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

Version MCC1997/1

FOREWORD

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

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

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

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

SA GUIDE TO GMP

CONTENTS

INTRODUCTION

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

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

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

GLOSSARY

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

ADVERSE DRUG REACTION

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

ADVERSE DRUG REACTION (SERIOUS)

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

ADVERSE DRUG REACTION (UNEXPECTED)

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

ADVERSE EVENT

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

AIR-LOCK

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

ANALYTICAL METHOD

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

AUDIT

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

BATCH (OR LOT)

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

A batch is sometimes described as a lot.

BATCH NUMBER (OR LOT NUMBER)

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

BATCH MANUFACTURING RECORD

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

BATCH PACKAGING RECORD

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

BIOLOGICAL

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

BULK PRODUCT

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

CALIBRATION

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

CONTRACT MANUFACTURE, ANALYSIS OR SERVICING

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

DEDICATED FACILITY

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

DOCUMENTATION

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

FINISHED PRODUCT

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

GOOD MANUFACTURING PRACTICE

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

IN-PROCESS CONTROL

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

INTERMEDIATE PRODUCT

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

LEGALLY AUTHORISED PERSON

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

MANUFACTURE

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

MASTER DOCUMENT

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

MONITOR

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

PACKAGING

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

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

PACKAGING MATERIAL

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

PROCEDURES

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

PROCESSING STAGES

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

PRODUCTION

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

QUALIFICATION

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

QUALITY ASSURANCE

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

QUALITY CONTROL

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

RADIOPHARMACEUTICALS

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

RECALL

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

RECONCILIATION

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

RECORDS

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

REPROCESSING

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

SPECIFICATION

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

STANDARD OPERATING PROCEDURE (S.O.P.)

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

STATUS

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

VALIDATE

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

WITHDRAWAL

Implies the total withdrawal of the product from the market.

CHAPTER 1:

QUALITY MANAGEMENT

1.1 PRINCIPLES

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

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

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

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

1.1.4.1 Basic quality responsibility rests with top management.

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

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

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

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

1.2 QUALITY ASSURANCE

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

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

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

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

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

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

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

1.3 GOOD MANUFACTURING PRACTICE

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

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

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

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

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

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

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

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

(f) operators are trained to carry out procedures correctly

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

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

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

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

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

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

1.4 QUALITY CONTROL

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

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

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

1.5 AUDITS

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

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

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

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

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

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

1.6 QUALITY EVALUATION AUDITS

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

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

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

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

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

1.7 CRITICAL PROCEDURES OR STANDARD OPERATING PROCEDURES

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

1.7.2 Critical or Standard Operating procedures should include:

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

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

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

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

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

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

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

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

CHAPTER 2

ORGANISATION AND PERSONNEL

2.1 PRINCIPLES

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

2.2 RESPONSIBILITIES OF KEY PERSONNEL

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

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

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

- responsibilities should be delegated and acceptance acknowledged in writing.

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

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

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

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

2.2.5 Key personnel should be provided with adequate supporting staff.

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