# THE APPLICATION OF TOTAL QUALITY PRINCIPLES TO THE SOUTH AFRICAN PHARMACEUTICAL INDUSTRY

by

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**SUMMARY**

The traditional quality culture in the pharmaceutical industry is driven by the regulatory process of marketing authorisation and manufacturing authorisation. These components of the South African regulatory control system are exclusively technically-orientated, with no managerial focus.

This study identifies several quality management principles which could find general application in the pharmaceutical industry. The research compares the current regulatory control system with the total quality concept, and highlights the positive contribution which the total quality approach is able to make in terms of its field of reference; the strategic business value of quality; quality policy formulation; the quality organisational structure; enhanced operations management; and management's control over quality costs, in particular.

KEY TERMS

Total quality; Pharmaceutical industry; Pharmaceutical regulatory control system; Good pharmaceutical manufacturing practice; Strategic business value of quality; Quality policy; Quality organisational structures; Quality and pharmaceutical production control systems; Quality cost management.

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# CHAPTER ONE: INTRODUCTION

## 1.1 GENERAL

Due to the nature of pharmaceutical products, and the consequent risk of serious unwanted reactions or therapeutic failure which may result from products that are substandard in quality, there is universal acceptance within the pharmaceutical industry of the need to assure the quality of these products. For the same reason, there is also universal insistence on the part of consumers that such assurance of quality should be verified wherever possible by independent regulatory authorities who have statutory powers. The assumption which underlies the creation of a system of regulatory control is that these controls will lead to better, safer and perhaps more economical medical treatment (Dukes, 1985, pp. 1 - 2).

The statutory controls imposed in terms of the Medicines and Related Substances Control Act (South Africa, 1965) by the South African Medicines Control Council (MCC) are consistent with similar systems established in the major industrial countries of Western Europe and North America. The statutory powers of the MCC include the authority to grant or refuse permission for a medicine to be marketed in the Republic of South Africa (hereafter referred to as South Africa), to determine such preconditions as it may deem necessary to control the manufacture and sale

of each product, and to punish offenders by for instance cancelling the marketing authorisation (registration)of a product, or by having specific batches of product recalled from the market. The MCC is also empowered to approve or prohibit the trial use of all investigatory new drugs during clinical investigations conducted in this country. Moreover, the MCC has established a national system for collating and monitoring adverse drug reactions (ADRs) related to any drug marketed in this country, whether such a reaction occurred within the country or was reported from elsewhere (Folb, *et al.*, 1988, pp. 772-778, and Pillans & O'Connor, 1992, pp. 492-493).

Before being granted marketing authorisation by the MCC, the prospective manufacturer (applicant) is required to submit a Medicines Registration dossier (the so-called MBR 1 dossier) in which details are given concerning the proposed formulation, pharmaceutical development, therapeutic efficacy, safety, stability, controls over incoming materials, the intermediate product, the final product, and the manufacturing process (see Section 3.6). This information is then evaluated by the various specialist sub-committees of the MCC, after which the Council makes known its decision regarding the registration status of the proposed product (see Section 3.4). If registration is granted, the MCC will also determine the conditions of sale (scheduling status) and the conditions of manufacture of that

product. With regard to the conditions of sale or scheduling status of a medicine, it may briefly be stated that the provisions of the Medicines and Related Substances Control Act determines who may sell a medicine, and under what conditions such a sale may take place, or such a product may be advertised. The exact requirements differ according to the scheduling status allocated to each individual product by the MCC (see Section 3.7).

With reference to the determination of the conditions of manufacture of a product, the MCC has adopted the policy of granting marketing authorisation for a particular product on condition that an acceptable standard of "good manufacturing practice" (GMP) be maintained in the place of manufacture, thereby conferring a *quasi*-legal status upon GMP guidelines (see Chapter 4). Various GMP guidelines have been published internationally, all of which are aimed at providing insight into generally-accepted principles of quality assurance within the pharmaceutical industry, and these guidelines may be said to represent the collective wisdom of the industry and the relevant regulatory authorities. These guidelines cover aspects such as the qualifications and experience of the responsible personnel; the layout and amenities of production and storage areas; sanitation; maintenance of equipment; verification of raw materials; supervision of manufacture; in-process quality controls; documentation; and control over labelling and packaging (see Section 4.6).

It should however be noted that GMP guidelines were never intended to be a blueprint for a total quality system, and this limitation is clearly acknowledged in most GMP publications. There is a danger, however, that as a result of the *quasi*-legal status accorded to GMP guidelines in South Africa, the scope of quality control within the local pharmaceutical industry may be limited to the field of reference dictated by regulatory requirements only. Such a situation would be unsatisfactory not only from a regulatory point of view, but industry itself may thus be prevented from benefiting from the positive contribution to business profitability which a well-designed total quality system is able to make.

When seen from a quality management perspective, it is clear from the aforementioned background that the South African regulatory control system dovetails into many, but not all, of the activities that are routinely performed by an enterprise which operates an effective total quality system. In the course of this research the existing system of regulatory control (in its broadest sense) will be "superimposed" upon the structure of a total quality system in order to identify areas of common purpose and, more importantly, to highlight those areas where the present approach to quality control in the pharmaceutical industry may be enhanced by a total quality system.

## 1.2 A DESCRIPTION OF THE SOUTH AFRICAN PHARMACEUTICAL INDUSTRY AND ITS PRODUCTS

For the purposes of this dissertation the South African pharmaceutical industry will be defined as being that part of the chemical industry which is engaged in the manufacture of final dosage forms that are suitable for human and animal medicinal use. Activities related to the bulk manufacture of raw materials, i.e. fine chemical manufacture, and the manufacture of any remedy not manufactured in terms of the provisions of the Medicines and Related Substances Control Act, are not considered to be part of the pharmaceutical manufacturing process. However, the packaging process as well as that part of the distribution process which falls under the direct control of the manufacturer will, for the purposes of this research, be considered to be part of the pharmaceutical manufacturing process.

Five distinguishing characteristics according to which pharmaceutical products may be classified are presented in Table 1.1, which was adapted from a study by the National Productivity Institute (1989, p. 7). These characteristics relate to the product dosage form; therapeutic category; product differentiation status; point of sale; and scheduling status. The therapeutic category into which a particular product may be classified is determined by the pharmacological

TABLE 1.1 : A CLASSIFICATION OF PHARMACEUTICAL PRODUCTS

| A | B | | C | D | E |
|---|---|---|---|---|---|
| PRODUCT DOSAGE FORM | THERAPEUTIC CATEGORY STATUS | | PRODUCT DIFFERENTIATION | POINT OF SALE | SCHEDULING |
| Capsules (Hard Gelatin)<br>Capsules (Soft Gelatin)<br>Tablets (Uncoated)<br>Tablets (Coated)<br>Liquids (Non-sterile)<br>Liquids (Sterile, Non-parenteral)<br>Powders (Sterile)<br>Powders (Non-sterile)<br>Aerosols<br>Large and Small Volume Parenterals<br>Ointments/Creams (sterile)<br>Ointments/Creams (Non-sterile)<br>Suppositories<br>Pessaries<br>Lozenges | 1<br>2<br>3<br>4<br>5<br>6<br>7<br>8<br>9<br>10<br>11<br>12<br>13<br>14 | Alimentary Tract and Metabolism<br>Central Nervous System<br>Respiratory system<br>Cardiovascular System<br>Systematic Anti-Infectives<br>Musculo-Skeletal System<br>Dermatologicals<br>Genito-Urinary System and Sex Hormones<br>Other<br>Sensory Organs<br>Blood and Blood-forming Organs<br>Systematic Hormones<br>Parisitology<br>Cytostatics | Branded medicines i.e medicines identified by trade name.<br><br>Generic Medicines i.e medicines identified by a descriptive or formulary name. | Over the counter (O.T.C) medicines i.e available without prescription.<br><br>Prescription medicines i.e available only on prescription. | Unscheduled<br><br>Schedule 1 to 2<br><br>Schedule 3 to 7 |

action(s) of the active ingredient(s) of that product. This particular method of classification may therefore be used to define the market segment in which a particular product will compete. Fourteen such therapeutic categories are listed under column B of Table 1.1; these categories have been arranged in order of descending market share in South Africa during 1988 (*ibid.*, p. 14).

Products marketed in the same therapeutic market segment may compete with one another on the basis of therapeutic value despite the fact that opposing products may not necessarily be generically equivalent. This may explain why, according to the Steenkamp Commission of Inquiry (South Africa, 1978, pp. 8 - 9), market concentration within therapeutic submarkets is appreciably smaller in the pharmaceutical industry than in a considerable number of other manufacturing industries in this country. This, however, does not mean that oligopolistic or even monopolistic structures may not be present in submarkets that are for instance highly specialised or technologically very complex, but which represent a very small proportion of the overall market for pharmaceutical products.

One such example is to be found in the category for systemic hormones where, in 1978, the largest market share was 49,76 per cent of the total sales; however,

this market segment at that stage represented only 1,2 per cent of the total market for pharmaceutical products (*ibid.*, p. 12).

An important feature of the industrialisation of pharmaceutical production has been the introduction of branded medicines which are identified by means of trade names, as opposed to generic medicines which are not patented products and are identified by means of chemical names or pharmacopoeial references. The degree to which one product may be differentiated from a competing product has a direct influence on the marketing strategy that will be adopted for that product. Consequently, one of the most commonly-used methods of classifying pharmaceutical products is based on the distinction between "branded" medicines and "generic" medicines (see column C of Table 1.1) Product differentiation is of particular significance to the pharmaceutical industry, due mainly to the unique characteristics of the market in which it operates. In particular, the market for prescription medicines (see column D of Table 1.1) is unique because of the fact that the final consumer does not himself select the product which he is about to use; instead, a physician makes this decision on behalf of the consumer. Moreover, the final consumer often does not foot the bill for a prescription medicine because of the subsidies that are provided by medical aid societies or state-operated medical services.

The abovementioned characteristics result in the so-called "isolation effect", which tends to isolate the decision to purchase a medicine from sensitivity to the price of the product concerned. In addition, the very nature of a patient's clinical condition usually gives rise to the so-called "necessity effect", thereby further contributing to the low elasticity of demand which has traditionally been associated with the market for prescription medicines (*ibid.*, p. 19). Fiscal constraints in particular, however, necessitate careful revue of this traditional viewpoint regarding the demand characteristics of prescription medicines (see Section 2.2.2).

Health service strategists are increasingly emphasising the need for the individual to assume greater responsibility for his personal state of health. In keeping with this philosophy, there is a strong trend towards self-medication, i.e. the use of proprietary medicines without professional supervision, for the treatment of minor illnesses (National Productivity Institute, *loc cit.*, p. 22). Self-medication is seen as playing an important role in future cost containment within the healthcare system (Sutherland, 1985, p. 120). Products that are classified as "over the counter" (OTC) medicines (see column D of Table 1.1) would be available to this particular market sector. Unscheduled medicines would typically be available to the consumer via general

dealers, supermarkets and pharmacies, whereas schedule 1 and 2 medicines are available without prescription from pharmacies only, in terms of the provisions of the Medicines and Related Substances Control Act (South Africa, 1965, Section 22A). The sale of schedule 3 to 7 medicines may in terms of the same statutory provisions, be initiated only upon prescription (see column E of Table 1.1). The scheduling status of a medicine is in practice probably the most frequently used method for classifying pharmaceutical products, because of its legal implications regarding the sale and advertising of a medicine. This aspect, as it relates to the statutory controls over the advertising and sale of medicines, is discussed in greater detail in Section 3.7 of this dissertation.

## 1.3 NEW DESIGN CONTROL IN THE PHARMACEUTICAL INDUSTRY

The possible consequences of design failure in a pharmaceutical product are much more acute than would be the case with a product which does not put lives at risk. Probably the most chilling example of this truism is the thalidomide disaster which occurred in the early 1960's, and which lead to the birth of grossly deformed infants to some of the mothers who had used a supposedly safe sleeping pill containing the drug (see Section 2.4.2.1). One of the lessons learned from the thalidomide tragedy is that even investigatory drugs need to be carefully controlled;

although thalidomide was never commercially available in the United States of America, the drug had been distributed to over 1 000 doctors in that country on an investigatory basis. Seventeen cases of birth defects were subsequently reported in the United States, although ten of these were traced to purchases of the drug in other countries (Janssen, 1981, p.437).

New design control in the pharmaceutical industry is indeed a moving target, with some problems being identified after having eluded even the most exhaustive clinical investigations, and in some cases defying explanation altogether. Conlan (1990, p.32) notes that, of the 198 drugs granted marketing authorisation in the United States of America between 1976 and 1985, 102 had "serious postapproval risks" which necessitated labelling changes or withdrawal from the market. Van Andel (1985, pp. 234 - 239) observes that absolutely safe drugs do not, and probably never will exist; the degree of risk to the consumer must therefore be counterbalanced by the level of benefit derived from the use of a particular medicine. Certain elements of the risk involved in the use of a medicine may be self-induced by the final consumer. Non-compliance with the prescribed dosage regimen, interactions with other medicines used to self-medicate, and the non-medicinal use of a medicine in order to satisfy a craving or habit, are but a few examples of such self-induced risk elements.

Similarly, the irrational use of medicines by prescribers of these products may also put the final consumer at risk. This would serve to explain the rationale behind regulatory controls over the information which is communicated to prescribers and consumers in advertisements, package inserts and labels, and the preconditions that are applied to the sale of medicines (see Section 3.7).

In order to reduce the risk associated with the use of a medicine, it is incumbent upon the manufacturer to take all steps possible to assure the safety and therapeutic efficacy of the product concerned. To this end, the manufacturer is required by the Medicines and Related Substances Control Act (South Africa, 1965, Section 14) to submit an application for registration (i.e. an application for marketing authorisation) to the MCC. This application for registration must be submitted in the form of the so-called MBR 1 registration dossier (see Section 3.6) in which the applicant furnishes scientifically-based proof concerning the safety and therapeutic efficacy of the proposed product. In effect, the MBR 1 dossier is a summary of the new design control routine performed by the applicant; the MCC functions as the external auditor of that routine (see Chapter 3).

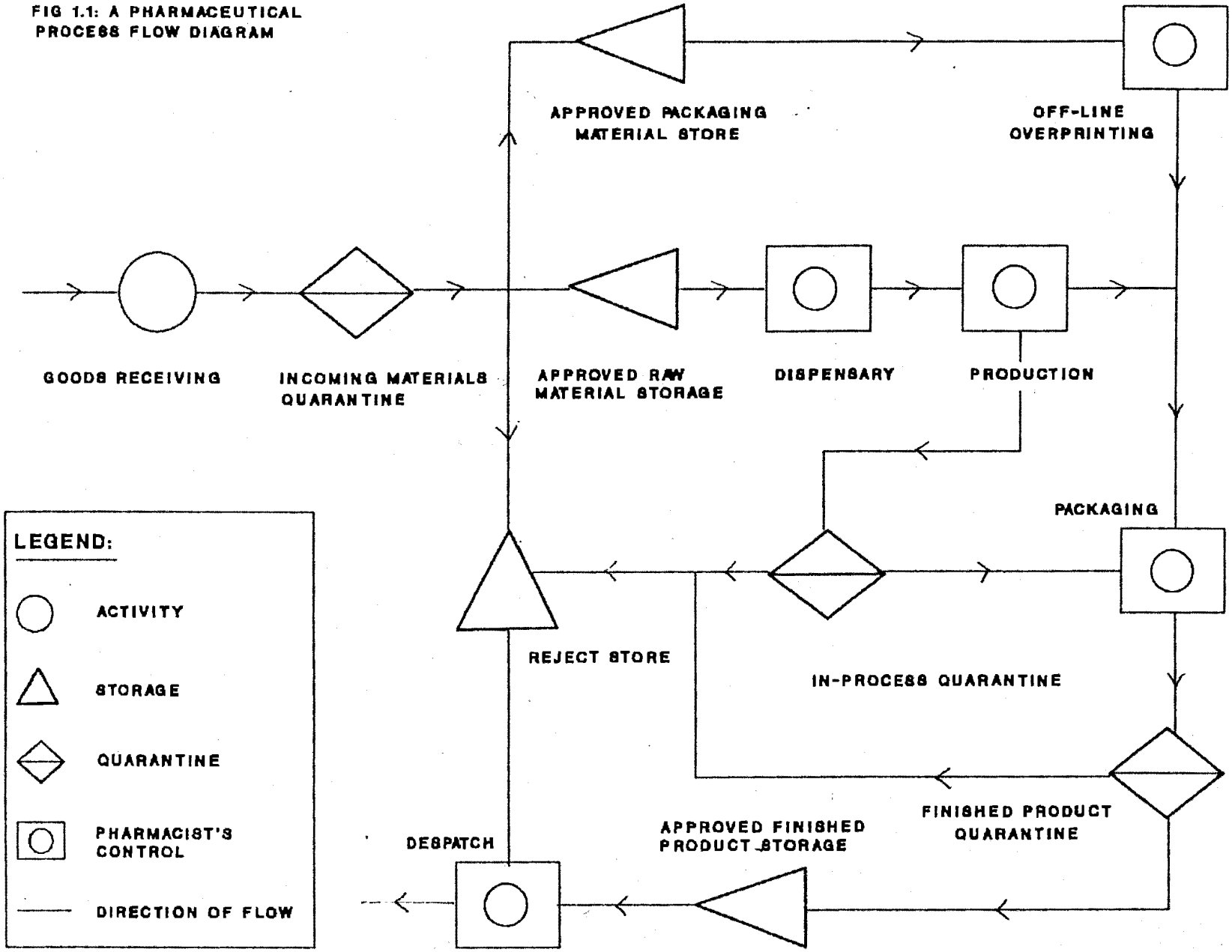
## 1.4 A DESCRIPTION OF THE PHARMACEUTICAL MANUFACTURING PROCESS WITH REFERENCE TO CRITICAL AREAS OF CONTROL

The classification of pharmaceutical products which is presented in Table 1.1 includes a large variety of dosage forms listed under column A of the table. The diversity of dosage forms (product types) thus listed is an indication of the fact that the individual manufacturing processes involved are equally diversified. For instance, the production line which is used to produce a tablet will differ considerably from that used to produce a liquid dosage form, both in terms of the equipment used as well as the nature of the processes involved. Moreover, the nature of the in-process controls and the manufacturing environment are both directly related to the type of product being manufactured. The production of a sterile product, for instance, is possible only in an environment that will ensure a specific air quality in terms of the limits set for micro-organisms and particulate matter, and the in-process controls that are used are consequently designed to verify compliance with those environmental limits in particular. The production of radio-pharmaceuticals, be they liquid or solid dosage forms, similarly requires a very specialised manufacturing environment and unique in-process controls.

Schroeder (1985, pp. 134 - 155) states that the manufacturing process in general may be classified under two main categories: Firstly a classification which is based on the type of product flow and, secondly, a classification which is based on the type of customer order (i.e. make-to-stock, or make-to-order). In the experience of the present author, the pharmaceutical manufacturing process can best be described as being an intermittent-flow process, which Schroeder (*ibid.*, pp. 136 - 138) describes as being characterised by production in batches at intermittent intervals; equipment and labour are organised into work centres requiring similar types of skill or equipment, and the product will flow only through the work centres necessary for its manufacture. Due to the unpredictable demand for pharmaceutical products, these products are usually made-to-stock rather than made-to-order.

Despite the diversity of manufacturing processes encountered within the pharmaceutical industry, it is possible to present a process flow diagram which is representative of the pharmaceutical manufacturing process in general. Such a flow diagram is presented in Figure 1.1, and is based upon the author's personal observations within the industry. Figure 1.1 highlights in particular the critical areas of control in the pharmaceutical manufacturing process. A brief description of each of these areas of control is given

FIG 1.1: A PHARMACEUTICAL PROCESS FLOW DIAGRAM



in the paragraphs which follow. This summary contains references to documents and procedures that are either unique to the pharmaceutical industry, or that are of particular significance in the pharmaceutical industrial context. Later chapters of this dissertation describe these documents and procedures in greater detail. The nature, content, and purpose of the MBR 1 registration dossier is for instance described in Chapter 3. It is also important to note that the critical areas of control which are identified in Figure 1.1 generally correspond to those that are focused upon by the so-called good manufacturing principles to which both the pharmaceutical industry and the regulatory authorities subscribe; the nature and importance of GMP principles are highlighted in Chapter 4 of this dissertation, which also includes a detailed description of the various control documents used.

### 1.4.1 Incoming material receipt and quarantine

Figure 1.1 shows that the pharmaceutical manufacturing process commences with the receipt of incoming materials. Materials are visually screened by goods receiving personnel for any obvious signs of contamination, cross-contamination or damage, in accordance with written standard operating procedures.

The delivery note is matched to the relevant purchasing order originally issued by the purchasing department, in order to verify the receipt of materials from approved vendors only. The consignment is then placed into quarantine by physically isolating the material in a demarcated storage area and/or by means of a status labelling system. Quality control personnel sample the material in accordance with written sampling procedures, whereafter the analytical and other test controls are carried out as specified under Annexures 6 (raw materials) and 9B (packaging materials) of the product's MBR 1 registration dossier (see Sections 3.6.9 and 3.6.15). Depending on the results of these control procedures, the batch of incoming material is either accepted or rejected. Approved and rejected materials are identified as such by means of a status labelling or other suitable control system, and moved to an approved or rejected materials storage area as the case may be.

1.4.2 Dispensing

A picklist of raw materials is provided by the production planning department. The materials required are drawn from the approved raw materials warehouse on a "First In First Out"-basis. The appropriate quantities of materials are then weighed or measured in a dispensary under the supervision of a pharmacist, and all details regarding the dispensing process are recorded on the relevant batch manufacturing document.

Dispensed materials are labelled and then staged in a staging area to await collection by the relevant production department. Much emphasis is placed during this process upon the accuracy of measurements, the prevention of mix-ups, and the avoidance of contamination and cross-contamination. The signatures of both the technician and the supervising pharmacist are recorded on the relevant batch manufacturing document in respect of every action for which they are responsible. Unused raw materials are returned to the approved raw materials warehouse, and the relevant inventory records are updated accordingly.

### 1.4.3 Production

The relevant production department collects the staged, dispensed raw materials which are then identified and, in some cases, re-weighed or re-measured on the production floor under the supervision of a pharmacist, who also supervises and records the addition of each material to the mix. In-process controls are undertaken at the prescribed intervals by production personnel, while independent checks are done by personnel from the quality control department. Step-by-step processing instructions appear on the batch manufacturing document as they appear in Annexure 11 of the product's MBR 1 dossier (see Section 3.6.17). All in-process controls and

activities are recorded on the batch manufacturing document. Machine maintenance and cleaning records are checked according to written standard operating procedures before production commences.

### 1.4.4 In-process quarantine

In-process bulk product may in some cases be transferred directly onto a packaging line, but in most production lines the bulk product is placed into quarantine to await sampling and analysis by the quality control laboratory. Bulk product which is found to comply with the relevant specifications is then transferred to the packaging department, whereas rejected material may be reworked or destroyed at the discretion of the quality control manager. The results of all tests, including the above-mentioned tests, are recorded. These records will also contain the signed release or rejection decision by the quality control department.

### 1.4.5 Packaging

A Packaging Instruction specifies the nature and quantities of bulk product and packaging components that are required at the designated packaging line. A pharmacist certifies that all materials and components brought onto the line are of the correct identity and quantity. A pharmacist also certifies in writing that

the line is clear of any foreign packaging components or bulk product. In-process checks relating to fill volume or mass for instance, are made at prescribed intervals by operators and line supervisors, while independent checks are made by personnel from the quality control function during the entire packaging run. Upon completion of the run, a pharmacist again certifies the line to be clear of all bulk product and packaging materials. All the above-mentioned checks and controls are recorded on batch manufacturing documents. The packaged final product is then transferred to the finished product quarantine area to await sampling and analysis by the quality control laboratory, prior to final release or rejection.

### 1.4.6 Off-line overprinting

Particular attention is paid to the control of all printed packaging components during the pharmaceutical manufacturing process. The accuracy of the printed information, which for instance relates to aspects such as product identity, potency and dosage instructions, are considered to be of critical importance to product safety. Printed components are typically sourced in one of three ways: (i) From third party suppliers; (ii) by means of on-line overprinting during the production process, or; (iii) by way of in-house off-line overprinting. The overprinting process usually involves the addition of batch-specific information such as an expiry date and lot

number on a preprinted label and/or carton. A pharmacist will proofread the overprinting before allowing the process to continue. If the overprinting is done on-line, this check will form part of the particular manufacturing procedure. A facsimile of the overprinted component thus approved is attached to the relevant batch manufacturing record, together with the signature of the pharmacist who verified the accuracy thereof. In some cases the product itself is overprinted, as in the case of a logo or statement regarding product potency, which may appear on a tablet, capsule, or other dosage form. This process is controlled in the same manner as that which is described above.

1.4.7 Finished product quarantine

At the end of the packaging run, the packaged product will await sampling and analysis by the quality control laboratory prior to final approval or rejection. As in the case of incoming materials discussed under Section 1.4.1, sampling is done according to a prescribed sampling plan and written standard operating procedures. Laboratory analysis is done in accordance with the methods specified in the relevant MBR 1 dossier (see Section 3.6). The finished product will remain in quarantine until the relevant analytical results are known, and a document audit has been carried out on the batch manufacturing records.

The approved product is thereafter transferred to the approved product warehouse to await despatch, whereas rejected product is transferred to a reject store to await disposal under the control of the quality control manager. Samples of every batch of product are kept in a retention sample store under the control of the quality control department until one year after the date of expiry of that particular batch (in practice this usually relates to a total storage period of four years). Regular samples are taken from retained stock; these samples are then analysed to verify product stability during the product's entire shelf life (see Section 3.6.16).

### 1.4.8 Final product despatch

The following activities of the final product despatch process represent important measures of control: (i) In accordance with the requirements of Section 22A of the Medicines and Related Substances Control Act (South Africa, 1965), scheduled medicines may be sold only to authorised customers, and the control of customer validity therefore forms an important part of the despatch process (see Section 3.7). (ii) Batch distribution records must be kept in respect of every product despatched because any product recall procedure which may be necessary, will be based on these data (see MCC, 1988, Circular to applicants ref. 7/88). (iii) Measures must be taken to assure the protection of the product against environmental or mechanical damage whilst in transit.

