC for aall matters relating to pharmacovigilance.
- The preparation of the following for submission to the Authority
  - adverse drug reaction reports
  - Periodic Safety Update Reports (PSURs), when necessary
  - company-sponsored pre- and post-registration study reports
  - ongoing pharmacovigilance evaluation during the post-registration period.
- Ensuring that any request from the Authority for additional information deemed necessary for the evaluation of the risk-benefit ratio of a medicine, is provided to the Authority promptly and fully.

3.1.5 Report Format and Details:

(i) **Post-registration:** Reporting can be done using the adverse reaction report form available from the NADEMC (appendix 3), or applicants may use their in-house report forms, provided all the necessary data elements are included on the form in a readable format.

(i) **Pre-registration:** A Serious Adverse Event/Reaction (SAE) reporting form (appendix 4) should be used for reporting of pre-registration clinical trial adverse event/reaction reports. Applicants may use their in-house Adverse Event report forms to submit such reports, provided all the data elements are included on the form in a clearly readable format.

(ii) Applicants should submit **ALL** the **relevant** information available at the time of initial notification of an adverse drug reaction report, i.e., not only the minimum information required for a report. The attachment of discharge summaries, post-mortem reports, relevant laboratory data and other additional clinical data, is encouraged.

(iii) The original words/description (verbatim) used by the initial reporter to describe the adverse reaction should be provided. The medicine (or trade) name must be provided as reported by the initial reporter.

(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
Fax: (012) 323 4344

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

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
(j) 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 intermixing.

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.

5.6.9 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.