## 1.5 THE RESEARCH APPROACH AND METHODOLOGY

### 1.5.1 General

The nature of this research is that of an overview of domain phenomena which are of universal importance, mainly by means of exploratory research but also including descriptive surveys.

### 1.5.2 Miniature investigation

A preliminary study regarding the application of a system of total quality control to the pharmaceutical industry in South Africa was submitted by the author to the Department of Business Economics (Honours Studies) of the University of South Africa (Mader, 1989). This study highlighted certain shortcomings in the guidelines for Good Manufacturing Practice which at present is considered to be the linchpin of quality control in the pharmaceutical industry. This study also touched briefly on the broader role played in quality control by the registration process in terms of which pharmaceutical products are screened by the South African Medicines Control Council. The present research is aimed at expanding on these findings.

### 1.5.3 Hypothesis development

From the literature, and from personal observation, the following hypotheses were developed concerning the use of a quality management approach to the evaluation of the regulatory control system used to assure the quality of medicines manufactured in South Africa:

(i) *The existing system of regulatory control may be enhanced by a quality management approach to the problem of assuring the quality of medicines*

This hypothesis is based upon the perception that, generally speaking, a commitment by top management to the total quality management philosophy, and the resultant strategic business decisions that are based on quality considerations, does not appear to be the primary motivational force behind the quality control activities routinely performed by the industry. Instead, with a few notable exceptions, the quality control programmes operated by the industry appear to be driven firstly by a preoccupation with defect detection (as opposed to defect prevention) in order to limit product liability risks and, secondly, by what is perceived within the industry to be a trade-off situation between regulatory demands regarding quality control and the cost of implementing those demands (i.e. without regard for any positive contribution to cash flow or profitability).

(ii) *The establishment of a system of total quality will result in a superior operations management system as compared to the good manufacturing practice principles presently used*

The so-called good manufacturing practice guidelines currently used by industry are characterised by a number of inherent limitations with regard to their scope, approach, and financial, managerial, and strategic considerations. These limitations can be overcome by means of a total quality system, which also forms an integral part of modern operations management systems such as just-in-time management.

(iii) *Quality management principles may be used to develop a structured approach to the problem of delegating quality authorities and responsibilities within the pharmaceutical industry*

In terms of the provisions of the Pharmacy Act (South Africa, 1974, Section 22), the managing director of a body corporate which is engaged in the manufacture of medicines must be a pharmacist who in fact manages the business of that body corporate. There are sound reasons for this requirement, related mainly to ethical and disciplinary considerations. This statutory requirement is however based upon the assumption that a person who received training in the natural sciences only will have the necessary managerial skills to effectively delegate his quality

responsibilities within the modern business enterprise. The managerial hierarchy dictated by statute may therefore in practice be distorted by the realities faced by industry. The strong link that is established by a total quality system between the managerial decision making process and the technical activities related to quality control, is seen to be of particular value in this situation.

(iv) *There is a need for more accurate quality cost data in the pharmaceutical industry*

There appears to be a growing concern within the pharmaceutical industry about what is perceived to be a possible over-capitalisation in the present system of statutory quality control, particularly in view of the pressures being experienced in what has up to now been a relatively price inelastic market. Empirical evaluation of this viewpoint will largely depend on the availability of accurate and reliable quality cost data. It is however anticipated that the research will identify a need for more accurate quality cost data within the industry.

### 1.5.4 The research methodology

The hypotheses were researched by means of personal interviews with randomly selected pharmaceutical companies. A structured questionnaire was used during these interviews (see Annexure 1). A detailed description of the methodology employed is given in Chapter 6.

## 1.6 THE LIMITATIONS OF THE RESEARCH

The research is limited to a business economic approach to the problem of quality control in the South African pharmaceutical industry. More specifically, a microeconomic approach based on the economic principle is adopted in order to research the achievement of the highest possible quality output through the most efficient use of company resources, as seen from the point of view of the individual enterprise. No attempt is made to evaluate the South African regulatory control system *per se*, other than to refer to its quality management implications. In particular, it must be stressed that the research does not attempt to contribute, other than in an indirect manner, to what Dukes (*loc.cit.*, pp. 21 - 30) refers to as the "regulatory controversy" regarding the relaxation or intensification of the regulatory controls presently applied to medicines, or the much broader controversy surrounding social regulation in general. Due to the dynamic nature of the regulatory control environment the research should moreover not be considered to be an up to date source of reference regarding current regulatory requirements.

## 1.7 THE EXPECTED CONTRIBUTION TO KNOWLEDGE BY THE RESEARCH

It is anticipated that this research will demonstrate the relevance of a total quality system to pharmaceutical production in South Africa. Moreover, it will

be shown that quality control is much more than a mere grouping of production-oriented technical projects and motivational activities without any clearly articulated managerial focus.

A degree of confusion appears to surround the definition of the various quality-related concepts currently used by the pharmaceutical industry. In particular, the inter-relationship between concepts such as "quality assurance", "good manufacturing practice", and "quality control" is not made clear in the technical literature. It is anticipated that the company-wide scope of the total quality concept, and its application to the entire industrial cycle, will provide greater clarity concerning the concepts currently used within the industry.

It is anticipated that this research will be of value to the pharmaceutical industry particularly with regard to the emphasis which is placed upon the strategic business value of quality. Moreover, the approach adopted in this research is expected to be of value to regulatory authorities in their role as external auditors of the industrial quality control system, as well as with regard to the formulation of regulatory control policies.

# CHAPTER TWO: MACROENVIRONMENTAL DEMANDS ON THE QUALITY OF PHARMACEUTICAL PRODUCTS

## 2.1 GENERAL

This chapter reviews those economic, technological and political macroenvironmental factors which impact upon quality in general, and the quality of pharmaceutical products in particular. The potential of the total quality management philosophy to contribute positively to the formulation of a response by management to these microenvironmental factors, will be highlighted in Chapter 5 of this dissertation. The present chapter is also intended to provide a philosophical background to the regulatory controls currently applied to medicines; the actual mechanism according to which the South African regulatory control system operates is discussed in Chapters 3 and 4 of this dissertation.

## 2.2 THE ECONOMIC ENVIRONMENT

Markets require not only people, but purchasing power as well. Total purchasing power is a function of current income, prices, savings and credit availability (Kotler, 1980, p. 108). The main economic trends that have quality implications for the pharmaceutical industry in particular are described in the paragraphs which follow.

### 2.2.1 Slowdown in real-income growth, and continued inflationary pressure

According to Feigenbaum (1986, pp. 29 - 30), one of the least understood effects of inflation, when it has occurred in world markets, has been the corresponding growth of buyer and consumer insistence upon basic quality; buyers are likely to view a higher price as payment for what they expect to be higher quality. In the 1960's the annual rate of inflation in South Africa averaged 2,7 per cent, with a growth in real Gross Domestic Product of 5,7 per cent. In the 1970's inflation averaged 10,8 per cent and the growth in Gross Domestic Product had declined to 3,4 per cent, while in the 1980's this situation had worsened to an average rate of inflation of 14,7 per cent, with growth down to a mere 1,5 per cent (Barnard & du Toit , 1989, pp. 1 - 4). During 1992, inflation averaged 13,9 per cent with Gross Domestic Product declining to minus 2,1 per cent; during 1993 inflation decreased to 9,7 per cent whilst Gross Domestic Product had increased to 1,2 per cent (ABSA Bank, 1994, p. 1).

The cost of materials has been identified as the cost item which exerts most influence on the cost of sales ratio of a pharmaceutical product, and has been calculated to vary between 23,82 per cent and 53,39 per cent (National Productivity Institute, 1989, p. 57). The elimination of waste, which is fundamental to

the just-in-time/total quality control concept should therefore be of strategic importance to the South African pharmaceutical industry. Imported raw materials on average account for approximately 80 per cent of the total materials requirements of the pharmaceutical industry (*ibid.*, p. 101), and a high domestic rate of inflation relative to the country's major trading partners, coupled to a deteriorating rate of exchange, must therefore reduce the ability of the local pharmaceutical industry to compete on international markets, and serve to inflate domestic prices of medicines. The real effective rate of exchange of the rand has weakened by 6,4 per cent over the 15 months to March 1994 (ABSA Bank, *loc. cit.*, p. 2).

Domestic prices of medicines have indeed increased significantly in recent years. According to a survey started in 1988, the domestic prices of certain medicines have for instance been found to be 20 per cent higher than in Great Britain, and 70 per cent higher than in Australia (Die Burger, 30 April 1990, p. 3). This same survey found that, compared to the prices in twelve Western countries, medicine prices in South Africa were higher than in all but three of those countries. Boyce & Bartlett (1990, p. 147) report that, during 1984 to 1989, the medicines price index in South Africa increased by 152 per cent (20,3 per cent per annum), while the consumer price index

increased by 108,4 per cent (15,8 per cent per annum) over the same period. They conclude that the annual increase in the domestic price of pharmaceutical products has exceeded the annual increase in the consumer price index by an average of 4,5 per cent per annum during the period 1984 to 1989. According to Feigenbaum (*loc. cit.*, pp. 29 - 32),consumer insistence upon basic quality may be expected to grow under the circumstances described above. However, other pressures are being unleashed as a direct result of the spiralling cost of medicines, which also have a direct bearing on product quality; these aspects are discussed below.

### 2.2.2 Fiscal constraints on the use of medicines

The market for prescription medicines is unique in the sense that the choice of product is not made by the consumer but by a third party (the physician, or prescriber), and in many cases is paid for by a fourth party (the patient's medical aid fund). Moreover, this market is characterised by the so-called "necessity effect" which results from the fact that the price of the product has little influence on the willingness of the consumer to use the product prescribed by the physician; he buys what the physician prescribes, regardless of the price.

According to the Steenkamp Commission of Inquiry (South Africa, 1978, p. 19), these factors have traditionally combined to give this market low elasticity of demand. New developments are placing these traditional concepts under increasing pressure, however, and the cost of medicine has for some time now been of prime concern not only to Government but also to the man in the street (Retief, 1984, p. 590).

According to figures released by the Registrar of Medical Schemes for the year ended December 1989 (South Africa, 1990), only 5,5 per cent of the Black population group in South Africa, 30,2 per cent of Coloureds, 33,8 per cent Asians, and 68,8 per cent Whites are members of medical aid schemes. This means that only 19,5 per cent of the total South African population are members of medical aid schemes, and that the State and private individuals who are not members of medical aid schemes accept direct liability for the medical expenses of 80,5 per cent of the population.

Boyce & Bartlett (*loc. cit.*, pp. 147 - 148) state that expenditure on medicines by medical schemes in the private sector in South Africa accounted for 26,1 per cent of total expenditure on medical services during 1988. Because of the fact that this figure

excludes the contributions of patients in the form of co-payments, as well as the cost of medicines administered to hospitalised patients, these authors consider a more accurate estimate of aggregate expenditure on medicines in the private sector to be 30 per cent of the total expenditure on medical services. This figure for the relative expenditure on medicines in South Africa is considerably higher than the corresponding figure in other Western countries, notably the United States of America (nine per cent), the United Kingdom (twelve per cent), and the average for all European Economic Community countries (sixteen per cent). Boyce & Bartlett (ibid.) are of the opinion that differences in the patterns of utilization of medicines are of key importance in explaining this disparity in expenditure, but note that higher price levels in South Africa also play a role in this regard. The Association of Medical Schemes cite the continued rise in medicine prices as constituting a "major factor" in pushing up medical aid subscriptions (Eastern Province Herald, 18 April 1990, p. 2).

South Africa currently spends between 5,5 and 5,9 per cent of Gross National Product on health, and there is little prospect of this being substantially increased in the forseeable future (Folb, 1990, p. 120). Under these circumstances it is therefore easy to understand

why methods are being sought to reduce overall expenditure on medicines, or at least to reduce the rate at which these costs are increasing, in both the public and private sectors. Central to the various options available for achieving this goal is the use of generic medicines.

"Generic substitution" is said to have taken place when a medicine containing the same active ingredient(s), in the same dosage, and in the same dosage form, is dispensed instead of the branded product originally prescribed. Savings from the use of generic medicines can be significant, as price differences between generic products and their branded equivalents vary between 15 per cent and 85 per cent (Boyce & Bartlett, *loc. cit.*, p. 148). The issue of generic substitution is, however, shrouded in controversy.

Early in November 1984 the South African Pharmacy Council resolved to request the Minister of Health to approve the amendment of the Council's Ethical Rules in such a manner as to allow pharmacists to supply cheaper, generically equivalent medicines to the public in the place of branded products prescribed by physicians, subject to a number of conditions (South Africa Pharmacy Council, 1984, pp. 2 - 3). The concept

of "generic substitution" became a reality on 16 November 1984 with the gazetting of the above-entioned amendment to the Ethical Rules governing the pharmacy profession. On 26 April 1985, in his address to the 18th Annual General Meeting of the then Pharmaceutical and Chemical Manufacturers Association (PCMA) the chairman, Dr Hugo Snyckers, announced that individual members of the PCMA were to apply to court to have the S.A. Pharmacy Council's amended Ethical Rule set aside (Anon., 1985, p. 274). The Pharmacy Council did not oppose this application by members of the PCMA upon the advice of the then Minister of Health, and the amended Ethical Rule was withdrawn (Van Zyl, 1990).

Generic substitution has, however, been common practice in South African State and Provincial hospitals for several decades. Basic to the logistical system employed in the supply of medicines by the public sector, is the so-called open bid or tender system of purchasing whereby bids are called for the supply of medicines on the basis of generic (not brand name) specification. Although no studies have been reported of the savings achieved by means of generic substitution in the public sector in South Africa, expenditure on medicines by the State constitutes less than ten per cent of total public health expenditure. The extent of these savings is dramatic when compared

with current expenditure on medicines in the private sector, which amounts to 30 per cent of total expenditure on health services in that sector (Boyce & Bartlett, *loc. cit.*, p. 148).

In an attempt to generate similar savings in the private sector, the Pharmaceutical Society of South Africa (PSSA) devised the so-called "maximum medical aid price" (MMAP) system for the supply of cheaper medicines to the patient within the legal constraints that apply at present. The MMAP system described by Sutherland (1985, pp. 89 - 119), is based upon a limited list of widely prescribed medicines for which generic alternatives are available. In terms of the MMAP system, the financial liability of members of participating medical aid schemes will be restricted to the price level set out in the MMAP list of medicines. Should a patient or the prescriber prefer to receive the original (more expensive) brand prescribed, the patient will have to pay the difference in price. This aspect of freedom of choice is important, particularly in the light of objections from within the medical profession to what is perceived to be a limitation on the clinical discretion of the prescriber.

Bloom & Goldston (1989, pp. 199 - 201) describe the impact of the MMAP system on a private sector medical aid scheme for municipal employees in the Cape Province, which in the first twelve months of operation generated savings of 9,3

per cent on medicines. Boyce & Bartlett (1989, pp. 142 - 146) report on a MMAP programme that was conducted on a voluntary basis in the Orange Free State during 1985. They state that savings on the cost of medicines amounted to 6,2 per cent during the first six months of its operation, and are of the opinion that savings could have been greater had participation in the scheme by physicians and pharmacists been made mandatory. Price (1990, pp. 158 - 160) describes a study comparing prescribing patterns and costs at a public sector health care centre with that of the private fee-for-service medical aid sector, and concludes that the substantial difference in the cost per item (25 per cent of that in the private sector) should be ascribed mainly to generic substitution, in-house repacking of medicines, and the use of treatment protocols in the public sector. Repacking of medicines in advance of their sale is illegal in terms of Section 14(4) of the Medicines and Related Substances Control Act (South Africa, 1965); it is however common practice in most State-operated institutions.

The Pharmaceutical Manufacturers Association (PMA) in particular has been consistent in its opposition to the implementation of generic substitution of prescribed medicines. The PMA believes that this concept "cannot be associated with the principles of a

free market economy", and describes it as being a form of "interference" rather than a legitimate attempt to introduce a measure of competition in the market (Pharmaceutical Manufacturers Association, 1989, p. 13). The PMA also contends that "... the savings to be achieved (by means of generic substitution) would be minimal compared to the risk to the patient and compared to the resultant distortion of the free market concept *(sic)*". In support of this viewpoint, the PMA quotes a study by Scott & Reekie who conclude that if for every possible product available in South Africa in June 1984 a generic prescription was written, the savings would amount to only 4,6 per cent to 6,6 per cent of the total private sector market. This same study concluded that "... price increases (of medicines) have been below the rate of inflation ..." (*ibid.*, p. 14).

Boyce & Bartlett (*loc. cit.*, p. 146) however point out that the theoretical projections made by Scott & Reekie are based upon the so-called HEW-formula developed by the Department of Education and Welfare in the United States of America, and that this formula does not take into account practices in respect of quantities prescribed, or the dispensing tariff of pharmacists. However, despite their reservations about its validity, Boyce & Bartlett (*ibid.*) applied this formula to the Orange Free State sample referred to

above. Whereas Scott & Reekie postulated maximum overall savings in the region of six per cent, the Orange Free State sample yielded a figure of 11,5 per cent. Moreover, the claim that increases in the domestic price of medicines prior to 1984 have remained below the rate of inflation cannot today be reconciled with the figures presented by Boyce & Bartlett (1990, p. 147).

The opinions of the PMA are also not shared by the National Association of Pharmaceutical Manufacturers (NAPM). The latter association was formed in the mid-eighties *inter alia* as a result of differences within the local pharmaceutical industry concerning the issue of generic substitution. The NAPM is mindful of the value of product differentiation strategies (based on brand names), but is willing to accept the implementation of the generic substitution concept in the public interest (Midlane, 1990).

It does not fall within the scope of this research to expand upon all the issues surrounding the concept of generic substitution, nor is it intended to present generic substitution as being the only issue which is relevant to the problem of reducing the financial burden on the financiers of medicine consumption. However, both Price (*loc. cit.*) as well as Boyce & Bartlett (*loc. cit.*) conclude from their studies

that a rationalisation in the prescribing habits of physicians is of crucial importance in this regard, and these authors also agree that generic substitution is an important component of this rationalisation process. Moreover, the use of generic medicines is a basic tenet of the Essential Drugs Programme which was formulated by the World Health Organisation (WHO) with the objective of extending the accessibility (including the financial accessibility) of the most necessary medicines to populations whose basic health needs cannot be met by the existing systems of supply (World Health Organisation, 1990, pp. 7 - 23).

Suffice it to state that there is compelling evidence to support the viewpoint that generic (and therapeutic) equivalency will be an essential component of any future response to the macroeconomic environment of the market for medicines. From a quality management point of view, this scenario would serve to accentuate the strategic business importance of quality which is inherent in the generic concept: Considerations related to patient safety demand that products be equivalent in all respects. Such equivalency can, however, be established only on the basis of comparable quality.

## 2.3 The technological environment

Spectacular technological advances have been made during the relatively short history of the pharmaceutical industry. The increased production of medicines from synthetic as opposed to natural materials, the shift from so-called symptomatic to curative medicines, and the evolution from back-shop dispensaries to factory production and ultimately to research-based speciality manufacturing, have characterised this process of technological advancement (Steenkamp Commission of Inquiry, *loc. cit.*, pp. 4 - 6). This rapid change in the technological environment has by no means been restricted to the pharmaceutical industry alone, and the changes in the technological environment described in the paragraphs which follow, can be said to have been shared by industry in general. It should be noted, however, that technological advances in the pharmaceutical industry have been characterised by a concomitant increase in the risks (to patients) associated with the use of modern medicines.

### 2.3.1 The accelerating pace of technological change

It is a sobering thought that most of the technologically complex products which we take for granted today were not available even one hundred

years ago. In the wake of such rapid technological change, the management of those factors which affect product quality has assumed major strategic business importance. Materials are worked to closer limits than ever before. The diversity of materials has expanded. Visual inspection methods have been replaced by precise chemical and physical measurements using highly specialised laboratory equipment that match the need for rapid and accurate information demanded by the modern production process. Manufacturing equipment has become more complex and much more dependent upon the quality of materials fed into it. The manufacturing environment itself often has to be controlled as part of the modern production process; dust in an electronic assembly area, floor vibration transmitted to a numerically controlled machine tool, or room temperature variation during adjustments to aerospace guidance systems, are but a few examples of such controls from outside of the pharmaceutical industry (see Feigenbaum, *loc. cit.*, pp. 59 - 61).

The lesson has been sharply taught that major technological changes cannot simply be overlaid upon old manufacturing; logistical; or managerial foundations (*ibid.*, p. 49). This would explain why quality management has assumed such universal strategic importance in modern industry.

## 2.3.2 Pressures on research and development programmes

Modern technological development is generally characterised by huge expenditure on research and development. According to Cromie, quoted in Dukes (1985, pp. 81 - 82), the return on investment in research by pharmaceutical companies in the United Kingdom averaged 3 per cent during the period 1975 to 1976, while the average for the industry as a whole during the same period was 10 per cent. Careful management of the investment in research and development is therefore necessary in order to maximise the rate of return on that investment. The concept of new design control, which is an integral part of a total quality control system, is therefore particularly relevant to achieving this goal.

Compared to the research-based industries of the West, the South African pharmaceutical industry is still at an early stage of development. An analysis of the cost structure of 51 pharmaceutical firms in 1974 and 1975 showed an average expenditure on research and development of 2,3 per cent of sales (Steenkamp Commission of Inquiry, *loc. cit.*, p. 28). Due to the high percentage of raw materials imported from overseas it would, however, be fair to conclude that expenditure by local companies on research and development may in reality

be higher than this figure, since elements of the costs of research and development are build into the transfer pricing policies and licensing agreements prescribed by overseas principals.

### 2.3.3 Increased regulation of technological change

According to Kotler (*loc. cit.*, p. 114), technological change is encountering more regulation and opposition than ever before; as products in general become more complex, public demands for the assurance of product safety in particular can be expected to increase. By the middle of the twentieth century, the rapid expansion in the number of synthetic drugs had greatly increased the chances not only of achieving therapeutic advances, but also of creating new risks (Dukes, *loc. cit.*, p. 8). Evans & Cunliffe (1987, p. 11) note that present day controls on the manufacture and marketing of medicines were brought in to protect the public because of the growing power, for good and ill, of modern medicines. Government agencies have thus responded to public demands regarding the safety of medicines, by expanding their powers to investigate and ban products that might be directly harmful or have questionable side effects.

Legislation aimed at protecting the public against adulterated and misbranded medicines in particular, soon became outmoded as a result of the onrush of technological change in the international pharmaceutical industry. The major system of current drug legislation in the United States of America can for instance be traced back to an incident in 1938 when more than one hundred people died after using the product "Elixir Sulfanilamide", which contained a poisonous solvent. According to Dukes (*loc. cit.*, p. 8), this tragedy was the result of the untested use of diethylene glycol as a solvent for sulfanilamide. The Federal Food, Drug, and Cosmetic Act which became law in the United States of America on June 30, 1938 contained, amongst others, the following provisions: (i) Proof of intent to defraud was no longer required in order to stop false claims for medicines, thereby closing a loophole which had existed in that country's legislation since 1912. (ii) Federal court injunctions against violations were added to the previous legal remedies of product seizures and criminal prosecutions. (iii) Specific authority was provided to enable inspection of factories. (iv) Pharmaceutical manufacturers were required to provide specific proof that new products could be safely used before putting those products on the market (Janssen, 1981, pp. 428 - 429).

It also became apparent that many modern medicines, which were of great value if used under the direction of a physician, were too dangerous for uncontrolled use by lay persons. Different approaches to controlling the sale and distribution of medicines were adopted in different countries. In the United States of America, for instance, the Food and Drug Administration published a series of "Trade Correspondence Letters" in which it gave notice that it would in future be illegal to distribute particular substances "for indiscriminate use by the general public in a manner which constitutes a serious danger to public health". The first such notice was drafted in 1938, and dealt with the substance sulfanilamide. In terms of the so-called Humphrey-Durham Amenment Act, which became law in the United States of America in 1951, the first statutory definition was given of the kinds of medicines that could be sold only upon the prescription of a physician (*ibid.*, pp. 430 - 435).

In South Africa, statutory controls over the sale and distribution of medicines during the period immediately preceding current legislation, were embodied in the provisions of the Medical, Dental and Pharmacy Act, No. 13 of 1928, as amended; medicines were classified either as so-called "Division One

Poisons", "Division Two Poisons", "Potentially Harmful Drugs", or "Habit Forming Drugs", in order to prescribe the conditions under which each category of medicine could be acquired, imported, sold, or supplied. The category under which a particular substance was classified was determined after agreement between the Medical and Dental Council and the (then) Pharmacy Board in the form of a resolution approved by the Minister of Health and published in the Government Gazette under the signature of the State President (Pannall, 1967, pp. 32 - 65). The Medical, Dental and Pharmacy Act was superceded by the Medicines and Related Substances Control Act (South Africa, 1965), which may be described as being part of the international wave of drug legislation which followed in the wake of the thalidomide disaster in the early Sixties (see Dukes, *loc. cit.*, pp. 8 - 9). The thalidomide disaster, which lead to an outbreak of phocomelia (gross foetal deformities) in a number of countries, is described under Section 2.4.2.1 of this dissertation.

The system of marketing authorisation, which is currently applied by regulatory authorities worldwide, ensures that all medicinal products are assessed by a competent authority and also that contemporary standards of safety, quality and efficacy are adhered

to (see EEC draft GMP guide, 1989, p. 7). Some countries impose additional criteria, for instance, "medical need" and "therapeutic value" standards have been applied in Norway since 1928 (Wardell, 1983, pp. 6 - 7). In terms of the provisions of Section 1(3) of the Medicines and Related Substances Control Act (South Africa, 1965), however, standards of safety, quality and therapeutic efficacy are the sole criteria used by the South African Medicines Control Council (MCC) to determine whether or not the availability of a particular medicine is in the public interest. A description of the South African regulatory control system is given in Chapter 3 of this dissertation.

2.3.3.1 Self-regulation by the pharmaceutical industry

From the few examples given in Section 2.3.3, it would appear that regulatory controls over medicines were often introduced in response to mishaps and disasters connected with their use. The pharmaceutical industry has tended to oppose these developments, while arguing the case for self-regulation (Dukes, *loc. cit.*, pp. 9 - 11). It is suggested for instance that responsibility for proper procedures during experimental trials on humans should be shared by the investigator, his peers, and the industrial sponsor concerned (Lasagna, 1983, pp. 177 - 182). However, the likelihood of this particular suggestion being accepted by any regulatory authority is considerably reduced by

reports such as that of a French scientist who allegedly ignored rules for human-subject research by injecting ten children in Zaire with a trial AIDS vaccine (Cape Times, 11 March 1991, p. 4 ). Herxheimer & Collier (1990, pp. 307 - 311) review the results of an attempt by the Association of the British Pharmaceutical Industry to regulate the promotion of prescription medicines by means of its own code of practice during the period 1983 to 1988. These authors describe the nature of the complaints referred to the Association, the method used by the Association for dealing with these complaints, and the results of the investigations (which were undertaken with the full support of the British Department of Health). They conclude that the Association's code of practice has failed to deter promotional excesses, and that the Association's attempt at self-regulation "...seems to be a service to itself rather than the public", mainly because the Code of Practice Committee is not publicly accountable and also because it lacks the necessary authority.

Folb & Schlebusch (1989, pp. 643 - 645) counter the argument that self-regulation may be achieved with the assistance of a court of law if necessary, by referring to the legal battle in South Africa between Colgate-Palmolive and Elida-Ponds concerning their respective claims for the anti-tartar activity of

toothpaste (not a medicine), and the fact that legal fees alone amounted to six million Rands. These authors contrast this costly settlement with the fact that, notwithstanding the legal right of a party who is aggrieved by a decision of the Medicines Control Council to take that decision on appeal to a court of law, the industry had since 1967 without exception preferred to settle such differences directly by negotiation (the first such appeal was subsequently lodged in 1993).

A feature of the introduction of legislation requiring marketing authorisation as part of the modern regulatory control process has been the sharp decrease in the number of products marketed. Dukes, *loc. cit.*, p. 10) for instance draws attention to the fact that 39 000 pharmaceutical product licences existed in the United Kingdom in 1971 when the Medicines Act of 1968 was implemented in that country; by 1983 some 22 000 of these had been withdrawn from the market. A similar trend was observed in Spain (Dukes, *ibid.*), In South Africa, an estimated 780 new products would have appeared on the local market immediately before the Medicines Control Act came into force in July 1968; this figure had declined to 70 products by the end of 1968 (Snyman, 1971, pp. 297 - 299). A number of authors ascribe this phenomenon as being related in part to the inadequacy of the doctrine of self-regulation by the pharmaceutical industry (Dukes, *loc. cit.*, 9 - 11).

## 2.4 The political / legal environment

Regulatory authorities have a certain margin for discretion when making decisions concerning the safety of a medicine in that administrative law allows for differing cultural, philosophical, religious, and ethical convictions. In other words, decisions concerning the risk/benefit ratio of a medicine are not based solely on scientific criteria but must also reflect a societal point of view. Consequently, regulatory authorities all over the world may take different decisions regarding product safety (and other attributes), even in cases where the facts of the matter are the same. Such risk/benefit evaluations are, in theory, undertaken by statutory bodies on the assumption that members of society are prepared to pay for accepted risks either as taxpayers or as buyers. In view of the fact that any decision by a regulatory authority has an effect on society-at-large, such decisions must have a political dimension. It therefore follows that regulatory authorities are subject to political pressures (Van Andel, 1985, pp. 231 - 239).

Kotler (*loc. cit.*, p. 115) describes the political system as being a broad term for the interacting set of laws, government agencies, and pressure groups that influence and constrain the conduct of various organisations and individuals in a particular society.

He states that legislation affecting business in the United States of America has three purposes: (i) To protect companies from each other by preventing unfair competition, such as in the case of selective predatory pricing policies for instance. (ii) To protect consumers from unfair business practices; it is felt that, if left alone, some firms would for instance adulterate their products, mislead through advertising, deceive through their packaging, and bait through their prices. (iii) To protect the larger interests of society against unbridled business behaviour; a characteristic of recent legislation has for instance been that the social costs created by certain production processes or products are shifted back to the industries concerned (Kotler, *ibid.*, pp. 116 - 117). Certain of the features of the political environment described by Kotler (*ibid.*, pp. 115 - 121), are considered to be of particular relevance to this research, and are referred to below.

### 2.4.1 More vigorous government agency involvement

Kotler (*ibid.*, p. 120) is of the opinion that government agencies are driven by self-interest, which requires them to demonstrate their usefulness in order to justify their need for larger budgets. Moreover, he describes the relationship between such agencies and

business in general as being of an adversarial nature, and states that these agencies attract personnel with an anti-business attitude. Approximately twenty years before these viewpoints of Kotler were published, this same situation was viewed in an entirely different light by fellow-American Vance Packard (1960, pp. 234 - 235), who accused government agencies of being preoccupied with the promotion of industrial interests to the virtual exclusion of consumer interests. Packard alleged that government officials were deeply involved in fraternizing with the industries they were supposed to regulate, and specifically referred to a statement allegedly made to a Senate Investigational Committee to the effect that a senior official of the Food and Drug Administration was more concerned with maintaining cordial relations with the pharmaceutical industry than he was with a proposed warning against drug addiction on the label of a certain product.

These contrasting viewpoints of Kotler and Packard are possibly a reflection of the changes that have occurred in the political environment of the United States of America, and elsewhere, during the timespan which separates their respective viewpoints. The tendency of a more vigorous involvement by government agencies in the regulation of the pharmaceutical industry in particular was most certainly accelerated

by disasters such as the thalidomide affair (see Section 2.4.2.1), but should also be seen in the light of the growth of public interest groups and the resultant political pressures which were brought to bear on regulatory authorities world-wide (see Section 2.4.2).

The protection of the public interest with regard to medical matters is not a new concept. The first Act of Parliament dealing with the regulation of medical affairs in England, for instance, was passed in the year 1511, during the reign of King Henry V111. This act, which prescribed the qualifications necessary for persons to practise as physicians or surgeons, was not repealed until 1948. Apothecaries gained their own Royal Charter from James 1 in 1617. Again the accent was on the protection of the public interest, and the Charter reads in part: "(whereas)...unskillful and ignorant men do abide in the City of London...do make and compound many unwholesome, hurtful, dangerous and corrupt medicines...to the great peril and daily hazard of the lives of the King's subjects..." (Wolstenholme, 1983, pp. 13 - 14). Human nature, whether typified by indomitable inventiveness, shameless greed, or sheer ignorance, has not changed over the years; man's ability to inflict harm has, however, increased apace with his technological ability to do good. Serious concern is therefore today

still being expressed about the extent to which standards of health care may be compromised by pharmaceutical products that are poorly formulated, degraded, or criminally inspired (World Health Organisation, 1989, p. 19).

A recent reminder that such concern is not misplaced, was provided by a report concerning substandard and counterfeit pharmaceuticals which are being marketed worldwide (Masland & Marshall, 1990, pp. 18 - 23). The report refers to large quantities of counterfeit burn remedies, confiscated in Mexico, which were found to contain sawdust, coffee, or dirt, and which caused raging skin infections. In Europe, millions of doses of a counterfeit cardiac medicine were used by unsuspecting patients, luckily without any known casualties. American pharmaceutical manufacturers are said to be losing 16,2 million dollars per year as a result of trade in counterfeit medicines in the United States of America. More than a quarter of all medicines marketed in Nigeria are estimated to be counterfeit, and 109 children died in that country during September 1990 due to a poisonous raw material having been incorporated into a paediatric medicine as the result of the raw material having been mislabelled (Masland & Marshall, *ibid.*).

Feigenbaum (*loc. cit.*, pp. 56 - 57) draws attention to yet another dimension of regulatory control which is of direct concern to government policymakers; namely the impact of the internationalisation of quality on world trade. He states that the maintenance of world trade patterns that are as free as possible, and yet are consistent with restrictions on inequitable practices such as dumping or the unfair pricing of comparable products, are important aspects of governmental economic policy. He notes that products are comparable only if their quality is comparable, and that this requires clear and measurable quality and quality practices which in turn places increasing emphasis upon the quality control programmes necessary to maintain these (international) requirements. The World Health Organisation Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce (World Health Organisation, 1989, p. 109) is an example of international collaboration in the field of transnational commerce in pharmaceutical products. It is an administrative instrument through which each particular Member State can provide another Member State with attestation on whether a particular product has been granted marketing authorisation, or whether a particular manufacturing plant has been granted manufacturing authorisation, based upon internally recognised standards of quality assurance or, as it is termed in the industry, standards of

good manufacturing practice (good manufacturing practice principles applied in the pharmaceutical industry are discussed in Chapter 4 of this dissertation). This scheme is seen as offering a mechanism not only for controlling legitimate trade in pharmaceutical products, but also for combating illicit trade in falsely labelled, counterfeited, or substandard goods (World Health Organisation, *loc. cit.*, p. 110). James E. Wavle Jnr (1986, p. 5), speaking in his capacity as president of the Parke-Davis division of the multinational pharmaceutical manufacturer Warner-Lambert,is of the opinion that the pharmaceutical industry in the United States of America owes a large share of its success in world markets to the activities of the Federal Food and Drug Administration. He considers regulators and the regulations which they enforce to be among the nation's prized national resources because they add a dimension to the national health care system that makes it the standard for the world to follow.

### 2.4.2 The growth of public interest groups

The rapid growth of public interest groups that are dedicated to lobbying for increased consumer protection and business regulation has been one of the main features of the international political environment in recent times. According to Kotler (*loc. cit.*, p. 121) the eight major public interest groups in the

United States of America had, in the mid-Seventies, collectively attracted more members and funds than the two national political parties of that country. The main principles of consumer protection in nearly all developed countries are: (i) That products should be safe and not of inferior quality. (ii) That business practices which negatively affect the economic interests of consumers should be regulated. (iii) That consumers should have the information necessary to make rational choices. (iv) That procedures should be provided for the speedy redress of complaints (Price, 1986, p. 30).

The gullibility of the lay public, especially with regard to the treatment or alleviation of disease, has provided a fertile market for the unscrupulous entrepreneur throughout the history of mankind. Before the introduction of modern regulatory controls, the market abounded with products that were labelled with false or misleading claims regarding their therapeutic efficacy; labels commonly did not declare ingredients nor did they contain warnings regarding misuse; adulteration was widespread, and many products contained dangerous narcotics. One of the most infamous examples of the latter state of affairs is the addiction of infants to so-called "soothing syrups" marketed in the United States of America at the turn of this

century, and which contained varying amounts of morphine, opium, or heroin. This was the era of "Dr Johnson's Mild Combination Treatment for Cancer", "Warner's Safe Cure for Diabetes", and "Kick-a-poo Indian Sagwa" (Janssen, *loc. cit.*, pp. 420 - 441). Following the industrial revolution and the rise of a large urban working class, the patent medicine industry in Europe blossomed, and intensive advertising was conducted by means of the new printed media to promote a variety of relatively innocuous herbal laxatives, sedatives, expectorants, and antacids, but also for the promotion of medicines that were claimed to offer cures for tuberculosis, cancer, and syphilis (Dukes, *loc. cit.*, pp. 5 - 9).

South African history, too, abounds with tales of quacks and quack remedies which serve to illustrate the limited medical knowledge of the period, especially amongst the lay public. The State Gazette dated 14 August 1866, for instance, carried an advertisement by a Dr Jacobus Otto of Potchefstroom in which he introduces himself to the public as the "Wonder Doctor who cured cancer without cutting; stone (*sic*) without stabbing; water (*sic*) without tapping; consumption; piles; and indeed any other trouble" (Laidler & Gelfand, 1971, p. 317). A cure for lung disease in cattle was advertised in "The Friend" dated 19 April 1856 as consisting of a teaspoonful of

blue stone (copper sulphate), a tablespoonful of salpetre, and two tablespoonsful of soot, mixed in a bottle of water (*ibid.*, p. 323). An advertisement which appeared in the "Cape Times" in 1901 advised the public to smoke Taddy's Myrtle Grove cigarettes "as protection from the plague" (Joyce, 1981, p. 54).

Most of the drug legislation passed in Europe during the nineteenth century dealt with the regulation of the pharmacy profession, i.e. with training and licensing requirements as well as the assurance of adequate standards of quality for drugs. However, pressures for further change were starting to emerge, and these pressures came largely from independent investigators and protest movements. The Bruinsma brothers, for instance, published a book in the Netherlands in 1878 in which they presented an analysis of many of the useless remedies on sale at the time, the methods used to sell them, and the true cost of their ingredients (Dukes, *loc. cit.*, p. 7).

In the United States of America, national magazines in 1904 began to crusade against what was perceived to be flagrant social injustice and exploitation of the ill by patent medicine promoters. The Pure Food Movement, which was started in the 1870's, is considered to be the original and principal source of the political support for the Food and Drug Act of 1906; it was

primarily a trade movement, but a number of concerned journalists assisted in arousing public opinion with their cartoons, articles and editorials, despite strenuous opposition from whiskey distillers and patent medicine manufacturers in particular, who were at the time the largest advertisers in that country. The "Chicago Tribune" was at the forefront of the fight against paediatric medicines containing narcotic substances; support came from the "Ladies Home Journal", the medical and pharmacy professions, and the lay public.

Public indignation reached a boiling point, and the issue was finally addressed by the passing of the Harrison Narcotic Act in 1914. During the economic hardships of the 1930 depression, Stuart Chase and F.J. Schlink published a book entitled "Your money's worth", which signalled the start of a new consumer movement world wide. Various mishaps involving medicines, such as the "Elixir Sulfanilamide"-incident of 1938 (see Section 2.3.3) attracted public interest, but the one disaster which is generally considered to have resulted in the modern regulatory control systems that are applied world wide to this day, is the so-called thalidomide incident (see Section 2.4.2.1). According to one author, this incident can be summarised in one sentence: "The headlines screamed, the public was aroused, the drug manufacturers ran scared, and the opponents of a tough bill jumped for cover" (Janssen, *loc. cit.*, pp. 420 - 441).

Shuster (1983, pp. 81 - 88) is of the opinion that pressure groups in the field of medicine are a concomitant of social evolution and the spread of education, opportunity, and the diffusion of power which goes with what he terms the "democratic mode". In particular, he believes that pressure groups are media-sustained and are consequently exposed to "irresponsible" media pressure in the form of "eccentric" and "inflammatory" reporting; that they are used to the professional advantage of politicians; that consumerism coupled with what he refers to as "a primitive view of democracy", has lead to the enunciation of the "right to more" as a social principle (particularly in the field of medicine) and that, because of the emphasis that is placed upon freedom of speech by Western Democracy, equality of expression is often confused with equality of ideas. Lay pressure groups are consequently not concerned or constrained by their own lack of expertise. Moreover, he cites a fundamental distrust of science and scientists (to which he refers as the "anti-science movement"), as well as a fear of the market ethic and its perceived lack of concern for the needs of society, as further encouragement for the activities of pressure groups. He states that the problem being faced by the pharmaceutical industry (and medicine in general) is the widespread impression that technology is the servant of finance and state, rather than of mankind.

Van Andel (*loc. cit.*, pp. 234 - 239) notes that drugs with side-effects that can be perceived and related to by lay people, are more likely to become public targets than those which are not. He states that absolutely safe drugs do not, and probably never will exist; consumers therefore have to accept a certain degree of risk, particularly in cases where the level of benefit counterbalances the level of risk. Regulatory authorities, apparently under pressure from the media or pressure groups, however, seem to be prepared to accept only "zero risk", as he puts it.

Whatever its aetiology, consumerism should be recognised as being a permanent and powerful force with which business management in general must deal on a routine basis. In the early sixties however, an event occurred which had such an emotional impact on society worldwide that it has had a permanent effect on public demands for the regulation of the pharmaceutical industry in particular. That event was the thalidomide disaster, which involved the birth of thousands of badly deformed infants to mothers who had used this drug during pregnancy.

The story behind the thalidomide disaster borders on the fictional, and is characterised by examples of Machiavellian cunning and dishonesty which resulted in a human tragedy, the effects of which are still

evident more than thirty years after the event. A review of the international impact which these events had, and still has, on the pharmaceutical industry is deemed relevant to an understanding of the regulatory controls presently applied to that industry. The following section is devoted to a summary of the events surrounding the thalidomide incident, based on that given by Folb (1977).

### 2.4.2.1 The thalidomide tragedy

According to Folb (*loc. cit.*), the firm of Chemie Gruenenthal was formed after the Second World War by the Maurer family of Stolberg, near the German-Belgian border. Their original interests were in soap and cosmetics, and they began their career in synthetic drugs by clearing a section of their packing plant and hiring a small research staff of scientists and technicians. The average age of the members of the team was thirty; they were inexperienced, and none of the scientists involved was a pharmacologist, competent to predict the effects that a new compound might produce in humans.

The Gruenenthal team developed a new sedative, derived from glutamic acid, which they labelled K-17, soon to be notorious as thalidomide. Gruenenthal executives presented K-17 as a wonder sleeping pill. One of the

mysteries of the affair is that these men reported experimental results which no one else has been able to reproduce. They claimed high potency as a sleeping pill, complete absence of side-effects, and a drug that was so safe that it was impossible to take an overdose. The experimental data on which these claims were based were subsequently destroyed by the firm and were never seen by others.

Intensive marketing of the new "wonder drug" commenced amidst great interest from the European medical profession. The drug was available without prescription, due to its claimed safety and lack of side-effects; tens of thousands of West Germans used the new product. Despite its claims to the contrary, Chemie Gruenenthal had, between 1957 to early 1961, been informed of 1 600 cases of serious side-effects associated with the use of thalidomide, including 400 cases of peripheral neuritis (painful damage to the nerves of the extremities, producing paralysis), which several eminent German neurologists regarded as irreversible. The reaction of Chemie Gruenenthal to these reports was less than honest; they lied when doctors wrote to enquire whether side-effects of such a nature had been encountered before, and brushed aside highly relevant questions from worried doctors; they tried to suppress publication of unfavourable

reports; they sought publication of favourable medical reports by means of bribery and influence; and they opposed suggestions that thalidomide should be available on prescription only.

Thalidomide was also sold to the Distillers Group of companies in Britain for marketing on the domestic market. The Biochemicals Division of the group had been commissioned in 1942 by the Ministry of Supply to produce penicillin for the war effort, but after the war it was never very profitable. The company was impressed by the Chemie Gruenenthal personnel and their product; they perceived the new product as representing an opportunity to gain a foothold in the British market for sedatives, which at that stage was worth several million pounds per annum. The most important competing product, the barbiturate group of products, had the serious disadvantage of being fatal in large doses. Gruenenthal's research work, their supposedly massive clinical experience, and their scientific claims were all taken at face value, and the large-scale distribution of thalidomide in the United Kingdom commenced.

Despite the fact that they had no scientific basis for believing that thalidomide did not cross the placenta, the manufacturers later extended the claims made for this drug to include its recommended use in pregnant

women and nursing mothers. In fact, from elementary principles concerning the chemistry of thalidomide, it could with certainty have been predicted that the drug would gain access to the foetus; this was later confirmed by means of a simple experimental investigation involving the use of the radioactively-labelled drug.

In June 1961, a leading Australian obstetrician, Dr William McBride, reported that there appeared to be a connection between thalidomide and the birth of deformed infants at the Woman's Hospital in Sydney. Dr McBride reported this information to the Australian branch of the Distillers Group, but it was never passed on to the parent company. Meanwhile, Professor W. Lenz, head of the University Clinic for Children in Hamburg, had brought to the notice of both Chemie Gruenenthal and the State Ministry of the Interior his suspicions that the birth of approximately fifty to one hundred deformed infants per month in West Germany was linked to the use of thalidomide. Gruenenthal responded aggressively, but was compelled to withdraw its product from the market by the Ministry. At this stage Dr McBride's views were published in "The Lancet" and, in the wake of the ensuing publicity, Distillers Corporation withdrew thalidomide from the market in the United Kingdom in December 1961.

Having suffered the trauma of being delivered mutilated children, the grief of parents was compounded by the ineptitude of the legal system of the day to adequately compensate them and their children. British Commonwealth law at the time held that a foetus injured by a drug taken by its mother could not be viewed as the purchaser of that drug, and therefore had no privy of contract with the drug manufacturer or retailer. Moreover, it was regarded as being unlikely that the culpability of the drug manufacturers could be established in a court of law, because they had not broken any statute or regulation in their production and distribution of the drug. A British judge furthermore ignored actuarial advice to the contrary and determined in 1967 that financial compensation of the handicapped children should not take into account inflation, and the consequent depreciation of the amount awarded. The courts also could not find any formula for compensating intangibles such as the nervous shock suffered by mothers, and the effects on the families involved.

Under these circumstances it is easy to understand how public dismay and resentment were mobilised by the news media, notably the London "Sunday Times", in support of a worldwide boycott of Distillers products. Eventually, in the mid-seventies, the Distillers

Group, with annual profits after tax of 40 million Pounds Sterling, established a trust of 25 million Pounds Sterling for the affected children.

Despite the fact that the United States of America was largely unaffected by the thalidomide disaster, the Federal Food and Drug Act of 1906 was amended in 1962 by the so-called Kefauver-Harris Amendment which dealt *inter alia* with requirements relating to the pretesting of drugs for safety and effectiveness, and which gave the Food and Drug Administration control over the production, distribution, and advertising of prescription medicines, including quality control and periodic inspection of manufacturing plants.

In the United Kingdom, a voluntary system of regulating the introduction of new drugs was introduced in 1963 under the aegis of the Committee on Safety of Drugs, and this was superceded by the promulgation of the Medicines Act in 1968, which provided for more elaborate statutory control of medicines (Weatherall, 1983, p. 47). Control bodies were similarly established worldwide, and the establishment of the South African Medicines Control Council in 1965 was part of this international trend (see Chapter 3). Pressure by public interest groups had thus culminated in the increased international involvement of government agencies in the regulation

of the pharmaceutical industry. The macroenvironmental impact of the thalidomide affair on the pharmaceutical industry was indeed of a cataclysmic nature.

## 2.5 SUMMARY

The modern marketing environment places a strong emphasis on product quality. Certain economic, technological, and political macroenvironmental factors may be singled out as being fundamental to the demands made on the quality of pharmaceutical products in particular.

With reference to the economic environment of the pharmaceutical industry it should be noted that, in any market which is characterised by increasing costs to the consumer, a concomitant increase in consumer demands for product quality may be anticipated. Whereas the market for pharmaceutical products has traditionally been considered to be relatively price inelastic, fiscal constraints on the use of medicines are now causing this market to become increasingly price elastic in the private as well as the public market sectors. A basic tenet of the international response to the problem of making essential medicines financially more accessible to all market sectors is the use of generic (as opposed to branded) medicines.

Generic equivalence between products can however be established only on the basis of comparable quality.

The accelerating pace of change in the technological environment and the resultant strategic business importance of those factors that affect product quality, together with the need for effective management of what amounts to a substantial investment in research and development, are factors common to all industrial sectors. Technological advances in the pharmaceutical industry have, however, been characterised by an increase in the risks associated with the use of modern medicines; legislation originally aimed at protecting the public against adulterated and mislabelled medicines soon became outmoded as a result of the onrush of technological change. Current statutory controls focus instead on aspects such as the advertising, sale, and distribution of medicines, as well as the maintenance of contemporary standards of safety, quality, and therapeutic efficacy. The pharmaceutical industry has tended to oppose many of these statutory controls, but the ability of the industry to regulate itself is disputed by numerous informed observers.

With reference to the political environment of the pharmaceutical industry, the extensive involvement of government agencies and the growth of public interest

groups are seen as being of particular importance. The involvement of government agencies in the protection of the public interest with regard to medical matters is not a new concept. Serious concern is however still being expressed about the extent to which standards of healthcare may be compromised by pharmaceutical products that are poorly formulated, degraded, or criminally inspired. Government agencies furthermore play an important role in the Certification Scheme of the World Health Organisation regarding the quality of pharmaceutical products traded between countries.

One of the main features of the international political environment during recent years has been the rapid growth of public interest groups dedicated to lobbying for increased consumer protection and business regulation. The market for pharmaceutical products has been characterised by some early examples of consumer exploitation which resulted in public protest and political pressure. Pressure groups are however themselves prone to misuse, and are sometimes at a disadvantage due to a lack of technical knowledge. Absolutely safe medicines do not, and probably never will, exist; pressure by public interest groups and the mass media has, however, resulted in regulatory authorities adopting a very conservative approach to evaluating the degree of risk to which a consumer is necessarily exposed. The events

surrounding the thalidomide disaster, which occurred in the early sixties, and the inability of the legal system of the day to properly protect the public interest, is generally accepted as having had a profound effect on shaping the regulatory controls presently imposed on the pharmaceutical industry worldwide.

# CHAPTER THREE: A DESCRIPTION OF THE SOUTH AFRICAN REGULATORY CONTROL SYSTEM

## 3.1 GENERAL

The South African Medicines and Related Substances Control Act (South Africa, 1965) which came into effect on 1st April 1966, is the statutory foundation of the South African pharmaceutical regulatory control system (the macroenvironmental background of this control system is discussed in Chapter 2). This Act provides for the establishment of a Medicines Control Council (MCC) which functions independently of government and industry. The MCC is mandated to serve the public interest with regard to the granting or refusal of marketing authorisation for medicines, as well as the determination of the conditions under which such products may be manufactured, sold and advertised. The statutory powers of the MCC include authority to carry out its decisions, and the power to punish parties who seriously offend the terms of the Act; marketing authorisation may for instance be withdrawn, or specific batches of a product may be removed from the market, if the MCC deems such action to be in the public interest (Folb, *et al.*, 1988, pp. 772-778).

Reference is made in Chapter 2 to the fact that the regulatory controls which are applied to pharma-

ceutical products internationally are subject to a degree of controversy (see Sections 2.4.2 and 2.3.3.1 for instance). A number of different issues underlie what Dukes (1985, pp. 21-30) refers to as the "regulatory controversy".

Arguments in favour of a relaxation of regulatory controls include the danger that excessive regulation will delay the marketing of useful new medicines and hinder the research process leading to useful new products; the possibility that the return on investment of the pharmaceutical industry will decline to a point where that industry will no longer attract sufficient capital to survive; and the danger that adverse effects on the pharmaceutical industry will cause unemployment and decrease export earnings, thereby harming the national interests of individual countries. Conversely, arguments which favour the intensification of regulatory controls include the need to avert drug disasters, of which the thalidomide tragedy (see Section 2.4.2.1) is the classic example; the alleged high incidence of serious adverse effects which were not recognised prior to the release of a medicine onto the market; and the notion that society should in principle exert more rigid control on a large and multinational industry such as the pharmaceutical industry (Dukes, *ibid*, pp. 24-28).

With reference to the South African regulatory control system in particular, it may be noted that this system was designed to cater predominantly for the country's First World needs. In order to make this system more relevant to the country's needs, demographic issues such as the fact that 17 languages are spoken in South Africa and that two thirds of the population cannot read or write need to be considered alongside the cultural issues (e.g. the use of traditional medicines) and economic issues peculiar to this country (Folb, *et al.*, *loc. cit.*).

The international and domestic debate concerning regulatory issues falls beyond the scope of this dissertation (see Section 1.6 ). However, it is felt that the application of the total quality concept (see Section 5.5) to regulatory issues will be of value in making the necessary adjustments to the current system of regulatory control in South Africa.

This chapter of the dissertation is devoted to a concise overview of the relevant sections of the Medicines and Related Substances Control Act in terms of its practical implications to the control of product quality in the pharmaceutical industry. In particular, the mechanism whereby an application for manufacturing authorisation and marketing authorisation is screened by the MCC will be reviewed with reference to the external quality auditing function

of the MCC and the Directorate of Medicines Control and Registration of the Department of Health. The relationship between much of the information which by law must be submitted to the MCC in support of an application for marketing authorisation (see Section 3.6) and the new design control; incoming material control; product control; and post marketing surveillance activities routinely performed as part of a total quality control system, will be highlighted.

## 3.2 A HISTORICAL PERSPECTIVE

Before the advent of the Medicines and Related Substances Control Act, there was no independent control over toxicological, teratogenic, or carcinogenic factors relating to the safety of medicines intended for human use. With reference to the therapeutic efficacy of medicines that were marketed in South Africa prior to 1966, little or no control existed; clinical trials were often conducted only after a product had already been introduced to the market, while no effective controls existed to counter false or misleading claims made with regard to these medicines. Quality was judged according to the standards published in official compendia such as the British Pharmacopoeia and the British Pharmaceutical Codex, which related to a limited range of pharma-

ceutical preparations; all other preparations were manufactured without any reference to specifications being necessary. Many products were marketed with no in-process or final release controls having been carried out (Van der Merwe, 1979).

It is ironic that in the period up to 1966, when modern regulatory controls came into force, animals in South Africa enjoyed greater statutory protection than humans with regard to the safety and efficacy of the medicines intended for their use. In terms of the provisions of the Fertilizers, Farm Feeds and Remedies Act, No 36 of 1947, which still applies to a limited range of stock remedies to this day, an application for the registration of an agricultural or stock remedy has to be submitted to the Registering Officer of the Department of Agricultural Technical Services before it can be sold. Such an application has to be accompanied by details concerning every label, advertisement and other literature relating to the product; two samples of the product; experimental data relating to biological tests conducted in South Africa; full details regarding product composition; details concerning toxicity (including precautionary measures, symptoms of poisoning, and the use of an antidote); as well as a formal statement describing the properties claimed (Pannall, 1967, pp. 71 - 76).

To the extent that this research was able to reveal, consumers of medicines intended for human use at that time enjoyed statutory protection from dangerous and useless medicines only insofar as the provisions of the Food, Drug and Disinfectants Act, No 13 of 1929 and the Medical, Dental and Pharmacy Act, No 13 of 1928 allowed. According to Pannall (*ibid.*, p. 92), the objective of the Food, Drug and Disinfectants Act was stated to be: "...the prevention of the importing and sale of food, drugs and disinfectants which are unwholesome, adulterated or incorrectly described". According to Cluver (1960, p. 379), much evidence had been collected by South African health authorities prior to the introduction of this Act showing both the frequency of product adulteration and the extent to which the public was being defrauded. This particular statute was in many respects similar to legislation passed in the United States of America at the turn of this century in that foods and medicines were placed under the purview of the same statute, and that the primary focus of these controls was directed at adulteration and misbranding (see Janssen, 1981, pp. 420 - 429).

The Medical, Dental and Pharmacy Act is of interest in two respects. Firstly, it provided the statutory basis for control over the sale and distribution of medicines (see Section 2.3.3). Secondly, the so-called "Therapeutic Substance Regulations" were promulgated under this Act; these regulations may be regarded as

the forerunner of the statutory controls that are applied to pharmaceutical products in South Africa today. Therapeutic substances were defined to include vaccines, toxins, antigens, sera, antitoxins, insulin-preparations, pituatry extract, antibiotics, intra-vascular injections, enzymes, heparin preparations, corticotrophin, and human blood products only. The controls embodied in the regulations related *inter alia* to the issuing of licences to conduct research, manufacture or import therapeutic substances; container requirements; labelling requirements; potency; quality; toxicity; and expiry dating. The scope of this particular statute was by definition very limited, and the discretionary powers of the regulatory authority (the Secretary for Health) were basically restricted to the granting or refusal of licences, and the inspection of product storage conditions (Pannall, *loc. cit.*, pp. 116 - 125, and Cluver, *loc. cit.*, pp. 655 - 717).

Before and immediately after the implementation of the present system of regulatory controls in 1966, serious problems were experienced with the quality of some of the medicines marketed in South Africa; particularly with regard to product safety and conditions of manufacture. The advent of the Medicines and Related Substances Control Act did not result in an immediate improvement in this state of affairs, due mainly to

the fact that it was impossible for the newly-constituted Medicines Control Council to immediately screen all the thousands of products already on the market at the time. It was also not possible to conduct quality audits at all the manufacturing facilities that were in operation at the time. Once these audits were introduced a general concern was voiced within the pharmaceutical industry regarding the financial implications of the new quality control measures. This initial reticence however soon gave way to enthusiasm for the benefits derived therefrom (Schlebusch, 1990).

The present author recently had occasion to gain insight into some of the conditions of manufacture that were likely to have been routinely encountered in some sectors of the pharmaceutical industry thirty or more years ago, during a visit to a non-pharmaceutical manufacturing facility where certain ointments intended for human use were being manufactured illegally. Figure 3.1(a) depicts a general view of the production floor of this facility; dirty equipment and a general untidiness are apparent. The medicines in question were being manufactured in the green 200 litre container featured in the centre of Figure 3.1(a). The container had been fitted with a heating collar (visible around the base of the container) to melt the contents, which was mixed by means of an ordinary garden spade. This spade, which is depicted

Figure 3.1(a): General view of production floor

Figure 3.1(b): Mixing implement

Figure 3.1(c): Warehouse

in Figure 3.1(b), showed visible signs of rust as well as ointment residues of unknown origin. Figure 3.1(c) depicts a general view of the raw materials warehouse; bulk containers are shown to be stored directly on the warehouse floor (instead of being palletised), no status-labelling or physical quarantine system is evident, and there are signs of spillage on the warehouse floor around two bulk containers labelled to contain paraffin wax. The layout of this plant was of such a nature that production and storage areas were not segregated, access was not controlled, and both areas were open to uncontrolled cross-flows of personnel and materials. No attempt had been made to address the potential problems of environmental contamination and cross-contamination; traces of titanium dioxide (a raw material used in the manufacture of a non-pharmaceutical product in the same plant) were evident over the entire floor area, including the administrative offices, and had even been carried out to the parking area outside the building. What was most striking however, was the total lack of appreciation on the part of management of the implications to product quality of the above-mentioned aspects when it was brought to their notice.

## 3.3 THE SCOPE OF THE SOUTH AFRICAN REGULATORY CONTROL SYSTEM

The scope of the South African regulatory control system is determined firstly by the legal definition of a medicine as given under Section One of the Medicines and Related Substances Control Act (South Africa, 1965, *loc. cit.*) and which reads as follows:

> *"Medicine* means any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in (a) the diagnosis, treatment, mitigation or prevention of disease, abnormal physical or mental state or the symptoms thereof in man; or (b) restoring, correcting or modifying any somatic or psychic or organic function in man, and includes any veterinary medicine."

In terms of the provisions of the Medicines and Related Substances Control Amendment Bill (South Africa, 1991, Section 1(c)), medical devices such as instruments, appliances, materials, machines, implants, or diagnostic reagents used in the diagnosis, treatment or prevention of disease, or which affect bodily functions, or which are used in the diagnosis or prevention of pregnancy will, at a date still to be determined, become subject to the same regulatory control system which is presently applied to medicines.

The scope of the South African regulatory control system for medicines is determined, secondly, by the criteria which the Medicines Control Council by law must apply when deciding whether or not the registration or availability (i.e. marketing authorisation) of a particular product is in the public interest. In terms of the provisions of Section 1(3) of the Medicines and Related Substances Control Act (1965, *loc. cit.*), the Medicines Control Council (MCC) must base such a decision solely on criteria related to the safety, quality and therapeutic efficacy of the medicine in question.

As is the case with regulatory authorities world-wide, the MCC has fairly wide discretionary powers with regard to the practical application of these criteria (see Section 2.4). In fact, one of the hallmarks of international pharmaceutical regulatory controls is the phenomenon that regulatory policies may differ markedly between countries. Such variations may be due *inter alia* to specific therapeutic approaches; local therapeutic traditions; national medical practice and opinion; cultural traditions (as reflected in the prescribing habits of physicians, and public expectations); religious and ethical norms; and national economic structures (Dukes, *loc. cit.*, pp. 11 - 16). These variations may for instance be reflected in differences in the total number of products and dosage forms marketed in a particular country; differences in the list of approved indications and the dosage regimen for a particular

drug, and differing acceptance rates for new drugs. Variations also exist with regard to the so-called "intensity" or "density" of drug regulation, i.e. the extent to which matters other than safety, quality and efficacy are officially regulated (Dukes, *ibid.*, pp. 11-20).

There is, however, an international movement towards the harmonisation of regulatory requirements. South Africa is now a full member of the so-called PER-Scheme (Scheme for the mutual recognition of evaluation reports on pharmaceutical products) which was established by countries belonging to the European Free Trade Association. This scheme provides for the mutual recognition of a member authority's evaluation of the scientific data that had been submitted by a manufacturer, and in respect of which marketing authorisation (product registration) has been granted. The PER-Scheme applies to new chemical entities only, and is aimed at eliminating a duplication of the regulatory evaluation process. The unconditional acceptance of foreign evaluation reports is however not obligatory, and the regulatory authority concerned remains autonomous with regard to its own decisions in this regard (MCC, 1993, Circular to applicants ref. 4/93).

Table 3.1, which is adapted from Dukes (*loc. cit.*, p.20), depicts those specific aspects of the industrial cycle for pharmaceutical products which are

TABLE 3.1 : ASPECTS OF THE PHARMACEUTICAL INDUSTRIAL CYCLE WHICH ARE SUBJECT TO DIRECT REGULATORY CONTROL IN SOUTH AFRICA

(a) DEVELOPMENT AND INVESTIGATION

Animal studies (scientific and ethical aspects).

Safety and comparative safety in man.

Efficacy and comparative efficacy in man.

Clinical trials (protocols and licensing of investigators).

Efficacy/safety ratio.

Adverse reaction monitoring (throughout product life cycle).

Product stability trials.

(b) GOOD MANUFACTURING PRACTICE

Quality control systems and procedures.

Qualifications and training of personnel.

Manufacturing documentation (records, procedures, etc.)

Premises and equipment (suitability, product contamination etc).

Process controls (materials handling, in-process controls, process validation, etc.)

Rework policy and procedure.

Complaints and recall procedures.

Analytical laboratory controls (reliability of systems and procedures).

(c) MARKETING

Package insert (format).

Advertising (written or oral claims).

Distribution (conditions of sale and possession).

Prescription requirements (to authorise a sale).

Import-export transactions (including narcotic substances).

Removal of violative products from the marketplace.

subject to regulatory control in South Africa, and also reflects the regulatory "intensity" of the South African regulatory control system.

It is interesting to note in this regard that matters which are subject to official regulation in other countries include: (a) The classes of physicians who are permitted to prescribe certain drugs (in South Africa, this system is presently applied in State-controlled hospitals and institutions but not in the private sector); (b) eligibility for health service payments; and (c) pricing policies (Dukes, ibid.). Norway has, since 1928, imposed additional criteria relating to the so-called "medical need" and "therapeutic value" as preconditions for the granting of marketing authorisation to pharmaceutical products in that country (Wardell, 1983, p. 7).

An important recent development concerning the future role of the South African Medicines Control Council (MCC) is embodied in Section 10 of the Medicines and Related Substances Control Amendment Bill (*loc. cit.*), in terms of which the Council may, if it deems it expedient and in the public interest, disclose information in respect of the prescribing, dispensing, administration and use of a medicine, scheduled substance, or medical device. Moreover, the Director General of the Department of Health may publish this information or release it to the public in a manner which he thinks fit.

Previously, such information had to be withheld in terms of a preservation of secrecy clause of the principal Act; this latest amendment brings the statutory basis of the South African regulatory control system more closely in line with one of the main principles of consumer protection as applied in most developed countries, namely the right of the consumer to be informed (see Section 2.4.2). It may therefore be predicted that the MCC, through the Department of Health, will in future be a valuable source of unbiased information both to final consumers of medicines as well as to professional groups involved in the use of medicines, such as physicians, pharmacists and nurses.

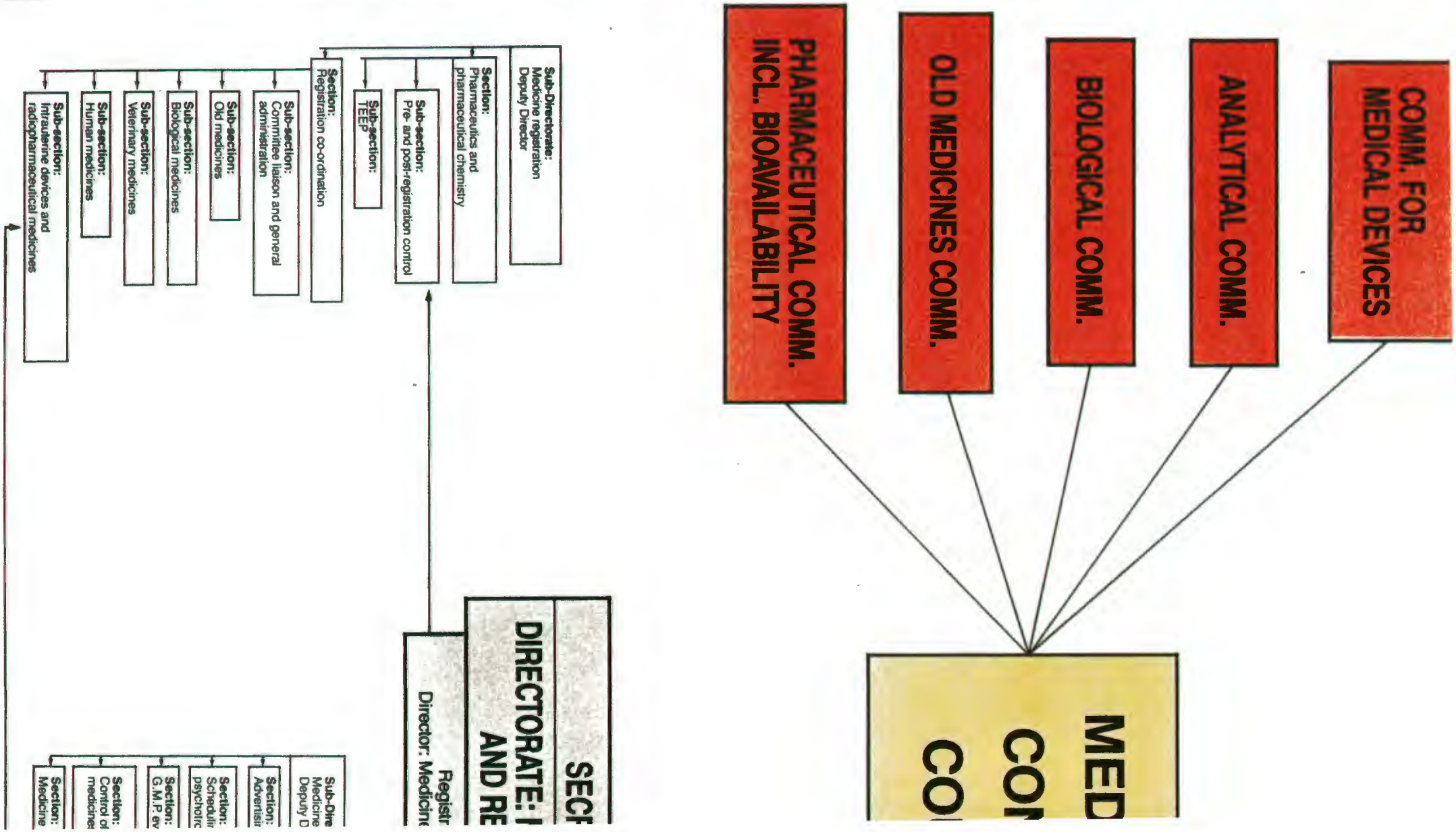
## 3.4 THE ORGANISATIONAL STRUCTURE OF THE SOUTH AFRICAN REGULATORY CONTROL SYSTEM

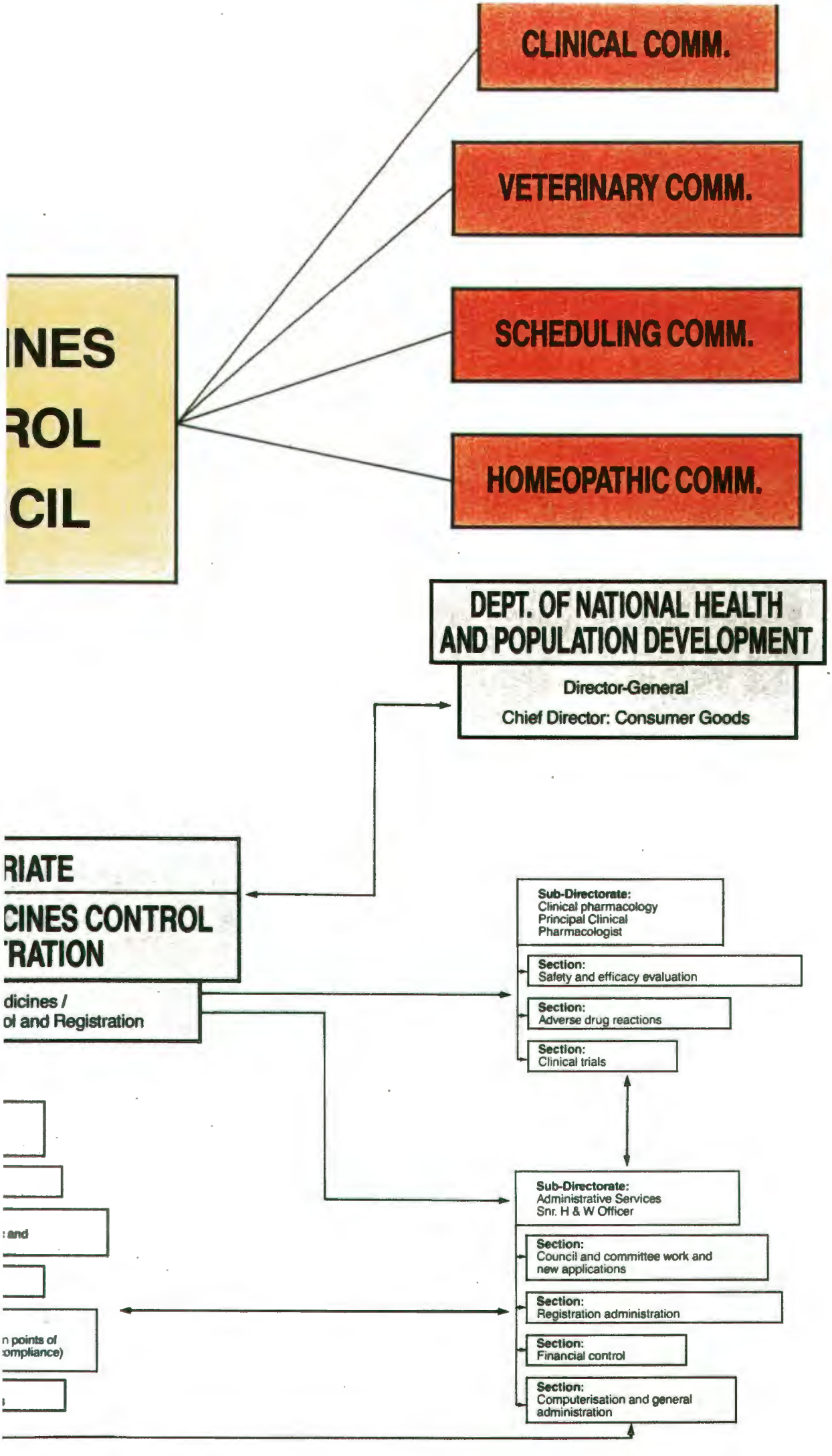
Section 3 of the Medicines and Related Substances Control Act (South Africa, 1965, *loc. cit.*) provides for the establishment of a Medicines Control Council (MCC) consisting of not more than 24 members, as determined by the Minister of Health; council members must collectively possess prescribed academic qualifications and practical experience in the fields of human and veterinary medicine, pharmacology, pharmaceutical chemistry, and pharmaceutics. The council has a Chairman and Vice Chairman, both of whom are also appointed by the Minister of Health.

In terms of Section 9 of the Medicines and Related Substances Control Act (*ibid.*), an Executive Committee may be appointed by the council from amongst its own members. The MCC may, subject to the approval of the Minister of Health, also appoint suitable persons to such other committees as it may deem necessary to investigate and report to it on any matter within the purview of the council. Nine such specialist sub-committees presently operate in terms of this provision, namely the clinical; veterinary; scheduling; homeopathic; medical devices; analytical; biological; old medicines; and pharmaceutical sub-committees (see Figure 3.2). Any sub-committee may in turn consist of so-called working groups composed of persons attached to academic institutions nation-wide, thereby giving the MCC access to highly specialised and experienced authorities in many different fields (Schlebusch, *loc. cit.*).

A secretary to the council, who is termed the Registrar of Medicines, is appointed by the Minister of Health after consultation with the MCC (South Africa, 1965, Section 12). The Registrar of Medicines constitutes the Secretariat (see Figure 3.2), and is also the Chief Executive of the Directorate Medicines Control of the Department of Health. The Registrar is accountable to the Minister of Health, the Director General of the Department of Health, and the Chairman

FIGURE 3.2: THE ORGANISATIONAL STRUCTURE OF THE SOUTH AFRICAN REGULATORY CONTROL SYSTEM




CLINICAL COMM.
VETERINARY COMM.
SCHEDULING COMM.
HOMEOPATHIC COMM.
INES
ROL
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DEPT. OF NATIONAL HEALTH AND POPULATION DEVELOPMENT
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Chief Director: Consumer Goods
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Clinical pharmacology
Principal Clinical
Pharmacologist
Section:
Safety and efficacy evaluation
Section:
Adverse drug reactions
Section:
Clinical trials
Sub-Directorate:
Administrative Services
Snr. H & W Officer
Section:
Council and committee work and
new applications
Section:
Registration administration
Section:
Financial control
Section:
Computerisation and general
administration
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of the MCC (Schlebusch, *loc. cit.*). The Directorate Medicines Control and Registration performs tasks delegated to it by the Registrar of Medicines, and consists of four Sub-Directorates: the Sub-Directorate Medicine Registration; Medicine Control; Clinical Pharmacology; and Administrative Services (see Figure 3.2). All personnel attached to the Directorate Medicines Control and Registration are employees of the Department of Health.

## 3.5 THE MARKETING AUTHORISATION PROCEDURE

This section of the dissertation gives a concise overview of the major stages of the review process for new chemical entities and certain generic medicines; a detailed description of the protocol for other product types or specific regulatory issues is beyond the scope of this dissertation. The procedure whereby the MCC judges safety, quality and therapeutic issues relating to applications for marketing authorisation will therefore be described in general terms only.

Applications for product marketing authorisation are submitted to the Registrar of Medicines (see Figure 3.2) in the form of a Summary Basis for Registration Application (SBRA); this document is intended to be a summary of the core data contained in the formal application, or so-called MBR 1 registration dossier

(see Section 3.6), which is submitted once the SBRA document has been accepted. The SBRA document will contain a brief and concise overview of aspects such as a description of the product itself (e.g. the active ingredient(s) and the quantity thereof, the dosage form, and the pharmacological classification); details concerning the product's proven pharmacological action, based upon at least two key supporting references; evidence of product efficacy, including details of the relevant clinical trials; main product safety issues and toxicological data, including human studies and pre-clinical studies (with reference to animal and in vitro toxicology); evidence of the product's long term safety and efficacy; evidence of the bioavailability and pharmacokinetics of the active component(s); the product's registration status in other countries (if applicable); and a motivated statement concerning the proposed scheduling status of the product (see Section 3.7 regarding the significance of product scheduling status). The SBRA document is reviewed by technical personnel attached to the Directorate Medicines Control and Registration of the Department of Health. The applicant will be informed of the outcome of the review of the SBRA document within four weeks of its submission. If the SBRA document is accepted, submission of the MBR 1 registration dossier for formal review by the MCC may proceed (MCC, 1986, Circular to applicants ref.15/86).

This system enables the applicant to receive an indication, which is not binding upon the MCC, of the likelihood of the proposal's success or failure. If the review of the SBRA document reveals that the formal MBR 1 application is unlikely to be successful, the document is returned to the applicant together with the appropriate comment. The applicant is not bound to accept this opinion, and is free to proceed with the formal MBR 1 application.

To further expedite the review process of new applications by the expert committees of the MCC, one copy of the fully-completed MBR1 dossier may be submitted to the Registrar of Medicines for "Quick Screening" of stability data and bioavailability or dissolution studies (which are submitted as proof of product efficacy). The applicant will be informed within 72 hours of any deficiencies in this regard (MCC, 1992, Circular to applicants ref. 2/92). In order to expedite the evaluation of pharmaceutical products which have already been registered (granted marketing authorisation) in certain nominated countries, the MCC has introduced the so-called Abreviated Medicines Review Process (AMRP). The AMRP-system is aimed at reducing the evaluation time of applications for registration of products already registered in the United States of America, Great Britain, Canada, Sweden and Australia with respect to the evaluation of pharmacotoxicological and clinical data in particular (MCC, 1993, Circular to applicants ref. 4/93).

The information that must be submitted by an applicant in the MBR 1 registration dossier for formal review by the MCC, is described under Section 3.6 of this dissertation. After the MBR 1 dossier has been submitted for formal review, the various specialist subcommittees of the MCC will review individual aspects of the application; decisions made by the various subcommittees are subject to further review and confirmation at a plenary session of the MCC. The Medicines and Related Substances Control Act empowers the MCC to impose any precondition it may deem necessary on the granting of marketing authorisation for a particular product. One of the preconditions routinely applied by the MCC relates to the requirement that an acceptable standard of good manufacturing practice (GMP) must be maintained in the place of manufacture. Members of the inspectorate attached to the Directorate Medicines Control and Registration (see Figure 3.2) will inspect the plant concerned to verify adherence to good manufacturing practice principles (see Chapter 4), and the MCC will base its decision on whether or not to grant that plant manufacturing authorisation on the report submitted by the inspectorate to its plenary session.

There are three possible outcomes to the formal review of the MBR 1 dossier:

(a) The MCC may decide to approve the application for marketing authorisation (product registration), whereafter the Registrar of Medicines enters the information prescribed by Regulation 7 of the Medicines and Related Substances Control Act (*loc. cit.*) into the Medicines Register, and issues the applicant with a Medicine Registration Certificate as prescribed by Regulation 8 of the Medicines and Related Substances Control Act (*ibid.*). The Registrar of Medicines also allocates a registration number to every product thus approved; this number is entered into the Medicines Register and on the Medicine Registration Certificate and, in terms of the provisions of Regulation 9 of the Medicines and Related Substances Control Act (*ibid.*), must also appear on every product label. The conditions under which the MCC has granted marketing authorisation is also entered into the Medicines Register and on the Medicine Registration Certificate.

(b) The MCC may decide to defer the application for marketing authorisation subject to certain specified conditions, depending on the nature of the council's objection to the application. The applicant is informed in writing of the reason(s)

for the deferment. If the applicant does not accept the council's reasons, an appeal may be made directly to the council, provided that this is properly motivated and is done within one month after the date of notification (South Africa, 1965, Section 15(3)(b)). If no such appeal is made, or if the MCC is still not satisfied, the application is rejected. The applicant may then appeal to an appeal committee appointed by the Minister, and which consists of a retired judge or advocate of the Supreme Court, who shall be the chairman, a pharmacologist and, depending on the field to which the appeal relates, a veterinarian and a pharmacist; a homeopath; a medical practitioner and a pharmacist; or a specialist or technician with expert knowledge concerning medical devices (South Africa, 1965, Section 24). The appeal committee may confirm or set aside or vary the relevant decision by the MCC. In the case of an application having to be resubmitted, reentry into the evaluation system may occur at any one of several different levels, depending on the nature of the council's original objection.

(c) The MCC may decide to reject the application for marketing authorisation, in which case the procedure regarding the disclosure of the reasons for

the decision and the right of the applicant to appeal against such a decision is the same as that described under (b) above.

## 3.6 THE MBR 1 REGISTRATION DOSSIER

Section 14 of the Medicines and Related Substances Control Act (*ibid.*) may be regarded as the corner-stone of the South African regulatory control system. This particular statutory provision empowers the MCC to declare a particular medicine or class or category of medicines to be registerable, and places a prohibition on the sale of any registerable medicine unless it has been so registered. Every application for marketing authorisation in respect of a medicine must be submitted to the Registrar of Medicines on the prescribed form, the so-called MBR 1 registration dossier, the only exception being biological medicines which are registered in terms of the format prescribed by Regulation 46 of the Medicines and Related Substances Control Act (ibid). For the purposes of this dissertation, only the data pertaining to the MBR 1 dossier for non-biological medicines will be reviewed.

The format of the MBR 1 registration dossier is described under regulation 15 of the Medicines and Related Substances Control Act (*ibid.*), and consists

of 25 annexures and sub- annexures in the case of a medicine intended for human consumption, and 26 annexures or subannexures in the case of a veterinary medicine. The purpose of the MBR 1 dossier is to supply the MCC with sufficient data on which to base its decision regarding the granting or refusal of marketing authorisation of the product concerned. It should be noted in this regard that the onus for submitting complete, accurate and truthful information concerning an application for marketing authorisation rests entirely with the applicant; it is not for the MCC to go in search of the relevant evidence, although the council may conduct any investigations of its own which it may deem necessary (Snyman, 1972, pp. 280 - 287). The cover page of the MBR 1 dossier contains a declaration by the applicant to the effect that all the information contained in the dossier is true and correct; and Section 29 (h) of the Medicines and Related Substances Control Act (*loc. cit.*) makes it an offence for an applicant to give false or misleading information in this regard. Notwithstanding this statutory provision, it may be stated that the contractual relationship between the applicant and the MCC is one which is very much based on trust.

The paragraphs which follow contain a summary of the information required to be submitted by the applicant in the various annexures of the MBR 1 dossier. The

close relationship between this information and that which will routinely be generated during the activities associated with the implementation of a total quality system, will be highlighted.

### 3.6.1 The package insert

The printed information leaflet or package insert which accompanies each package of medicine, either as a separate entity or an integral part of the package, is by law required to disclose *inter alia* details concerning product composition; pharmacological action; clinical indications for use; contra-indications; warnings; directions for use; side-effects and special precautions; known symtoms of overdosage and details of its treatment; product identification (physical attributes); and storage conditions (South Africa, 1965, Regulation 10). All the information contained in the product package insert has to be scientifically substantiated to the satisfaction of the MCC, and this information must be summarised in the prescribed format under Annexure 1A of the MBR 1 dossier. In terms of Regulation 11(3) of the Medicines and Related Substances Control Act (*ibid.*), no advertisement for a medicine may contain a statement which deviates from or goes beyond the evidence submitted in the MBR 1 registration dossier. The information contained in the approved package

insert of a pharmaceutical product thus defines the parameters of the promotional claims that may be made in connection with that particular product; the accent being on full disclosure of relevant product information, and accurate advertising.

### 3.6.2 The product label

Annexure 1B of the MBR 1 dossier requires the applicant to provide a facsimile or specimen of the proposed product label in order to verify compliance with the labelling requirements detailed under Regulation 9 of the Medicines and Related Substances Control Act (*ibid.*). These labelling requirements include the disclosure of information relating to the identity and quantity of each active ingredient contained per dosage unit; indications for use; recommended dosage; the lot number; the expiry date; the name of the applicant; storage conditions; and prescribed warnings (e.g. "keep out of reach of children"). As in the case of the package insert (see Section 3.6.1), the accent here is on full disclosure of the relevant product information.

These requirements are in keeping with modern thinking on labelling policy. The reason for the adoption of this particular policy by the American Food and Drug Administration (FDA) is related to the perception that

drug manufacturers were replacing medical schools as the principal source of information regarding their use of new drugs. The FDA felt that the informative labelling agreed upon with manufacturers in the course of processing new drug applications, was not reaching potential prescribers of the products concerned. According to the legal requirements applicable at the time, this information was referred to on the product label as being "available to physicians on request". This informative labelling was, however, usually not part of the product pack, and there was no assurance that it would be included in a response to a request for such information. The pharmaceutical industry moreover was promoting the use of these potent new drugs to physicians through detail men, mailing pieces, medical journal advertising, and reference publications that frequently failed to disclose their hazards. As the dangers of this situation were recognised, the FDA increasingly required informative labelling to be made part of the prescription drug package; this in turn lead to the promulgation of the so-called "full disclosure" regulations in 1961. These regulations called for the disclosure of complete professional information to the prescriber of a medicine, including the specific hazards, side effects, and special precautions regarding its use; this information now had to be included in prescription drug packages and the sales literature distributed to physicians (Janssen, *loc. cit.*, p. 436).

In South Africa, current legislation applies this requirement to all medicines, not only prescription medicines (South Africa, 1965, Regulation 10 and 11). The MCC is also presently engaged in compiling guidelines with regard to the use of layman's terminology in product package inserts, thereby further extending the doctrine of full disclosure of relevant product information (MCC, 1993, Circular to applicants ref. 20/93).

### 3.6.3 Product formulation

Full details relating to product formulation (design) must be disclosed under Annexure 2 of the MBR 1 dossier. The names and quantities of each active ingredient must be disclosed, and must conform to the relevant particulars in the package insert and on the label (see Section 3.6.1 and 3.6.2). The identity and quantity of each inactive ingredient, together with its purpose, must also be disclosed even when a particular ingredient may not be present in the final product (e.g. in the case of alcohol which is evaporated off during the manufacturing process). The purpose of each inactive ingredient must be disclosed in order to give the MCC an overall picture of the formulation, and because the same inactive may in some instances serve more than one function; for example, starch in a tablet formulation may serve as a dis-

integrating agent or a binding agent. Even the content of gelatine capsule shells (including the preservatives contained therein) and tablet coatings must be disclosed; details required include the colour index number of the colourants and the type of printing ink used to imprint tablets or capsule shells (Beaumont, 1991, pp. 18-19).

### 3.6.4 Chemical details of active ingredients

The chemical details of the active ingredient(s) of the formulation must be declared under Annexure 3A of the MBR 1 dossier with reference to the approved name(s) used under Annexure 2 (the formulation) of the application; structural formulae (i.e. formulae of organic compounds in which the covalent bonds between atoms are presented graphically) must be given; and the relevant data relating to solubility in water, and storage requirements, must be disclosed. Data relating to storage requirements must correspond to the stability data submitted under Annexure 10 of the application (see Section 3.6.16). Annexure 3A of the MBR 1 dossier relates only to the chemical details of active ingredients; raw material specifications for active as well as inactive raw materials are detailed under Annexure 4 of the MBR 1 dossier (see Section 3.6.7).

3.6.5 Identification of vendors

The names and addresses of primary and alternative suppliers of active ingredients must be declared under Annexure 3B of the MBR 1 dossier. The applicant will not be allowed to source active raw materials from any vendor other than those listed under this particular annexure. This implies that it would be in the interests of the applicant to initiate a formal vendor approval procedure (as would be done routinely during the implementation of a total quality programme) before nominating specific suppliers under this annexure.

3.6.6 Description of the method of synthesis of the active ingredients

Under Annexure 3C of the MBR 1 dossier, the applicant is required to refer specifically to impurities and degradation products which may be produced during the synthesis of the active ingredient(s) of the proposed product. The significance of the presence of these impurities and degradation products in the final pharmaceutical dosage form is therefore taken into account.

### 3.6.7 Summary of raw material specifications

Under Annexure 4 of the MBR 1 dossier, a summary of the specifications for all the active and inactive raw materials used in the manufacturing process must be supplied, including the names of the tests, limits, and criteria of acceptance relating to every parameter contained in the specification. The data supplied in this annexure therefore details the parameters according to which a raw material will be accepted or rejected. The analytical and other control procedures whereby compliance with these specifications are monitored, are described under Annexure 5 of the MBR 1 dossier (see Section 3.6.8). It should be noted that not all the specifications listed under Annexure 4 are necessarily tested for as a batch release requirement for raw materials; this aspect is explained more fully under Section 3.6.9.

### 3.6.8. Raw material control procedures

Annexure 5 of the MBR 1 dossier calls for a full description of the analytical and other (technical) control procedures relating to the raw material specifications disclosed under Annexure 4 (*supra*). In other words, full details of the inspection and test procedures that have to be carried out in order to accept or reject a raw material are given in this annexure of the MBR 1 dossier.

3.6.9 Raw material release criteria and laboratory details

Annexure 6 of the MBR 1 dossier calls for a description of those analytical and other (technical) control procedures that are actually carried out on raw materials as a batch to batch release requirement. The difference between the details that are disclosed under Annexures 5 and 6 of the MBR 1 dossier, is therefore related to the fact that only certain of the tests or procedures detailed under Annexure 5 (see Section 3.6.8) are in practice carried out as a batch to batch release requirement for raw materials. According to the guidelines issued in this regard by the Medicines Control Council, at least an identification test and assay must be performed on all active raw materials, although the council may demand any additional tests it may deem necessary for specific materials (MCC, 1983, Circular to applicants ref. 4/83). Supplier's certification by means of a Certificate of Analysis may therefore reduce the number of analytical and other controls carried out by the applicant to identification and assay procedures only, subject to the approval of the Medicines Control Council.

3.6.10 Final product specifications

A summary of the specifications of the final product must be given under Annexure 7A of the MBR 1 dossier.

The title of the specifications (e.g. average tablet mass, hardness, and assay values), together with the limits and criteria of acceptance of all physical, chemical and, where necessary, microbiological parameters that are to be used as release criteria for the final product, must be included in this summary. Specifications will naturally differ according to the dosage form involved. For example, the final product specifications for an uncoated tablet would typically include criteria such as physical description (colour, size, markings, shape, etc.); theoretical mass; average mass; mass uniformity; hardness; friability; disintegration time (under specified conditions); dissolution time (under specified conditions); degradation products; assay values (e.g. minimum and maximum percentage purity); identification; and moisture content, where applicable (Beaumont, *loc. cit.*, pp. 27 - 30).

3.6.11 Final product control procedures

Under Annexure 7B of the MBR 1 dossier, the applicant is required to give a full description of the analytical and other technical control procedures relating to the final product specifications set out in Annexure 7A. In other words, the applicant is required to give a full description of the analytical

and other (technical) control procedures that will be carried out to verify compliance with the final product specifications detailed under Annexure 7A (see Section 3.6.10).

### 3.6.12 Container specifications

Annexure 8A of the MBR 1 dossier calls for detailed specifications of the type, nature, size and grade of the immediate container (i.e. the container which is in direct contact with the medicine), including the method of closure and the material used as wadding. A brief description of the outer container (if applicable) must also be given, but specifications are not required in this case. The Medicines Control Council has adopted a policy which requires that, in the case of glass ampoules, statistically valid sampling procedures must be employed with respect to: (i) Complete physical specifications; (ii) a hydrolytic resistance test; (iii) a test for barium and other substances which may leach out of the glass; and (iv) validation of the cleanliness, sterility, and non-pyrogenicity of closed ampoules (MCC, 1983, Circular to applicants ref. 16/83). The Medicines Control Council has furthermore determined that child protective measures must be employed with regard to containers used in the sale of salicylates, paracetamol, iron tablets or capsules, and certain liquid camphor products (MCC, 1984, Circular to applicants ref. 10/84).

3.6.13 Container control procedures

Annexure 8B of the MBR 1 dossier calls for details concerning the control procedures that are carried out up to the point where the actual packaging process is about to take place, and therefore includes those control procedures relating to the specifications in Annexure 8A (see Section 3.6.12) as well as the additional checking procedures that are followed after overprinting and cleaning of packaging materials. It should be noted that some of the above-mentioned procedures will in fact be carried out by the vendor(s) concerned, but that final responsibility in this regard rests with the applicant.

3.6.14 Final product control

All control procedures that are carried out on the final product as a batch release requirement, and the name and address of the laboratory where these tests are to be carried out, must be disclosed under Annexure 9A of the MBR 1 dossier. It should be noted that not all of the control procedures detailed under Annexure 7A (see Section 3.6.10) are necessarily used as a batch release requirement for the final product. The inspection and test procedures detailed under Annexure 9A therefore relate only to those controls that are in fact used in the final release of the product.

In the case of products that are imported in finished form, the final product release controls must at least include an identification and assay in order to verify the maintenance of product integrity during transit. Samples may be drawn locally and returned for analysis by overseas suppliers in accordance with the details disclosed by the applicant under this annexure of the MBR 1 dossier.

The Medicines Control Council may exempt an imported product from having to be (chemically) identified and assayed, under certain prescribed conditions. These preconditions relate *inter alia* to the validation of conditions of transportation; a conclusive (not necessarily chemical) identification test performed in South Africa; the availability of product master specifications; certification of the quality control systems of the manufacturing plant; and a formal release procedure which includes details of the exact method and duration of transport, a certificate of analysis from the supplier, invoicing details, and confirmation of container integrity (South African GMP guide, 1992, Appendix II).

3.6.15 Final container control

Annexure 9B of the MBR 1 dossier calls for details concerning the analytical control procedures that are

to be carried out on the immediate container by or on behalf of the applicant, as well as the identity of the laboratory where these tests are to be performed. Summaries of all the tests listed under Annexures 8A and 8B (see Sections 3.6.12 and 3.6.13) must be given, in addition to which tests for cleanliness and accuracy of overprinting may be included here (Beaumont, *loc. cit.*, p. 36).

3.6.16 Stability data

Under Annexure 10 of the MBR 1 dossier, the applicant is required to provide the Medicines Control Council with a description of the characteristics of the product's active ingredients in respect of normal degradation patterns, the identity of known degradation products, and the storage conditions necessary to preserve raw material integrity. A full description of the experimental details of stability testing carried out on the final product, an interpretation of the results obtained, a description of the nature and suitability of the analytical procedures employed, and a comprehensive description of the stability programme used to determine the product's shelf-life, must also be included under this annexure of the dossier. The actual design of the stability studies and tests that are employed will depend on the nature of the product concerned and the known stability characteristics of

its ingredients; the type of packaging which is to be used (the product must be tested in the container-closure system in which it will be sold); and the variety of environmental conditions to which the product is likely to be exposed during its shelf-life (the product would typically be tested at elevated and cyclical temperatures, and under conditions of elevated humidity, as well as normal storage conditions). It is important to note that it is the responsibility of the applicant (not the regulatory authorities) to ensure that the stability testing methods and results accurately reflect expected stability characteristics during the product's entire shelf-life (MCC, 1991, Circular to applicants ref. 12/91).

The concept of product stability which is encountered in the pharmaceutical technical literature in many respects corresponds to the product reliability concept, which is an integral part of the total quality philosophy. Feigenbaum (1986, pp. 570 - 572) describes product reliability as being a quality characteristic, and defines the concept as follows: "Product reliability is the ability of a unit to perform a required function under stated conditions for a stated period of time." The prediction of product reliability and the demonstration that this reliability has been achieved, the improvement of

product reliability, the coordination of all the activities necessary to establish, achieve and maintain product reliability, and the integration of these activities into the complete company programme for quality, all form part of the product reliability activities of a total quality system.

3.6.17 Manufacturing procedures

Annexure 11 of the MBR 1 dossier calls for a step-by-step description of all the manufacturing and packaging procedures and in-process controls that are carried out during the product's manufacture. The information which is disclosed under this annexure would typically include the exact items of equipment to be used, and would detail processing parameters such as mixing times and temperatures. The product formulation detailed under Annexure 2 (see Section 3.6.3) will be repeated here, with quantities scaled up to the production batch size. All analytical and other (technical) in-process controls, their frequency and sequence, and the stage of production at which they are to be carried out, together with the relevant limits of acceptance, must also be disclosed under this annexure.

As soon as the Medicines Control Council has approved the application for registration, processes and procedures have to be validated with reference to the first two production batches of product (MCC, 1983, Circular to applicants ref. 14/83). These data must be retained for inspection by inspectors attached to the Sub-Directorate Medicines Control of the Department of Health (see Section 3.4). The above-mentioned validation procedure is considered necessary in order to ensure uniform quality on a batch to batch basis (Beaumont, *loc. cit.*, p. 39).

3.6.18 Foreign Registration

In order to expedite the registration process in South Africa of a product that has been registered in a foreign country, details concerning the conditions for registration in that country must be submitted to the Medicines Control Council under Annexure 12 of the MBR 1 dossier. If foreign registration is still pending, then details concerning the progress already made in this regard must be submitted. The South African Medicines Control Council is therefore able to rely on the expertise of foreign regulatory authorities when making decisions concerning the availability of a particular product on the South African market.

Reference is made under Section 3.3 to the PER-Scheme for the mutual recognition of evaluation reports on pharmaceutical products between South Africa and countries belonging to the European Free Trade Association. See also the reference in Section 3.5 to the so-called Abreviated Medicines Review Process, which involves the use of evaluation reports sourced from certain foreign countries.

3.6.19 Pharmaceutical and biological availability

Annexure 13 of the MBR 1 dossier calls for the applicant to disclose the experimental details and results of tests carried out on the product to confirm its pharmaceutical and/or biological availability. Pharmaceutical availability in principle refers to the quantity of active ingredient(s) which is/are dissolved *in vitro* from a pharmaceutical dosage form (such as a tablet for instance) in a given dissolution medium, as a function of time, compared to a suitable reference standard. Biological availability may be defined as the quantity of, and the rate at which, an administered medicine appears in the relevant body fluid (blood, for example); the data may be required to be established *in vivo* (Beaumont, *loc. cit.*, pp. 41 - 44).

The above data are required by the Medicines Control Council in support of the claims for safety and therapeutic efficacy made by the applicant for the product concerned, and will be of particular importance in the following circumstances: (i) When the results of clinical studies are not available; (ii) when clinical trial data are available, but relate to a product formulation which differs from that being submitted by the applicant; and (iii) when a new sustained release, repeat action or long acting dosage form is at issue (*ibid.*, p. 41).

3.6.20 Pre-clinical studies relating to toxicological data

Under Annexure 14A of the MBR 1 dossier, the applicant is required to provide toxicological evidence of the safety of the proposed product. Such data may include test results relating to acute toxicity, teratogenicity, carcinogenicity, and any other appropriate tests. In cases where well-known active ingredients are involved, the Medicines Control Council may grant exemption from the submission of some of the above information.

3.6.21 Pre-clinical studies relating to product efficacy

Annexure 14B of the MBR 1 dossier calls for the applicant to disclose experimental details and the

results of tests performed pre-clinically to demonstrate the therapeutic efficacy of the proposed product. These test results in particular must substantiate the medicinal claims that are to be made in connection with the proposed product when it is used as directed.

3.6.22 Clinical studies to demonstrate product safety

Under Annexure 15A of the MBR 1 dossier, the applicant is required to provide full details (including dosages and routes of administration) regarding the tests performed on human beings during clinical trials, together with the results obtained; including the side-effects observed. In the case of a product intended for veterinary use, Annexures 15A, 15B, and 15C are replaced by Annexures 17A, 17B, and 17C respectively. The above information enables the Medicines Control Council to evaluate the *in vivo* safety of the proposed product.

3.6.23 Clinical studies to demonstrate product efficacy

Under Annexure 15B of the MBR 1 dossier, the applicant must provide the Medicines Control Council with details regarding the tests conducted, and the results obtained, during clinical studies aimed at demonstrating the therapeutic efficacy of the proposed

product. Such studies would typically be based on any of a number of trial designs, such as double-blind, cross-over, or randomized trials for instance (MCC, 1986, Circular to applicants ref. 15/86).

3.6.24 Clinical data to support the claimed pharmacological action of the medicine

Under Annexure 15C of the MBR 1 dossier, the applicant is required to submit data obtained during clinical trials on human beings to demonstrate that a particular and predictable pharmacological action is obtained from specified concentrations of an administered medicine in a relevant body fluid (blood, plasma, or spinal fluid for instance).

3.6.25 Pharmaceutical development

Annexure 16 of the MBR 1 dossier calls for disclosure of details concerning the experimental and production -sized batches of product from which the final product specifications stated in Annexure 7A (see Section 3.6.10); the final product control procedures in Annexure 7B (see Section 3.6.11); the stability data in Annexure 10 (see Section 3.6.16); the manufacturing procedures in Annexure 11 (see Section 3.6.17); and the pharmaceutical and bioavailability data in Annexure 13 (see Section 3.6.19) were derived. The

relevant working documents must be made available for inspection by members of the inspectorate of the Sub-Directorate Medicines Control of the Department of Health (see Section 3.4).

## 3.7 Statutory controls over the advertising and sale of medicines

Experience with modern medicines has shown that many of these products are of great value if used under professional direction, but could be dangerous if used in an uncontrolled manner by a lay person (see Section 2.3.3). Dangerous side-effects and adverse reactions, as well as the problem of drug abuse, are examples of problems which could be exacerbated by the uncontrolled use of some of these medicines (Snyman, 1972, pp. 275 - 276). Self-medication is, however, a necessary and widely practised facet of health care, and individual countries have to devise statutory controls over the advertising and sale of medicines to best suit their individual needs. In South Africa, these statutory controls have to accommodate the needs of a heterogeneous community with multiple strata of development, customs and traditions, education, facilities, and economic levels (*ibid.*, pp. 287 - 288).

It was mentioned under Section 2.3.3 that earlier statutory controls over the sale of medicines in South Africa were instituted upon the advice of the Medical and Dental Council and the then Pharmacy Board. Following the promulgation of the Medicines and Related Substances Control Act, and the creation of the Medicines Control Council (MCC), a specialist sub-committee of the MCC, the Scheduling Sub-Committee (see Figure 3.2) now administers this task. The mission of this subcommittee is to advise the MCC on all matters regarding the scheduling of medicines; the MCC in turn advises the Minister who amends the Schedules to the Medicines and Related Substances Control Act by publication in the Government Gazette (Dreyer, 1986, p. 122). Depending on its particular risk/benefit profile, a medicine may be classified in one or more of nine schedules, or may remain unscheduled; specific preconditions for the advertising or sale of a medicine thus classified are prescribed by the Medicines and Related Substances Control Act in the interests of the final consumer.

Unscheduled medicines are those which have an acceptable safety profile and which are deemed necessary for public use where no pharmaceutical service is available; these medicines generally do not require professional counselling on their use or storage, nor is a differential diagnosis necessary to

initiate their use. Shedule One medicines are those with a proven safety profile, but which still require a certain degree of professional control with regard to their storage, merchandising, and the furnishing of advice concerning their use. Schedule Two medicines are for use in less serious (usually self-limiting) diseases upon the advice of a competent professional person. Schedule Three medicines are mainly for use in chronic conditions such as hypertension, epilepsy, angina, diabetes, and thyroid dysfunction. Schedule Four medicines are medicines whose use should be initiated only after a differential diagnosis has been performed and/or should be used under the constant supervision of a physician, or which possess a relatively high toxicity potential. Schedule Five is reserved for centrally acting medicines which have a sedative and/or hypnotic activity, and which have a degree of abuse potential. Schedule Six medicines are potentially dangerous and dependence-producing. Schedule Seven medicines relate to the so-called habit forming drugs, such as morphine and pethidine, whereas Schedules Eight and Nine are reserved for the so-called banned substances, such as cannabis and amphetamines (Dreyer, *ibid.*, pp. 122 - 125).

Briefly stated, an unscheduled medicine may be sold without restriction by any licensed person, whereas Schedule One and Two medicines may be sold only by a

pharmacist, veterinarian, dentist or a physician under certain prescribed conditions. Schedule Three to Seven medicines may only be sold on the prescription of a physician, subject to certain preconditions regarding the number of repeat issues that may be given; the quantity that may be supplied; the period of supply; and the records and registers that have to be kept with regard to such a sale. Schedule Zero (unscheduled) up to Schedule Two medicines are commonly referred to as "over the counter" or "OTC" medicines, whereas Schedule Three to Seven medicines are referred to as "prescription medicines" (see Table 1.1). "Over the counter" medicines may be advertised to the lay public, whereas "prescription only" medicines may be advertised to the professions only (South Africa, 1965, Section 22A). The Medicines and Related Subtances Control Act furthermore stipulates that an advertisement may not go beyond the information approved by the MCC in the product's package insert (South Africa, 1965, Section 18 read with Regulation 11).

## 3.8 SUMMARY

The South African regulatory control system is founded upon the provisions of the Medicines and Related Substances Control Act. This Act provides for the creation of the Medicines Control Council (MCC), an

autonomous body with statutory powers, which is mandated to act in the public interest when making decisions regarding the granting or refusal of applications for marketing authorisation (registration) of medicines, and to determine the conditions under which medicines may be manufactured, sold or advertised. Administrative and executive support for the functioning of the MCC is provided by the Directorate Medicines Control and Registration of the Department of Health.

Modern regulatory controls are applied to most aspects of the entire industrial cycle of a pharmaceutical product; from the commencement of clinical trials with experimental formulations to post marketing surveillance of the finished product. During the entire regulatory control process, information must be provided to the MCC regarding all aspects of product safety, quality and therapeutic efficacy. These regulatory requirements in many respects correspond to the new design control; incoming material control; product control; and post marketing surveillance activities of a total quality system. The regulatory authorities may therefore be seen as performing the role of external quality auditors within the pharmaceutical industry; this relationship is in many respects based on a mutual commitment to serving the public interest.

The regulatory decision making process is by its very nature not based exclusively on scientific criteria, but has to reflect the specific needs of the country concerned especially with regard to aspects such as local therapeutic conditions, national medical practice and opinion, cultural traditions, religious and ethical norms, and national economic structures (see Section 2.4). An important facet of what may be termed the current "regulatory controversy" in South Africa relates to the fact that the regulatory controls presently applied in this country were designed to cater predominantly for the country's First World needs; the relevancy of the existing regulatory control system is consequently being questioned. The application of a business economic approach to this problem is seen as being potentially valuable, both in terms of its market orientation and the emphasis that it places upon optimum resource utilisation.

The MBR 1 registration dossier, which is discussed in Section 3.6, and the good manufacturing practice principles which are discussed in Chapter 4 of this dissertation, are both seen as providing valuable guidelines to the identification of quality-related decisions during each step of the industrial cycle.

The MBR 1 dossier in particular may be described as being a valuable tool in the formulation of quality policy in the pharmaceutical industry (see Section 5.9). Moreover, the MBR 1 dossier relates to many of the key elements of the new design control; incoming material control; product control; and post-marketing surveillance activities of a total quality system. Similarly, the *quasi-legal* good manufacturing practice principles currently adhered to by the South African pharmaceutical industry upon the insistence of the MCC (see Chapter 4) also contain many elements which may be further developed and expanded into a formal total quality system.

From a business economic viewpoint, however, a major criticism of the above-mentioned components of the South African regulatory control system is the fact that they are exclusively technically-oriented, with no managerial focus. This contrasts with the business economic viewpoint that quality is in essence a way of managing an enterprise, and that managerial control over quality is achieved in the same manner as control over the financial, marketing and other functions of the enterprise. Managerial control over quality involves the continuous setting of the necessary quality standards, appraisal of quality conformance, correction of quality problems and their causes, and plan-

ning for future improvements (see Section 5.4). With reference to the South African regulatory control system, there appears to be a need to distinguish between the value of what amounts to a mere declaration of intent to adhere to certain (technically-oriented) principles, and the creation of a dynamic company-wide managerial structure which is aimed at the disciplined achievement of the quality goal.

# CHAPTER FOUR: A CRITICAL REVIEW OF CURRENT PHARMACEUTICAL GOOD MANUFACTURING PRACTICE PRINCIPLES

## 4.1 GENERAL

In the wake of the thalidomide disaster, which is described under Section 2.4.2.1, the so-called Kefauver-Harris amendment to Food and Drug Administration (FDA) legislation was introduced in the United States of America during 1962. In terms of this amendment, the American regulatory authority (the FDA) was given control over production, distribution and advertising of prescription medicines, including quality control and periodic inspection of manufacturing facilities (Folb, 1977). The regulations promulgated in terms of this new legislation require a complete and full description of the controls employed by a manufacturer to assure the quality of all medicines produced. The first good manufacturing practice (GMP) regulations were published in the United States of America during 1963 (Lachman, *et al.*, 1986, p. 829). The first World Health Organisation (WHO) draft text on GMP was prepared at the request of the Twentieth World Health Assembly in 1967 by a group of consultants (WHO draft GMP guide, 1990, p. ii).

A great many GMP texts have subsequently been published worldwide, and these guidelines may be seen as representing the collective wisdom of the industry and the various regulatory authorities with regard to

the assurance of the quality of pharmaceutical products. These guidelines are intended to ensure the maintenance of high standards of quality in the development, manufacture and control of pharmaceutical products; to promote uniformity in licensing decisions; and to facilitate the removal of barriers to trade in pharmaceutical products (PIC GMP guide, 1989, p. 1). In some countries, such as the United States of America, these guidelines are intended to assist members of the industry to comply with the legal requirements in that regard. In other countries, such as South Africa and the United Kingdom, these guidelines do not enjoy legal force and are intended merely as a summary of generally-accepted principles rather than a set of inflexible rules. However, the South African Medicines Control Council (MCC) has adopted a policy whereby marketing authorisation (product registration or product licensing) is granted subject to the proviso that an acceptable standard of GMP be maintained at the place of manufacture of that particular product, thereby conferring a *quasi*-legal status upon local GMP guidelines.

Medicines control officers attached to the Directorate Medicines Control and Registration of the Department of Health audit the standard of GMP maintained by the South African pharmaceutical industry. These audits are based upon a locally developed GMP checklist.

When compiling this checklist, the Department of Health borrowed extensively from the British GMP guide, as well as from other overseas GMP guidelines, while at the same time introducing various innovations that were developed in consultation with the local pharmaceutical industry (Kotze, 1990). In view of South Arica's expected admission to the "Convention for the Mutual Recognition of Inspection in respect of the Manufacture of Pharmaceutical Products" (PIC), local GMP requirements may also be influenced by the provisions of the PIC GMP guide. The practical effect of PIC GMP requirements is however likely to relate mainly to administrative matters such as the requirement for "site master files" to be prepared in respect of individual companies (Kotze, 1993). A site master file is a document which is prepared by the manufacturer, in which specified GMP information relating to the production activities at a specific plant is summarised for use by regulatory auditors (PIC, 1991, pp. 1-7).

Important revisions of international GMP guidelines and new GMP guidelines which have been published in recent times include the British GMP guide (1983); the French GMP guide (1985); the European Economic Community (EEC) draft GMP guide (1989) which was implemented on 1 January 1992; the World Health

Organisation (WHO) draft GMP guide which was published for comment in 1990; and the GMP guide published by the Convention for the Mutual Recognition of Inspection in respect of the Manufacture of Pharmaceutical Products published in September 1989 (PIC GMP guide). Even more recently, a revised edition of the South African GMP guide was published in 1992 by the Pharmaceutical Manufacturers Association of South Africa and the Proprietary Association of South Africa to serve as a voluntary standard for the industry in this country. In view of the dynamic approach adopted by the South African regulatory authorities in this regard, it was considered appropriate for the purposes of this chapter of the dissertation to include extracts from all of these publications in a review of the principles on which South African GMP theory is based.

It must be stressed that this review is not aimed at providing a detailed summary of the technical aspects of GMP theory. It is intended instead to highlight those aspects of GMP theory that may either complement a total quality system, or which may be better achieved by a total quality system.

## 4.2 THE CONCEPTS OF QUALITY ASSURANCE, GOOD MANUFACTURING PRACTICE AND QUALITY CONTROL

Reference is made throughout most GMP texts to the terms quality assurance (QA), good manufacturing practice (GMP) and quality control (QC). A discussion of these concepts follows.

### 4.2.1 Quality assurance

This term is defined as follows in the British GMP guide (*ibid.*, p. 10):

> "(Quality assurance) ... is the sum total of the organised arrangements made with the object of ensuring that products will be of the quality required by their intended use. It is good manufacturing practice plus factors outside the scope of this guide (such as original product design and development)".

This definition is similar to that given in the EEC draft GMP guide (*loc. cit.*, p.15), and also to the following description of the objective of a quality assurance programme given in the technical literature by Lintner (1980, p. 1425):

> "The main purpose of a quality assurance programme is to implement systems and procedures that provide a high probability that each dose or package of a pharmaceutical product will have

homogenous characteristics and properties (within reasonably acceptable limits) to ensure both clinical safety and efficacy of the formulation".

According to the South African GMP guide (1992, pp. 1/1 - 1/2), the "requirements and objectives" of quality assurance are achieved when:

(i) "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".

(ii) "The production operations and Good Manufacturing Practices are clearly specified and adhered to".

(iii) "The production environment and services to the production operation are monitored".

(iv) "Deviations are adequately recorded, investigated and responded to".

(v) "The supply and use of adequate starting and packaging materials is assured".

(vi) "All the necessary controls on intermediate and final products and other in process controls, validations and, if necessary, trend analysis are carried out".

(vii) "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".

(viii) "Medicines are stored, handled and distributed so that quality is maintained".

(ix) "Laboratory operation and Good Laboratory Practices are clearly specified and adhered to".

(x) "The Quality Assurance system is regularly audited by self-inspection for effectiveness and applicability".

4.2.2 Good manufacturing practice

This term is defined as follows in the British GMP guide (*loc. cit.*, p. 10):

> "(Good manufacturing practice is) ... that part of quality assurance aimed at ensuring that products are consistently manufactured to a quality appropriate to their intended use. It is thus concerned with both manufacturing and quality control procedures".

The narrow focus of this definition of the GMP concept is also apparent from the following definition given in both the EEC draft GMP guide (*loc. cit.*, p. 17) and the WHO draft GMP guide (*loc. cit.*, pp. 12 - 13):

> "Good manufacturing practice is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use as required by the marketing authorisation".

According to the South African GMP guide (*loc cit.*, pp. 1/2 - 1/3), the "basic requirements and objectives" of good manufacturing practice are achieved when:

(i) "The production processes are clearly defined, systematically reviewed and validated to ensure that products are of the required quality".

(ii) "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; and suitable storage and transport".

(iii) "Critical processing steps, key equipment and services are validated".

(iv) "All production operations are conducted in such a way as to produce products of the required quality".

(v) "Instructions and procedures are written in an instructional from in clear and unambiguous language, specifically applicable to the facilities provided".

(vi) "Operators are trained to carry out procedures correctly".

(vii) "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".

(viii) "In-process and final controls for materials, processes, imtermediates and products are adequate to determine suitability".

(ix) "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".

(x) "The distribution (wholesaling) of the products minimises any risk to their quality".

(xi) "A system is available to recall any batch of product from sale or supply".

(xii) "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".

4.2.3. Quality control

This concept is defined as follows in the British GMP guide (*loc. cit.*, p. 10):

> "Quality control is that part of good manufacturing practice which is concerned with sampling, specification and testing, and with the organization, 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. (The term) "quality control" is sometimes used in the sense of the organisational entity which has responsibility for these functions".

Exactly the same wording is used to define this concept in the EEC draft GMP guide (*loc. cit.*, p. 18) and the WHO draft GMP guide (*loc. cit.*, pp. 14 - 15), except for the rider which is added in the latter guide to the effect that quality control is not

confined to laboratory operations only, but "... must be involved in all decisions which may concern the quality of the product". However, when describing the various functions of the quality control department, the WHO draft GMP guide (*ibid.*, pp. 15 - 18) refers only to inspection and test procedures.

According to the South African GMP guide (*loc cit.*, p. 1/3) the "basic requirements and objectives" of quality control are as follows:

(i) "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".

(ii) "Samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by personnel and by methods approved by Quality Control".

(iii) "Test methods are validated".

(iv) "Adequate standards and reagents are maintained".

(v) "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".

(vi) "The finished product complies with all legal requirements and is enclosed within its specified container and correctly labelled".

(vii) "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".

(viii) "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".

(ix) "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".

(x) "Follow-up stability trials in final packaging are conducted to assess the validity of the shelf-life".

From the above review of key concepts, the following deductions may be made regarding current GMP philosophy:

(i) Quality is defined in terms of the "fitness for use"-doctrine, with special reference to product safety and clinical efficacy, and not as a strategic business concept.

(ii) Quality is seen as being affected mainly at the production stage of the industrial cycle; although it is recognised that factors such as original design and development play a role too, these factors are specifically identified as falling outside the scope of GMP guidelines.

(iii) A quality assurance system is seen as consisting mainly of a plant-based series of interrelated technical activities, with no obvious managerial focus, and without reference to its role in coordinating the quality inputs of people, machines, and information.

(iv) Quality control is defined in terms of the traditional inspection and test concept.

(v) Quality control is seen as being the responsibility of the quality control function, rather than being a companywide and plantwide activity.

## 4.3 THE PURPOSE OF GMP GUIDELINES

Good manufacturing practice guidelines may be described as being a collection of quality-related standards and procedures that are used by the pharmaceutical industry to complement relevant technical specifications during the production phase of the industrial cycle, with a view to assuring the quality (and related parameters of safety and efficacy) of medicinal products. Insofar as this basic objective is concerned, there is a similarity between the more generally-applicable quality systems and guidelines provided by the SABS ISO 9000 guidelines (see SABS, 1987), and the GMP guidelines specifically developed for use in the pharmaceutical industry.

A review by Anisfeld (1990) of the GMP codes, regulations and guidelines currently in use in 23 countries around the world however reveals significant differences of opinion with regard to the stated purpose of these publications. For instance, Anisfeld (*ibid.*, p. IT2) notes that the Italian GMP guide describes GMP as being a system of standards that have to be complied with in order to produce drugs of the specified quality. According to Anisfeld (*ibid.*, p. IS2), the Israeli GMP guide on the other hand adopts a more cautious approach by referring to GMP as "complementing" the various control procedures applied

during production in order to "contribute" to the manufacture of quality products. The British GMP guide (*loc. cit.*, p. 6) states quite succinctly that "The objective of GMP and any guide to it is, initially, the assurance of the quality of the product, and ultimately the safety, well-being and protection of the patient". The purpose of the South African GMP guide (*loc. cit.*, p. x) is stated as being "... to set out (GMP) principles so that the quality, safety and therapeutic availability of medicines can be assured". Yet another perspective of the purpose of GMP guidelines is given by the French GMP guide (*loc. cit.*, p. 5):

> "... (GMP is intended to) specify the various means to be used in the manufacture and production of pharmaceuticals in order to ensure that marketed products are of the quality intended, and thus describe the objectives to be reached in matters of organisation, personnel, equipment, premises, as well as control requirements and procedures".

One common denominator may however be identified in the approach to GMP by countries worldwide, namely that GMP is considered to be the benchmark against which any pharmaceutical manufacturer's quality assurance system is to be measured. The WHO draft GMP guide (*loc. cit.*, p. xii) for instance describes the purpose of that guide to be:

(i) For use in the assessment of applications for manufacturing authorisation (see Chapter 3) in support of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce.

(ii) To serve as a basis for inspection of manufacturing facilities.

(iii) For use as training material for government drug inspectors (quality auditors).

Moreover, it would appear from the wording of the objectives quoted above that GMP guidelines may be considered by industry and regulatory authorities alike to be in essence the equivalent of a total quality system. This deduction is supported by the fact that there is a tendency, especially amongst regulatory authorities, to look towards a tightening of GMP regulations as being a solution to quality problems experienced within the pharmaceutical industry. An example of this particular approach is provided by Food and Drug Administration (FDA) personnel who investigated the recurrence of labelling-related product recalls in the United States of America over the past several years. These investigators generally found firms to have complied with current GMP requirements, and they then make the

following deduction (Anon, 1989b, p.3): "The inescapable conclusion is that maybe there is something in the regulations that needs to be fixed; that the (GMP) regulations are not addressing the right things or are missing out some of the important elements." This same report states that the FDA is considering proposals aimed at "strengthening" GMP requirements in four "important" areas related to the problem of labelling and packaging mix-ups; namely gang-printing of labels, electronic label verification, the use of cut labels (as opposed to labels on a continuous roll), and the handling of packed products which are not immediately labelled. The scope of GMP guidelines is generally characterised by a narrow, technically-oriented approach similar to that displayed in the above example. This aspect is discussed in the following section.

## 4.4 THE SCOPE OF GMP GUIDELINES

Good manufacturing practice is by definition concerned with the assurance of product quality during manufacture (see Section 4.2.2), and it therefore follows that the scope of GMP guidelines will be limited to factors which may affect product quality during this particular phase of the industrial cycle. Some authors place an even narrower focus on their GMP texts, while others appear to be moving towards a recognition of

the fact that quality is affected at all stages of the industrial cycle, and not only during the manufacturing phase.

According to Anisfeld (*loc. cit.*, p. AT2) the Australian GMP guide for instance adopts a restrictive (narrow) approach: It specifically draws attention to the fact that it is intended to emphasise in particular technical aspects relating to labelling and contamination problems which experience within the pharmaceutical industry has shown to be the more frequent source of product recalls, and that it is not aimed at addressing all the factors which may affect product quality. The British GMP guide (*loc. cit.*, pp. 5 - 6) encourages the reader to adopt a broader perspective by stating that a publication of that nature could not possibly cover every facet of good practice in the manufacture of medicinal products, and that a full understanding and evaluation of the "total quality of the total (product) batch" may only be embraced by a consideration of many other factors; that is by a system of "quality assurance" which by definition includes aspects such as original product design and development (see Section 4.2.1). The French GMP guide (*loc. cit.*, p. 11) states that a system of quality assurance should cover all phases of development, manufacture and distribution, and specifically identifies GMP as being that part of the quality

assurance system which is concerned with the manufacturing process alone. According to Anisfeld (*loc. cit.*, p. NE2), the Dutch GMP guide similarly describes GMP as being that part of an "integrated quality assurance system" which deals with aspects of production and quality control, while the other part of the system relates to the quality of design. These viewpoints serve to underline the fact that good manufacturing practice should be viewed as being merely a component part of the wider range of activities necessary to assure the quality of the final product.

Any disagreement which there may be concerning the scope of GMP guidelines or principles, is probably related to inconsistencies in distinguishing between the concepts of quality assurance, good manufacturing practice, and quality control. All the latest GMP guidelines reviewed during this research define the concept of quality assurance in terms similar to that used by Feigenbaum (1986, p. 14) to define a quality system. In other words, quality assurance is defined as being a wide-ranging concept which covers all matters which individually or collectively influence the quality of a product (see WHO draft GMP guide, *loc. cit.*, p. 10). These guidelines also define quality control as being a sub-component of GMP, which in turn is defined as being a sub-component of a quality assurance system (see Section 4.2).

The clear distinction which is thus made between the concepts of quality assurance, good manufacturing practice and quality control, is however not maintained throughout the texts of the GMP guidelines reviewed. This results in the interrelationship between these concepts being misunderstood, and may explain why GMP principles may be internationally perceived, by both regulatory authorities and the pharmaceutical industry, to be the equivalent of a total quality system despite the fact that most introductions to GMP guidelines specifically warn against such an interpretation (see Section 4.6.1). The technical literature also reflects similar sentiments regarding too broad an interpretation of the scope of GMP principles. Lachman, et al. (*loc. cit.*, p. 829) for example remind the reader that current good manufacturing practice is an aid, not a substitute, for what is referred to as a "total quality assurance programme".

Current good manufacturing practice theory is characterised by the emphasis it places upon the purely technical aspects of the production process, to the virtual exclusion of the role played by management skills. It is however now recognised even in the technical literature that good manufacturing practice is attained only when technical expertise is combined with the necessary management skills (see Begg, 1984, pp. 31 - 32).

A practical example of the consequences of a purely technical approach to the assurance of product quality is provided by Avallone (1990, pp. 228 - 230), who discusses a number of problem areas relating to the production of sterile products which were identified during regulatory inspections of pharmaceutical plants in the United States of America. He refers to problems related to the chemical aspects of parenteral process validation; biological and chemical aspects of the lyophilisation of a sterile product; several aspects relating to process-environmental monitoring; validation of cleaning procedures; and the manufacture and control of bulk sterile powders, and concludes that the underlying cause of the problems that had been encountered in these areas could in most cases be attributed to the lack of a quality commitment by top management.

## 4.5 THE STATUS OF GMP GUIDELINES

A fundamental determinant of the status accorded to GMP principles in a given country, appears to be the extent to which the relevant regulatory authority is willing to subscribe to the notion that GMP is the linchpin of quality assurance in the pharmaceutical industry. Anisfeld (*loc cit.*, p. iii) singles out one of the most notable trends observed in GMP

philosophy internationally over the past ten years, to be the belief that GMP principles have to be complemented by "efficient inspection and enforcement"; otherwise pharmaceutical "quality enhancement" will not occur.

This observed trend, to which Anisfeld refers, would seem to point to yet another determining factor of GMP status; namely that regulatory authorities in general are of the opinion that a voluntary set of GMP guidelines is not as effective as one that is legally enforced, or that company top management in the pharmaceutical industry have to be coerced into a commitment to quality. If this were so, it is possible that, from the point of view of the pharmaceutical industry, the control of quality within that industry may then be limited to the field of reference dictated by regulatory requirements only.

The British GMP guide (*loc. cit.*, p. 3) is described as being "... a work of guidance, produced in consultation (with the industry), rather than as a set of inflexible rules". The South African regulatory authorities also firmly subscribe to this particular philosophy. However, as a result of an incident during which a manufacturer questioned the authority of the regulatory inspectorate to conduct a GMP audit, the Medicines Control Council decided to make compliance with an acceptable standard of GMP (as evaluated by

the inspectorate at the place of manufacture), a pre-condition for the granting of marketing authorisation of all medicines (Schlebusch, 1990). The practical effect of this decision was to elevate the status of GMP principles in South Africa to that of a *quasi*-legal requirement.

According to Government Regulation no. 664 (France, 1985), the French view GMP principles as being "... an aid to the more accurate interpretation of general, legal and regulatory provisions regarding the manufacture of pharmaceutical products, and as a basis of dialogue between the industry and the regulatory body of control." This approach is similar to that of the Canadian GMP guidelines (Anisfeld, *loc. cit.*, pp. CN 1 - 15), which are presented as being an "interpretation" of the Food and Drug Regulations, and also to the approach adopted within the United States of America (Begg, 1992). The GMP principles published per regulation in the United States of America are however described as representing the minimum statutory requirements with which industry must comply (Anisfeld, *loc. cit.*, pp. US 1 - 13), and are therefore basically prescriptive in nature. Japanese GMP principles may similarly be described as being prescriptive, in that they are embodied in the so-called "Pharmaceutical Affairs Law Concerning GMP" (Anisfeld, *ibid.*, pp. JA 1 - 32).

It would therefore be correct to state that GMP principles/guidelines occupy a strategic position in governing the relationship between the pharmaceutical industry and the regulatory authorities in South Africa, and also internationally.

All internationally accepted systems of regulatory control are concerned with assuring that only licensed manufacturers (who comply with GMP principles) produce medicinal products. GMP principles are also used as a basis for the inspection (auditing) of licensed manufacturing facilities by regulatory auditors (EEC draft GMP guide, *loc. cit.*, p. 7, WHO draft GMP guide, *loc. cit.*, p. xii). GMP principles furthermore play an important role in bilateral international trade in pharmaceutical products. The first World Health Organisation (WHO) draft text on good manufacturing practice was accepted as an integral part of the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce in 1969 (WHO draft GMP guide, *ibid.*, p. ii). A Member State who wishes to use the WHO Certification Scheme in connection with the exportation of pharmaceutical products and substances, must ensure *inter alia* that all manufacturers of such products conform to GMP requirements consonant with those recommended by the WHO (1989, p. 110). South Africa is a signatory to the WHO Certification Scheme (see Anisfeld, *loc. cit.*, pp. iv - vii for a complete list of signatories).

## 4.6 THE PRINCIPLES ON WHICH SOUTH AFRICAN GMP THEORY IS BASED

The purpose of this section of the dissertation is to provide an overview of the GMP principles according to which the South African pharmaceutical industry is evaluated for regulatory purposes. The checklist used by regulatory auditors to evaluate GMP compliance in South Africa, is largely based on the British GMP guide (see section 4.1). Moreover, the South African GMP guide which was produced by the local industry to serve as a voluntary standard, is also principally based on the requirements of the British GMP guide, as will be shown in the paragraphs which follow.

Due to the dynamic nature of GMP principles in general, these principles are more correctly referred to as "current" good manufacturing practice principles. The South African regulatory control authorities have furthermore shown a propensity to adapt and improve domestic GMP principles in line with current international thinking in this regard. It was consequently decided to include references to other recently revised international guidelines, in addition to the British and South African GMP guidelines, in this review of the principles on which South African GMP theory is based.

The British GMP guide is based upon eight general principles that are considered important to the assurance of quality in the pharmaceutical industry. These principles are discussed in Sections 4.6.1 to 4.6.8 under the headings of quality management; personnel and training; documentation; premises and equipment; manufacture; recovered materials; complaints procedure and product recall; and good laboratory practice. Specialised topics such as the manufacture of sterile products, biological medicines or radiopharmaceuticals, and technical aspects relating specifically to the manufacture of powders, liquids, creams, ointments and medical gases, as well as safety and security aspects, will not be included in this review. The rationale behind this approach to the research is that this review is not aimed at providing a detailed summary of the technical aspects of GMP theory, but is aimed instead at highlighting in particular the limitations of GMP principles as a quality management tool.

In order to present a more complete review of international thinking on the subject, it was decided to include under Section 4.6.9 a number of additional principles which appear in some of the latest GMP publications, but which are not specifically highlighted in the British GMP guide.

The French GMP guide was included in this review not only because it is one of the most recently updated GMP texts, but because it impressed as being the most management-oriented publication amongst those reviewed; despite this fact, it however shares most of the other shortcomings of GMP guidelines in general.

### 4.6.1 The GMP principle regarding quality management

This principle is worded as follows in the South African GMP guide (*loc. cit.*, p. 1/1):

> "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. 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".

This definition recognises the need for some form of quality system which is aimed at assuring customer satisfaction in terms of the "fitness for use" doctrine, and that this system should be based upon the involvement of all the different functionaries at all stages of production. The principle regarding quality management, as defined in the British GMP guide (*loc. cit.*, p. 10) and the EEC draft GMP guide (loc. cit., p. 15), is couched in similar terms but the latter guide makes specific mention of the fact that the attainment of the quality objective is the responsibility of "senior" management, and that it requires the participation and commitment of staff at all levels and across all functional boundaries. Moreover, the EEC draft GMP guide also broadens the scope of this quality commitment and participation in quality activities by specifically including the company's suppliers and distributors in this collective effort.

Having thus identified the need for an integrated quality management system to give top management control over the quality activities of all functional groups at all levels within the company, the texts of all the GMP guidelines reviewed during this research are essentially concerned only with the technical aspects of the production stage of the industrial cycle. This is in fact the logical consequence of the

narrow, production-oriented, focus of GMP theory which by definition is concerned with quality-related aspects of production only (see Section 4.2.2). This particular limitation should be seen as being the primary reason for the caveat which is added to most GMP texts to the effect that GMP guidelines should not be interpreted as being the equivalent of a total quality system (see Section 4.4); although, in practice, this appears to be precisely how GMP principles are viewed in a number of countries (see Section 4.3).

### 4.6.2 The GMP principle regarding personnel and training

This principle is worded as follows in the British GMP guide (*loc. cit.*, p. 13):

> "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. Training should cover not only specific tasks but good manufacturing practice generally and the importance of personal hygiene."

In terms of the definition quoted above, the scope of personnel training is thus restricted to individual (technical) tasks, general GMP principles, and the maintenance of acceptable standards of personal hygiene. The important role played by people in the assurance of product quality is also stressed in the South African GMP guide (*loc. cit.*, p. 2/1), the EEC draft GMP guide (*loc. cit.*, p. 21), the French GMP guide (*loc. cit.*, p. 17), and the WHO draft GMP guide (*loc. cit.*, p. 32). However, all these texts specify a personnel training programme which is focused on GMP theory which, by definition, is only a component part of the quality assurance system (see Section 4.2.2.).

Specific aspects regarding personnel and training that are highlighted in the British GMP guide (*loc. cit.*, pp. 13 - 15) and the EEC draft GMP guide (*loc. cit.*, pp. 21 - 26) include the following:

(i) The establishment of an organisation chart and written job descriptions, in order to outline authorities and responsibilities with regard to the application of good manufacturing practice in particular.

(ii) Identification of "key personnel", namely the heads of production and quality control (who should be independent from one another). According to the EEC draft GMP guide (*ibid.*, p. 22), one of these functionaries may

also be a "Qualified Person" or, alternatively, a third person may be appointed to fulfil that role. The "Qualified Person" referred to here is a legal term which is used to describe a specially-trained person who assumes legal responsibility with regard to product quality and whose responsibilities, which are defined by statute, may be delegated only to another "Qualified Person" (see Article 22 of Directive 75/319 quoted in the EEC draft GMP guide, *ibid.*, p. 89). In South Africa, section 29 of the Pharmacy Act (South Africa, 1974) requires a pharmacist to fulfil this function.

(iii) Job descriptions for both the head of the production department and the quality control department. Table 4.1 depicts the job descriptions of the production and quality assurance managers, as described in the text of the South African GMP guide (*loc. cit.*, p. 2/2) and the British GMP guide (*loc. cit.*, p. 14).

From the information contained in Table 4.1 it will be noted that the quality control manager in particular is given responsibility for mainly technical functions, some systems responsibilities, and no strategic business responsibilities.

Table 4.1: Job descriptions of the production and quality assurance managers in terms of GMP theory.

PRODUCTION MANAGER:

Direct responsibilities:

+ Production areas, equipment, operations, and records
+ Management of production personnel.
+ Manufacture of products in accordance with the approved master formula and method.

Shared responsibilities:

+ Protection of products and materials against spoilage and deterioration.
+ Authorisation of written procedures.
+ Monitoring and control of the manufacturing environment.
+ Plant cleanliness.
+ Process validation.
+ Personnel training.
+ Vendor approval and third party contactor approval.
+ Retention of records.

QUALITY ASSURANCE MANAGER:

Direct responsibilities:

+ Establish, verify, and implement all quality assurance procedures.
+ Approve or reject starting; bulk; and finished materials.

(iv) The need for structured training and continuing education programmes for all personnel whose activities could affect product quality, and the recording and periodic evaluation of such programmes.

(v) Personnel hygiene, with particular reference to procedures relating to the health, hygiene practices, and clothing of personnel.

According to the EEC draft GMP guide (*loc. cit.*, p. 22), the duties of the "Qualified Person" can be summarised as follows:

(i) A "Qualified Person" must ensure that each batch of product manufactured within the EEC has been produced and tested or checked in accordance with the Directives relating to GMP and the marketing authorisation.

(ii) A "Qualified Person" must ensure that each batch of an imported product has undergone, in the importing country, a "full qualitative analysis, a quantitative analysis of at least all the active constituents, and all the other tests or checks necessary to ensure the quality of proprietary medicinal products in accordance with the requirements of the marketing authorisation" (paragraph 1(b) of Article 22 of Directive 75/319 quoted in the EEC draft GMP guide, *ibid.*, pp. 22 and 89).

With reference to the fact that the EEC draft GMP guide (*ibid.*, p. 22) states that the "Qualified Person" may also function either as production manager or quality control manager, it can be deduced that this person would not necessarily occupy a top management position but is more likely to function at middle-management level. Moreover, in terms of Article 25 of Directive 75/319 (EEC draft GMP guide, *ibid.*, p. 90), the regulatory agencies of Member States within the EEC assume responsibility for ensuring that the duties of the "Qualified Person" are in fact carried out "... either by means of appropriate administrative measures or by making such persons subject to a professional code of conduct".

From the above description of the functions of a "Qualified Person", it is clear that the elements of the quality activities and decisions involved are only vaguely defined, and that basic quality responsibilities rest in the hands of a functional component (under regulatory control), rather than with top management. This vertical functional structure, which is complicated by the arbitrary involvement of a government agency, can be expected to experience some difficulty in effectively and timeously resolving multifunctional quality problems in particular.

French legislation, on the other hand, demands the presence of a "Pharmacien Responsible" (Responsible Pharmacist) who must personally perform at least the following functions (French GMP guide, *loc. cit.*, pp. 15 - 19):

(i) He should participate in the setting up of the company programme for research and development.

(ii) He should sign the application for marketing authorisation after taking due note of the expert's reports.

(iii) He should organise and supervise in particular the manufacture, packaging, storage, physical control and supply, as well as the advertising of medicines.

(iv) He should exercise control over assistant pharmacists, who are in charge of the following departments: purchasing and control of raw materials, manufacturing operations, control of finished products, preparation of orders for delivery, and storage, sale and supply.

(v) He should alert the other directors of the company "to any difficulties inherent in the operating conditions which are likely to hinder the performance of his responsibilities", and he should refer any dispute regarding the application of GMP regulations within the company to the Regional Pharmacist Inspector of the French Department of Health.

The functions of the "Pharmacien Responsible" are thus more broadly-defined than those of the "Qualified Person" described above. In addition to his responsibilities and authorities with regard to the manufacturing function, he is also directly involved with other functional aspects such as research and development, purchasing, advertising and distribution. Moreover, the "Pharmacien Responsible" functions at top management (director) level, and has recourse to arbitration by a statutory authority in the event of a dispute with company management on matters pertaining to product quality.

The basic criticisms of the GMP-approach to quality management are however also applicable to the French system. Firstly, the technical (GMP) principles on which the quality management activities of the "Pharmacien Responsible" are based, cannot be equated to an operation systems network which provides for powerful managerial and engineering decision making, and which gives quality organisationwide impact.

Secondly, the approach to quality control which is adopted in the French GMP guide is again restricted to the traditional inspection and test approach.

With regard to the statutory requirements relating to the organisation and management of a South African pharmaceutical manufacturing concern, no reference is made to a functionary such as a "Qualified Person" or a "Responsible Pharmacist", nor does any GMP requirement apply in this regard either. Section 22 of the Pharmacy Act (South Africa, 1974) does, however, require a pharmacist who is also the managing director to manage the business of a company registered under that Act. The responsibilities of this pharmacist/managing director are not detailed other than by way of a broad statement regarding the fact that the managing director must in fact "manage the business" of his company. Moreover, Section 29 of the Pharmacy Act (*ibid.*) stipulates that a pharmacist must supervise the actual manufacture of a medicine, thereby establishing a managerial hierarchy of pharmacists which stretches from the production floor right up to the level of the managing director. There are sound reasons for this requirement, related mainly to ethical and disciplinary considerations, in view of the perceived need to protect the public interest in matters pertaining to a professional activity.

These statutory requirements are however based on the assumption that a person who received training in the natural sciences only, will have the managerial skills necessary to effectively delegate the quality respon-

sibilities which rest upon the managing director within the modern enterprise; the managerial hierarchy dictated by statute may consequently be distorted by the practical realities being faced by the pharmaceutical industry in this country. This appears to represent a major flaw in South African legislative and GMP requirements, and is seen as an area in which the adoption of a system of total quality will be able to make an important contribution.

### 4.6.3 The GMP principle regarding documentation

This principle is worded as follows in the South African GMP guide (*loc. cit.*, p. 8/1) and the British GMP guide (*loc. cit.*, p. 16):

> "Documentation is a prime necessity in quality assurance. 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."

An important feature of the above definition is the emphasis it places upon product and component traceability, from the point of incoming materials inspection through all the manufacturing and distribution processes and activities, right up to the final consumer. Product traceability is an important activity of what Feigenbaum (*loc. cit.*, pp. 737 - 805) terms the product control job of total quality control. Moreover, from the wording of the GMP principle regarding documentation which is quoted above, it is clear that documentation is viewed as being an important planning and control tool. The GMP principle regarding documentation is therefore an example of one facet of GMP theory which is entirely compatible with the total quality concept. However, it should be noted that the working documents required in terms of current GMP theory relate primarily to tactical decision making (i.e. the day-to-day control of quality), and not to strategic decision making. The total quality concept may therefore make a valuable contribution to the present system in this regard.

A summary of those aspects relating to documentation which are highlighted in GMP publications is presented in the paragraphs which follow. It will however be noted that these aspects are mainly of a technical nature.

4.6.3.1 General considerations relating to documentation

According to the British GMP guide (*loc. cit.*, pp. 16-17) and the South African GMP guide (*loc. cit.*, pp. 8/1 - 8/2), document layout should be orderly; revision systems should exclude the possibility of superseded documents being used; instructions should be written in the imperative, as numbered steps; entries made by persons should be confirmed by means of their signatures or initials; entries should be made in ink or other indelible medium; consideration should be given to the size, shape, paper quality and colour of the document; documents should not contain superfluous data; amendments should be formally authorised and signed. It is furthermore stated in the British GMP guide (*loc. cit.*, pp. 16 - 17) that "... it may be useful (sic) to prepare a manual which describes the overall quality assurance system, the procedures employed, and the documents used". The South African GMP guide (*loc. cit.*, p. 8/2 and the EEC draft GMP guide (*loc. cit.*, p. 33) state that documents should correspond to the relevant parts of the product registration dossier (see Section 3.6), thereby highlighting the importance of the registration dossier as a basic planning tool.

In terms of current GMP principles, data may be recorded by electronic data processing systems or by photographic or other reliable means, provided that access to data can be limited to authorised persons only, and provided furthermore that data remain readily available. In the experience of the author, master documents are usually photocopied to obtain batch manufacturing documents (i.e. working documents), while back-up copies of master documents are stored in more than one secure location.

4.6.3.2 Suggested format for specification documents

According to the EEC draft GMP guide (*ibid.*, p. 33), specification documents are defined as documents which describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform, and which serve as a basis for quality evaluation. A specific format for master specification documents is suggested by the South African GMP guide (*loc. cit.*, pp. 8/3 - 8/4) and the EEC draft GMP guide (*loc. cit.*, pp. 35-36) with reference to starting materials packaging materials, intermediate or bulk products, and finished products.

These documents should be approved by the "person responsible for quality control" (South African GMP guide (*loc. cit.*, p. 8/4).

Specifications for starting materials and packaging materials should be dated and include, if applicable, the following information:

(i) A description of the materials concerned. This would include references to the designated name and in-house code reference of the material; a description of the physical form of the material; reference to a pharmacopoeial monograph (if applicable); the name(s) of the approved supplier(s) and, if possible the name of the original producer of the material (with reference to active raw materials, these data should correspond to the information disclosed under Annexures 3B and 3C of the MBR 1 registration dossier described in Section 3.6); and, in the case of printed packaging components, a specimen of the item concerned.

(ii) Directions for sampling and testing, or reference to such procedures. This information should correspond to that disclosed under Annexure 5 (raw material control procedures); Annexure 6 (raw material release criteria); Annexure 8B (container control procedures); and Annexure 9B (final container control laboratory) of the MBR 1 dossier (see Section 3.6)

(iii) Qualitative and quantitative requirements, together with acceptance limits. This information should correspond to the data disclosed under Annexure 4 (raw material specifications), and Annexure 8A (final container specifications) of the MBR 1 dossier.

(iv) Storage conditions and safety precautions, where applicable. This information should correspond to that given under Annexure 3A of the product's MBR 1 dossier.

(v) The retest date, i.e. the maximum period of storage of the material before re-examination becomes mandatory. With regard to the drug substance or bulk drug substance, this information should correspond to that disclosed under Annexure 10 of the MBR 1 dossier.

Specifications for finished products should be dated and include:

(i) The designated name of the product and the in-house code of reference where applicable.

(ii) The formula, or a reference thereto. This information should correspond to the data disclosed under Annexure 2 (formulation) of the MBR 1 dossier (see Section 3.6.3).

(iii) A description of the pharmaceutical dosage form and package details. This information should correspond to that disclosed under Annexure 1 of the MBR 1 dossier with respect to data which appears on the product label and package insert (see Section 3.6.1).

(iv) Directions for sampling and testing, or reference to such procedures. This information should correspond to the data disclosed under Annexures 7B (final product control procedures) and 9A (final product control) of the product's MBR 1 dossier (see Sections 3.6.11 and 3.6.14 respectively).

(v) The qualitative and quantitative requirements, and acceptance limits, to be used as release criteria for the final product. This information should correspond to the data disclosed under Annexure 7A (final product specifications) and Annexure 9A (final product release criteria) of the MBR 1 dossier (see Sections 3.6.10 and 3.6.14 respectively).

(vi) Storage conditions and safety precautions, where applicable. These data will have been determined experimentally in the course of generating the product stability data detailed under Annexure 10 of the product's MBR 1 dossier (see Section 3.6.16).

(vii) The shelf-life of the stored product. The shelf-life of the final product is based upon the extrapolated stability data detailed under Annexure 10 of the MBR 1 dossier.

4.6.3.3 Manufacturing and packaging instructions

These are defined as documents which detail all the starting materials to be used, and lay down all processing and packaging operations (EEC draft GMP guide, *ibid.*, p. 33). These documents are usually issued by the production planning department, and signal the formal commencement of the production process. A suggested format for these documents follows, based on that given in the South African GMP guide (*loc. cit.*, pp. 8/5 - 8/6), the British GMP guide (*loc. cit.*, pp. 19-21 and the EEC draft GMP guide (*loc. cit.*, pp. 36-38).

A formally authorised manufacturing formula and processing instructions should exist for each product and batch size; these are often combined into one document known as the master manufacturing formula instructions (this document is also referred to as the "master formula and method"). Formal authorisation of this document would typically require the signatures of the managing director, quality control manager, and production manager.

The manufacturing instructions should be dated and include the following details:

(i) The name of the product, together with a unique in-house product reference code relating to its specifications.

(ii) A description of the dosage form and potency of the product, and a reference to the standard batch size.

(iii) A list of all the starting materials to be used, with the amount of each, as per Annexure 2 of the MBR 1 dossier (see Section 3.6.3). Each material should be described by the use of the designated name and a in-house reference code which is unique to that material.

(iv) A statement regarding the expected intermediate and/or final yields, together with the acceptable limits.

Processing instructions should include:

(i) A statement regarding the processing location and the principal equipment to be used.

(ii) The methods, or reference methods, to be used for preparing these items of equipment (i.e. cleaning, assembling or calibrating such equipment).

(iii) Detailed stepwise processing instructions, as detailed under Annexure 11 of the product's MBR 1 dossier (see Section 3.6.17), including details of in-process controls and their limits of acceptance.

(iv) Where necessary, the requirements for bulk storage of the product, including the identity and labelling of the storage vessel, and special conditions for storage.

(v) Special precautions (if any) to be observed during this stage of production.

The South African GMP guide (*loc. cit.*, p. 8/6), the British GMP guide (*loc. cit.*, p. 21), as well as the EEC draft GMP guide (*loc. cit.*, pp. 37-38) require that formally authorised packaging instructions should be drafted for each product, pack size and dosage form. These instructions, which are referred to as "master packaging instructions", should include or refer to the following aspects:

(i) The name of the product.

(ii) A description of the dosage form and potency, where applicable (e.g. tablets, each containing 500mg of active raw material).

(iii) The pack size expressed in terms of the number, weight, or volume of product in the final container.

(iv) A complete list of all the packaging materials required for a standard batch size (i.e. a bill of materials or picking list), including details relating to quantities, sizes and types, with the in-house reference code relating to the specifications of each packaging material.

(v) Where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where data relating to the product lot number and expiry date are to be applied during the packaging process.

(vi) The line opening procedure to be carried out and verified in writing by the pharmacist in charge. This procedure should include verification that the line is clean, is free of any foreign packaging materials and product residues, and that the correct packaging components and bulk product have been staged for the packaging operation to commence.

(vii) A description of the packaging operation and the equipment to be used, including special precautions to be observed and any significant subsidiary operation (e.g. temperature and/or humidity control, agitation of the bulk product, etc).

(viii) Details of in-process controls, together with sampling instructions and acceptance limits.

4.6.3.4 Standard operating procedures

According to the South African GMP guide (*loc. cit.*, p. xvi), a standard operating procedure (SOP) is 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 EEC draft GMP guide (*loc. cit.*, pp. 40-42) requires that "written procedures" be available with reference to the receival of incoming materials; sampling and testing materials and products at different stages of manufacture; quarantine procedures, including the disposal of accepted or rejected materials; batch distribution records of finished products; process validation procedures; equipment assembly and calibration; maintenance, cleaning and sanitazation of the manufacturing facility; personnel matters, including training, dress requirements and personal hygiene; environmental monitoring; pest control; a product complaints procedure; a product recall procedure; and a procedure for handling products returned to the plant. In addition, the EEC draft GMP guide (*ibid.*, p. 42) requires that written operating instructions be available i.r.o. major items of manufacturing and test equipment; that the validation (qualification), calibration and maintenance of such items of equipment be recorded in log books; and that the use of major or critical equipment (and the production areas where products have been processed) be recorded.

The South African GMP guide (*loc. cit.*, p. 1/5) identifies the following as being "critical procedures":

(i) Self-inspection (audits).

(ii) Recall of medicines from the market.

(iii) Handling of technical complaints.

(iv) Handling of returned goods.

(v) Vendor inspection/approval of printed packaging materials.

(vi) Purchasing procedures.

(vii) Procedure for handling and disposal of dangerous, highly toxic or sensitising materials.

(viii) Rodent and pest control.

Caplan (1980, pp. 8-9) views the process of communicating a quality policy to all functionaries within the organisation as consisting of an interlinked chain of documents at four levels, the third and fourth levels consisting of procedures and instructions respectively. In view of the limited scope of the "critical procedures" identified in the South African GMP guide (*supra*) it may be concluded that these procedures are intended primarily as working documents rather than vehicles for the communication of quality policy.

4.6.3.5 Records

Records are defined in the South Arican GMP guide (*loc cit.*, p. xv) and the EEC draft GMP guide (*loc. cit.*, p. 33) as documents which provide a history of each batch of product, including its distribution, and also of all other relevant circumstances pertinent to the quality of the final product. A suggested format for documents relating to starting materials; packaging materials; batch manufacturing records; batch packaging records; intermediate, bulk and finished product records; distribution records; analytical records and complaints records is given in the South African GMP guide (*loc. cit.*, pp. 8/6 - 8/13).

The South African GMP guide (*ibid.*, p. 8/12) recommends that batch manufacturing and packaging records, as well as the relevant test records, be retained for at least one year after the expiry date of the batch; and that finished product samples be retained for at least one year after the expiry date of the product concerned. Moreover, it is suggested that records of starting materials should be retained until at least the expiry date of the product batch in which they are used.

4.6.4 The GMP principle regarding premises and equipment

This principle is worded as follows in the British GMP guide (*loc cit.*, p. 28):

> "Buildings should be located, designed, constructed, adapted and maintained to suit the operations carried out in them. Equipment should be designed, constructed, adapted, located and maintained to suit the processes and products for which it is used. Building construction, and equipment layout, should ensure protection of the product from contamination, permit efficient cleaning and avoid the accumulation of dust and dirt."

Aspects that are addressed in the text of this particular chapter of the British GMP guide (*ibid.*, pp. 28 - 32), the South African GMP guide (*loc. cit.*, pp. 3/1 - 3/5), and the EEC draft GMP guide (*loc. cit.*, pp. 27 - 32) include the following:

(i) Premises should be constructed, situated, equipped and maintained in such a manner as to limit the risk of contamination to materials or products, provide a suitable environment for the manufacture and storage of medicinal products, and control unauthorised access. The British GMP guide makes special mention of the construction requirements for floors, pipework, service points, drains, lighting and ventilation.

(ii) The production area in particular should be designed with a view to the prevention of cross-contamination by highly sensitizing materials (such as penicillins or micro-organisms, for instance). The British GMP guide (*loc. cit.*, pp. 89 - 90) includes an appendix which deals specifically with the control of cross-contamination.

(iii) The layout of the production area should correspond to the logical sequence of operations, with adequate provision for in-process storage space and the logical positioning of equipment and materials "... to avoid cross-contamination and to minimise the risk of omission or wrong application of any of the manufacturing or control steps" (EEC draft GMP guide, loc. cit., p. 28). The British GMP guide (*loc. cit., p. 30*) furthermore recommends that manufacturing areas should not be used as a general right of way for personnel or materials.

(iv) Packaging areas should be specifically designed so as to avoid mix-ups and cross-contamination.

(v) Weighing of starting materials should preferably be carried out in a separate weighing room designed for that purpose, with particular emphasis on dust extraction.

(vi) Storage areas should have sufficient capacity, provide optimal conditions of storage, and should also provide adequate protection from the weather at receiving and despatch bays.

(vii) Storage areas should include segregated quarantine areas (with access restricted to authorised personnel only); a separate sampling area for starting materials; segregated areas for the storage of rejected, recalled or returned materials or products; and separate and secure areas for the storage of highly active materials (such as hormones, narcotics and flammable substances for instance).

(viii) Quality control laboratories should be separate from production areas (to avoid cross-contamination), and should themselves have sufficient space to avoid mix-ups and cross-contamination; including the provision of separate rooms for the protection of instruments that are sensitive to vibration, electrical interference, humidity, etc. Separate facilities should be provided for the handling of biological and radioactive samples.

(ix) Ancillary areas such as rest- and refreshment rooms should be separate from other areas; toilets should not directly communicate with production and storage areas; maintenance workshops should as far as possible

be separated from production areas; and animal houses should be well isolated from other areas, with separate entrances and air handling systems.

(x) Manufacturing equipment should be designed, located and maintained to suit its intended purpose; should be easily cleaned; should not present a hazard to the product in process; and should be calibrated and checked at defined intervals where appropriate.

(xi) Waste material should not be allowed to accumulate, and special care is necessary for the disposal of highly toxic or highly active materials. Disposal of rejected raw materials, printed packaging materials and finished products should be carefully controlled and documented (e.g. by means of certified disposal).

All the above requirements may therefore be stated to be of a technical nature.

4.6.5 The GMP principle regarding manufacture

This principle is worded as follows in the British GMP guide (*loc cit.*, p. 33):

> "Manufacture should follow previously defined procedures which are known to be capable of

yielding finished products which are those intended and which conform to their specifications. Special attention must be paid to labels and labelling throughout the entire production cycle."

The South African GMP guide (*loc. cit.*, pp. 5/1 - 5/4) lists the production of products of the requisite quality as well as compliance with the relevant "manufacturing documents" and legal requirements as being the objective of pharmaceutical manufacturing operations. Specific guidelines are given regarding the dispensing of starting materials, technical aspects of manufacturing operations and in-process controls, as well as the prevention of contamination and cross-contamination of raw materials and product. Guidelines regarding the technical aspects of re-processing are also given in this section of the South African GMP guide, whereas the British GMP guide treats this as a separate GMP principle (see section 4.6.4).

The South African GMP guide (*ibid.*, pp. 4/1 - 4/3, pp. 6/1 - 6/4, and pp. 9/1 - 9/2) on the other hand identifies "materials management", "packaging" (operations), and (product/process/analytical method)

"validation" as being separate GMP principles, whereas the British GMP guide (*loc. cit.*, pp. 33-39 and pp. 44-48) discusses these aspects under the GMP principles of "manufacture" and "good control laboratory practice" (the latter aspect is discussed under section 4.6.8).

The following, mainly technical, aspects regarding manufacture are highlighted in the British GMP guide (*ibid.*, pp. 33 - 39) and the EEC draft GMP guide (*loc. cit.*, pp. 43 - 52):

(i) General concepts relating to the manufacture of the product in accordance with the "master formula and method" and/or the "master packaging instruction" (see Section 4.6.3.3), supplemented where necessary by standard operating procedures (see Section 4.6.3.4), and the recording of data on the batch manufacturing record (see Section 4.6.3.5), including supervision by competent personnel; handling of materials in accordance with written instructions; incoming material receipt and quarantine; reconciliation of quantities and checks on yields; segregation of operations on different products; identification of all materials, bulk containers, major items of equipment and rooms or cubicles used; identification of pipelines used for the transportation of products or materials; approval of deviations from procedures by a competent person; and restricted access to production areas.

(ii) The prevention of cross-contamination during production, with specific reference to production in segregated areas, or by campaign (i.e. separation in time), followed by appropriate cleaning; provision of appropriate air locks and air extraction; minimising the risk of contamination caused by the recirculation or re-entry of untreated air; use of protective clothing; the use of validated decontamination procedures; the use of "closed" production systems (i.e. isolated from the production environment); and testing for residues on equipment. These aspects are addressed in greater detail in an appendix to the British GMP guide (*loc cit.*, pp 89 - 90), which deals specifically with the subject of cross-contamination during production.

(iii) Procedures relating to validation studies. The suitability for routine processing of a new formula or method of preparation should be demonstrated with reference to its ability to consistently yield a product of the required quality; similarly, any significant amendments to the manufacturing process (such as a change in equipment or materials for instance) which may affect product quality and/or the reproducibility of the process, should be validated. The South African GMP guide (*loc. cit.*, pp. 9/1 - 9/2) refers to "validation" as a separate GMP principle which is aimed at achieving process

"efficacy" and reliability, a reduced number of rejects, a reduced risk of product recall, and a reduction in the "extent" (*sic*) of the quality control programme. The South African Medicines Control Council (MCC) requires the first two production batches to be validated by means of all the analytical control procedures described in Annexure 7A of the product's MBR 1 registration dossier (see Section 3.6.10), whereas subsequent production batches need to be subjected only to the batch release criteria described in Annexure 9A of the registration dossier (see Section 3.6.14). The WHO draft GMP guide (*loc. cit.*, pp. 10 & 19) identifies process and procedure validation as being one of the essential elements of what it terms "quality management in the drug industry". The MCC (1983, Circular to applicants ref. 14/83) has formally declared process and system validation to be "an essential component of quality assurance". According to the EEC draft GMP guide (*loc. cit.*, pp. 23 - 24), it is the responsibility of the quality control manager to ensure that the proper validation studies are done, while process validation (and presumably machine qualification too) is stated to be the shared responsibility of the quality control and production managers (see Table 4.1).

(iv) Procedures relating to starting materials. Only approved vendors may be used (as would be specified under Annexure 3B of the product's MBR 1 dossier); the

vendor contact programme should involve discussion of the specifications stipulated, aspects relating to the production and control of starting materials, including handling, labelling and packaging requirements, as well as the complaints and rejection procedures to be followed. Procedures should exist for the receipt, sampling, quarantining and dispensing of starting materials; each delivery or batch of material should be assigned a reference number which will identify that specific delivery (or batch) throughout storage and processing.

(v) Processing operations for intermediate and bulk products. The processing area and equipment must be clean and free from any starting materials, products, product residues, or documents not required for the current operation before any processing operation is started; conditions for storage, in-process controls and yield reconciliation should receive special attention.

(vi) Packaging materials. The method of purchasing, handling and control of packaging materials shall be identical to that employed for all starting materials; particular attention should be given to the identification and control of printed packaging materials in order to guard against mix-ups and the unauthorised use of such materials.

(vii) Packaging operations. Steps must be taken to minimise the risk of cross-contamination, mix-ups or substitution. These steps include the physical segregation of packaging lines; line opening procedures; in-process controls relating to physical specifications, proof reading of overprinting, and checks on the correct functioning of line monitors; disposal of rejected/ unused materials; and the reconciliation of materials.

(viii) Finished product disposal. Quarantine procedure and storage after release are the main considerations in this regard.

4.6.6 The GMP principle regarding recovered materials

This principle is worded as follows in the British GMP guide (*loc. cit.*, p. 40):

> "Material may be reworked or recovered by an appropriate and authorised method, provided that the material is suitable for such reprocessing, and that the resultant product meets its specification and there are no significant changes in product quality. Documentation should accurately record the reworking process carried out".

This principle is not accorded a separate chapter in the EEC draft GMP guide, but is instead included under the text dealing with manufacturing operations.

The following aspects are highlighted in this section of the EEC draft GMP guide (*loc. cit.*, pp. 51 - 52) and the British GMP guide (*loc. cit.*, pp. 40 - 41):

(i) Disposal of product residues. Product residues and reworked or recovered materials should not affect the quality of subsequent batches of product; their inclusion should be specifically authorised and documented according to the limits set by the quality control department; batches of final product containing such residues should not be released until the batches from which the residues originated have been released. All recovered materials should be clearly identified and stored separately in restricted areas.

(ii) Reprocessing. Reprocessing of rejected products is permitted only if the quality of the final product is not affected, if the final product specifications are met, and if it is done according to a defined and authorised procedure which includes record-keeping; additional testing of the final product is also recommended.

(iii) Returned goods. Refurbishing of final product labels/ cartons which are returned due to being soiled or damaged, may be carried out according to a specifically authorised and documented procedure aimed at

maintaining product quality and the avoidance of mix-ups or mislabelling; such products must first be assessed by the quality control department, who must make the final decision in this regard.

The South African GMP guide (*loc. cit.*, p. 10/1) treats the subject of returned goods as a separate GMP principle which is worded as follows: "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".

4.6.7 The GMP principle regarding complaints procedure and product recall

This principle is worded as follows in both the British GMP guide (*loc. cit.*, p. 42) and the South African GMP guide (*loc. cit.*, p. 11/1):

> "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. A complaint, or otherwise reported product defect 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 predetermined plan. The procedures to be followed should be specified in writing and made known to all who may be concerned."

In the South African context, certain statutory requirements determine the procedure to be followed with regard to product complaints and recalls. Insofar as product complaints are concerned, regulation 12(4) of the Medicines Control Act (South Africa, 1965) places a legal obligation upon a manufacturer to inform the Medicines Control Council (MCC) immediately of any formulation, labelling, or other error relating to its products, and also to inform the MCC of the steps taken, or which are intended to be taken, in order to rectify such error or with regard to the suspension of the sale of such a medicine. Regulations 12(3)(b) and (c) of the Medicines Control Act (ibid.) require the same actions to be taken with regard to any adverse drug reactions experienced with any of a company's products. A written and authorised procedure must be followed when dealing with these matters; this procedure must be coordinated by a designated functionary, and the action taken must be recorded and the record filed.

Insofar as product recall procedure is concerned, the MCC has issued a general circular (MCC, 1988, Circular to applicants ref. 7/88) in which the following procedure is prescribed for the removal from the market of any product representing a health hazard to the consumer or user:

(i) Immediately upon becoming aware of the problem, a designated functionary of the manufacturer must notify the Registrar of Medicines (see Section 3.4) and must disclose the following information: The name, strength, pack size and batch number of the product; details concerning the quantities, dates, and areas of distribution; the nature of the defect; suggested action to be taken and its urgency, and a fully motivated indication of the health risk involved.

(ii) The Registrar of Medicines will, after consultation with the MCC, make a health hazard evaluation based *inter alia* upon certain prescribed factors.

The affected manufacturer is accorded every opportunity to contribute to the information upon which this evaluation is based. As a result of this evaluation, either a Class "A", Class "B", or Class "C" recall-classification is assigned by the MCC.

A Class "A" recall will be required in a situation where there is a reasonable probability that the use of or exposure to the defective product will cause serious adverse health reactions or death. A Class "B" recall is indicated in a situation where the use of or exposure to the defective product may cause temporary adverse health reactions or where the probability of serious adverse health reaction is remote. A Class "C" recall will be conducted in a case where the use of or exposure to the defective product is not likely to cause any adverse health reactions. The ease of identifying the product concerned, the extent to which the product's deficiency is obvious to the consumer or user, and the risk/benefit ratio of the product, will be taken into account when deciding on the recall classification to be applied to a particular situation.

(iii) The recall strategy will determine the level in the distribution chain to which the recall must be extended, as well as the communications medium and content of a recall notice.

(iv) The MCC must be furnished with a report within 30 days of the recall having been instituted, in which certain specified information is to be given. This report must include a description of the steps taken by the manufacturer concerned to prevent a recurrence of the problem.

(v) Within 90 days of the recall having been instituted, a full reconciliation of recalled product (with reference to the relevant distribution records) must be submitted to the MCC.

(vi) A recall is terminated when the MCC and the manufacturer concerned are in agreement that the defective product has been removed from the marketplace, and proper disposition or correction has been made. A firm's recall action does not preclude enforcement actions being taken by the MCC, as may be deemed appropriate, either during or following the completion of a recall.

In order to minimise the disruptive effect on a firm's business operations, pharmaceutical manufacturers are advised to establish a detailed written recall system or plan; to ensure batch-to-batch identification of products; and to facilitate location of products through the maintenance of comprehensive distribution records. These aspects form part of the pharmaceutical manufacturing facility audit checklist used by regulatory auditors when evaluating a firm's ability to effectively deal with any product complaint or product recall, should the need arise (South African GMP guide, *loc. cit.*, Appendix 1).

With reference to product complaints and product recall procedure, the texts of the British GMP guide (*loc. cit.*, pp. 42 - 43), the EEC draft GMP guide (*loc. cit.*, pp. 63 - 65), and the WHO draft GMP guide (*loc. cit.*, pp. 22 - 23) correspond in essence to the guidelines given in this regard by the MCC in South Africa and the South African GMP guide (*loc. cit.*, pp. 11/1 - 11/2). In particular, the need for an authorised, written recall procedure which is coordinated by a designated functionary and which is capable of being put into operation at any time, is also emphasised in those texts, together with the need to be able to give progress reports on a particular recall, and to effectively quarantine any recalled products.

From the above review, the basic requirement may be restated as being that of an in-house mechanism which will enable a manufacturer of medicinal products to systematically and timeously deal with product quality problems. This mechanism will include activities aimed at identifying the nature and source of a quality defect, the improvement of product quality characteristics, and steps to ensure that such improvements are of a permanent nature.

This mechanism therefore closely resembles that part of a total quality control programme to which Feigenbaum (*loc. cit.*, pp. 806 - 821) refers as "special process studies".

4.6.8 The GMP principle regarding control laboratories

This principle is worded as follows in the British GMP guide (*loc. cit.*, p. 44):

> "It is essential that control laboratories should have appropriate facilities, with properly trained, managed and motivated staff, in order that reliable results may be obtained from any analytical or other test procedure, whether its nature is chemical, physical, biological or microbiological. Steps should be taken to ensure the reliability of the laboratory's own systems and test methods."

The following aspects relating to control laboratories are highlighted in this chapter of the British GMP guide (*ibid.*, pp. 44 - 48):

(i) The design and maintenance of premises, with specific reference to the prevention of cross-contamination, and the disposal of waste materials.

(ii) Aspects relating to servicing and calibration of laboratory equipment, operating instructions, warning systems to indicate failure of equipment or services to equipment (gas or electricity for instance), and qualification of equipment.

(iii) Aspects relating to basic hygiene; including the need for written cleaning schedules, the use of protective clothing , and the safe disposal of waste materials.

(iv) Aspects relating to expiry dating of reagents; preparation of reagents according to written procedures; validation of reagents; tests for suitability of microbiological culture media; as well as the storage; handling; and use of reference standards.

(v) Aspects relating to sampling procedure (see Section 4.6.3.2); labelling of sampling containers; handling of sampling equipment; and precautions to prevent contamination and cross-contamination of the materials sampled.

(vi) Documentation, which should be in line with the general guidance given (see Section 4.6.3), and the keeping of retention samples as part of laboratory records.

(vii) Aspects relating to records of analysis. Details are to be recorded of the receipt and testing of starting materials; packaging materials; and intermediate, bulk, and finished products; analysts' laboratory records are to be retained together with basic data such as weighings, readings, recorder charts and calculations.

(viii) Specifications approved by the quality control department should be established for all starting materials; packaging materials; and bulk, intermediate and finished products (see Section 4.6.3.2).

(ix) Laboratory management is responsible for the validation of all test methods; test methods used must be in accordance with those prescribed by the relevant specification; in-house controls to be carried out by production personnel must be approved by the quality control manager.

(x) Aspects relating to contract analysis. This refers to laboratory work which is contracted out to third parties, and relates in particular to the following requirements: clearly-defined contractual agreements are necessary; the responsibility of the quality control department cannot be delegated to a third party; it should be confirmed that the test methods used by the contract analyst are correct; and arrangements should be made for the retention of samples and records of test results.

The aspects referred to above are addressed under the chapter dealing with quality control principles in the EEC draft GMP guide (*loc. cit.*, pp. 53 - 57) as well as the WHO draft GMP guide (*loc. cit.*, pp. 14 - 18, pp, 45 - 46, and p. 85). This section of both the abovementioned guides is reviewed under Section 4.6.9.2 of this dissertation.

4.6.9 Additional GMP principles

The following principles are not specifically defined in the British GMP guide, but do appear in other recently published GMP guidelines.

4.6.9.1 Self-inspection, audits and quality evaluation audits

The GMP principle relating to self-inspection is worded as follows in the EEC draft GMP guide (*loc. cit.*, p. 67):

> "Self-inspection should be conducted in order to monitor the implementation and the respect (*sic*) of good manufacturing practice principles and to propose necessary corrective measures".

It should be noted that this guide does not specifically state wether the self-audit is product; procedure; or systems oriented, other than its focus on personnel matters, premises, equipment, documentation, technical aspects of production and quality control, distribution of final products, and

the arrangements for dealing with product complaints and recalls in order to verify their conformity with the principles of quality assurance. It would appear from the wording of this objective, and that of the general principle regarding self-inspection (*supra*), that the terms "good manufacturing practice" and "quality assurance" are again considered to be synonymous.

The South African GMP guide (*loc. cit.*, pp. 1/4 - 1/5) refers to the subject of self-inspection under the heading of quality (management), and refers to the need for regular audits on all "systems, procedures and operations" in order to monitor compliance with and the effectiveness of "good manufacturing practice and quality assurance" principles and to allow for improvement and corrective measures where required. It states that audits should be conducted by "competent and impartial persons from the company", and possibly external auditors as well. Audit reports should be made, corrective measures agreed upon should be recorded and followed up; no guidelines regarding the relevant authorities and responsibilities are however given. Audits should follow a pre-arranged programme and include inspection of the following:

(i) Organizational matters and responsibilities.

(ii) Qualifications and training programmes.

(iii) Compliance with hygiene requirements and access control (to production areas).

(iv) Cleaning and disinfection programmes.

(v) Medical checks on personnel.

(vi) Production facilities, premises and equipment.

(vii) Production operations, procedures and documentation.

(viii) Storage, handling, distribution and materials management.

(ix) Quality assurance aspects such as complaints, returned goods and "validation".

(x) Suppliers of starting materials and packaging material.

(xi) Third party contractors (including distributors of finished products).

The South African GMP guide (*ibid.*, pp. 1/4 - 1/5) furthermore refers to the need for "quality evaluation audits" which relate to a review of production records (see section 4.6.3.5) in order to "determine the need for changes in product specifications or manufacturing and control procedures".

Quality evaluation audits should include: (i) A review of every batch manufacturing record irrespective of wether the batch was approved or rejected; and (ii) A review of complaints, recalls, returned or salvaged products, and investigations conducted during normal product record reviews before a batch is released. Again, no guidelines are given regarding the relevant authorities, responsibilities and follow-up procedure in this regard.

The WHO draft GMP guide (*loc. cit.*, pp. 28 - 31) distinguishes between what it terms self-inspection and the quality audit. The purpose of self-inspection is stated to be the detection of any shortcomings regarding the implementation of GMP, and to recommend the necessary corrective action. A quality audit, on the other hand, is seen as being more broadly aimed at an assessment of "... all or part of a quality system", with the specific purpose of improving it, and it is thus seen as a useful supplement to self-inspection activities. It is furthermore recommended that such audits be extended to include suppliers and third party contractors. A "partial" self-inspection should be performed routinely and also under special circumstances such as after a product recall or repeated quality problems, or "when an inspection by the (regulatory inspectorate) is announced" (*sic*).

A "complete" self-inspection should be conducted at least once a year. No other guidelines are given regarding the timing of quality audits, except to state that vendor audits should be conducted before a supplier is included in specifications. Self- inspections should be conducted by a team of "experts" from inside or outside the company, whereas a quality audit is described as being a procedure which is usually conducted by "independent specialists" designated by management.

The French GMP guide (*loc. cit.*, pp. 12 - 13) is more consistent in its use of terminology and also more explicit in describing the managerial authorities and responsibilities involved in what it terms the "self-inspection and quality audit". The purpose of the self-inspection and quality audit is stated as being the assessment "... of the quality assurance system and to ensure the application of good pharmaceutical manufacturing practices ... ". The nature of the self-audit is described as being "... a periodic, detailed examination of the conditions and working procedures by a team from the production plant... (and)... an examination and assessment of all or part of the system of quality assurance". Both the functionaries involved as well as their relationship within the managerial hierarchy are described in more detail than in the EEC draft GMP guide.

It is stated that the self-audit is to be carried out by a team from the production plant or by specialist(s) designated for that purpose. A detailed report of the observations made and the corrective measures proposed must be submitted to the "Pharmacien Responsible" (see Section 4.6.2), as well as the head of the production department. Moreover, these self-audits are to be conducted over and above inspections by the French regulatory authorities (i.e. external audits performed by the regulatory inspectorate).

4.6.9.2 Functional aspects of quality control

The concept of quality control is defined in the South African GMP guide, the EEC draft GMP guide and the WHO draft GMP guide in terms similar to those used in the British GMP guide (see Section 4.2.3 of this dissertation); however, these guides devote a separate section to this particular subject. Aspects regarding the independence of the quality control department *vis a vis* other functional groups within the organisational structure and requirements relating to documentation, sampling and analytical records are identical to those referred to in the British GMP guide.

The WHO draft GMP guide (*loc. cit.*, pp. 45 - 46, pp. 14 - 18, and pp. 85 - 91) briefly refers to the physical requirements of what it terms the "quality control area", the duties of the quality control department, and the sampling and testing procedures for the various materials handled, including stability studies. In general, the provisions of the South African GMP guidelines the WHO draft GMP guidelines, and the EEC draft GMP guidelines correspond very closely to one another and differ from those of the British GMP guide mainly with regard to the emphasis placed upon the viewpoint that quality control activities are not confined to laboratory operations only. However, both the EEC and WHO draft GMP guidelines do not adequately define those functions of the quality control department that lie outside the field of inspection and testing. For instance, no mention is made of the business and systems responsibilities of the quality control function. The South African GMP guide (*loc. cit.*, p. 7/1) does, however, state that the functions of the quality control department includes "the review of all plant systems and procedures, audits, organization and documentation" as well as the "validation" of critical equipment and procedures, the approval of all deviations and reworks and the approval of third party contractors and vendors. Apart from the latter aspect, the functions of the quality control department set out in the South African GMP guide are therefore largely plant-based.

4.6.9.3 Contract manufacture and analysis

This principle is worded as follows in the EEC draft GMP guide (*loc. cit.*, p. 59):

> "Contract manufacture and analysis must be correctly defined, agreed and controlled in order to avoid misunderstandings which could result in a product or work of unsatisfactory quality. There must be a written contract between the contact giver and the contract acceptor which clearly establishes the duties of each party. The contract must clearly state the way in which the Qualified Person (see Section 4.6.2) releasing each batch of product for sale exercises his full responsibility."

The WHO draft GMP guide (*loc. cit.*, p. 24) defines this principle in identical fashion. The following aspects are highlighted in this particular chapter of the EEC draft GMP guide (*loc. cit.*, pp. 59 - 65):

(i) General aspects. All technical and other changes made in terms of the written agreement between parties must accord with the provisions of the marketing authorisation (see Section 3.5) of the product concerned.

(ii) Aspects relating to the contract giver. The contract giver is responsible for assessing the competence of the contract acceptor, for providing the contract acceptor with all necessary information regarding

technical and legal details relating to the product, and for assuring that all materials and processed products delivered to him by the contract acceptor comply with their relevant specifications.

(iii) Aspects relating to the contract acceptor. The contract acceptor must himself be the holder of a manufacturing authorisation, and must have adequate premises, equipment and suitably qualified personnel to carry out the work ordered by the contract giver; he must ensure that all products and materials delivered to him comply with the relevant specifications; he should not subcontract any work entrusted to him without the prior consent of the contract giver.

(iv) Aspects relating to the contract itself. The contract should be drawn up by a person with the necessary technical knowledge; it should specify the way in which each batch will be checked for compliance with the marketing authorisation; it should specify who is responsible for purchasing materials, testing released materials, carrying out production and quality controls (including in-process controls), sampling and analysis; manufacturing, analytical and distribution records, together with reference samples, should be available to the contract giver who should also be empowered to visit the facilities of the contract acceptor.

According to the British GMP guide (*loc. cit.*, pp. 77 - 79), the GMP principle regarding contract manufacture, analysis and servicing is considered to be a specialised topic; in other words, it is not considered to be part of generally-applicable GMP principles. This principle is worded as follows:

> "The relative responsibilities of the contract giver and the contract acceptor should be clearly understood and agreed, with the object of avoiding misunderstandings which could result in a product or work of unsatisfactory quality. In contract manufacture the contract giver bears the ultimate responsibility for ensuring that the product specification complies with the relevant legal requirements, that the product as manufactured meets that specification, and that the specified quality is maintained during storage, transport and distribution".

The South African GMP guide (*loc. cit.*, pp. 12/1 - 12/3) treats this as a separate GMP principle, but defines it in almost identical terms.

It will be noted that, in terms of the above definition, the British and South African GMP guides consider aspects such as storage, transport and distribution to be an integral part of the contractual agreement with third parties.

The South African GMP guide (*ibid.*, pp. 18/1 - 18/3) in fact refers to "good pharmaceutical wholesaling practice" as a separate GMP principle which is worded as follows: "Good wholesaling practices should be seen as an extension of the manufacturer's endeavours to assure the maintenance of product quality by having adequate storage conditions, record keeping and compliance with legal requirements". The recommendations of the South African GMP guide in this regard relate to the competence of personnel, suitability of premises, storage conditions, special precautions to be taken during transport, documentation, and control procedures. In most other respects, this definition corresponds to that given in both the EEC draft GMP guide and the WHO draft GMP guide.

The EEC draft GMP guide (*loc. cit.*, p. 59) emphasises the fact that this particular GMP principle deals only with the responsibilities of the manufacturer towards the relevant regulatory authorities, and that it is not intended to affect the respective liability of contract givers and contract acceptors to consumers. This fact is also apparent from the text of the French GMP guide (*loc. cit.*, p. 95), which states that a manufacturer is legally required to inform the French Ministry of Health of any arrangements relating to the subcontracting of manufacture, packaging, and analytical laboratory work.

It is important to note, for the purposes of this research, that GMP principles in general play an important role in the relationship between the pharmaceutical industry and the regulatory authorities, as a result of which GMP principles are most likely to be based upon regulatory demands rather than consumer demands. This would imply that there is a danger of the scope of quality control within the pharmaceutical industry being limited to the field of reference dictated by legally enforceable regulatory requirements only.

## 4.7 SUMMARY

The good manufacturing practice (GMP) principles currently applied by regulatory authorities in South Africa are largely based upon the British GMP guide, and this chapter of the research is consequently devoted mainly to a review of the GMP principles contained in that guide. However, due to the dynamic nature of GMP principles in general, and the propensity of the South African regulatory authorities to adapt domestic GMP principles in keeping with local and international trends, a review of other recently published GMP guidelines is included in this chapter of the research. It should be noted that this review is not aimed at providing a detailed summary of the technical aspects of GMP theory, but is aimed instead at evaluating the suitability of GMP principles as a quality management tool.

Good manufacturing practice may be described as being a system of quality-related standards and procedures which is based upon the collective wisdom of the pharmaceutical industry and regulatory authorities, and which is designed to complement relevant technical specifications with the aim of assuring the quality (as well as the safety and efficacy) of medicinal products. Insofar as this basic objective is concerned, there is a similarity between the GMP principles embraced by the pharmaceutical industry, and the more generally applicable quality system standards and guidelines embodied in the SABS ISO 9000 guidelines, for instance (see SABS, 1987).

From the status accorded to GMP guidelines (see Section 4.5), it appears that GMP is considered by the international industry and regulatory authorities alike to be the benchmark against which any quality assurance system may be measured. There also appears to be a tendency, especially amongst regulatory authorities, to look towards a tightening of GMP regulations as being a solution to quality problems still experienced within the pharmaceutical industry. GMP principles are in fact used by regulatory author-

ities as a basis for assessing applications for manufacturing authorisation and for the inspection of manufacturing facilities (see Section 4.3). The legal status of GMP guidelines published internationally appears to depend mainly on two factors; firstly, the extent to which the relevant regulatory authority subscribes to the viewpoint that GMP is the linchpin of quality assurance in the pharmaceutical industry and, secondly, the viewpoint that a voluntary set of GMP guidelines is less effective than one enforced by statute.

Good manufacturing practice is by definition concerned with the assurance of product quality during manufacture, and it therefore follows that the scope of GMP guidelines will be limited to that particular stage of the industrial cycle. Some authors place an even narrower focus on their GMP texts, while others appear to be moving towards a recognition of the fact that quality is affected at all stages of the industrial cycle. Inconsistencies in distinguishing between the concepts of quality assurance, good manufacturing practice, and quality control may be responsible for differences of opinion regarding the scope of GMP guidelines, and the viewpoint that GMP principles are the equivalent of a total quality system.

The British GMP guide is based upon eight general principles that are considered applicable to the manufacture and control of all medicines, namely the GMP principle relating to quality management; personnel and training; documentation; premises and equipment; manufacture; recovered materials; complaints procedure and product recall; and control laboratories. These principles are reviewed in Sections 4.6.1 to 4.6.8 of this chapter. Some additional principles mentioned in other international GMP guides are also reviewed in this chapter of the research; (see Sections 4.6.9.1 to 4.6.9.3). Despite the fact that most of the GMP guides reviewed recognise the need for an integrated management system to give top management control over the quality activities of all functional groups at all levels within an organisation, the texts of all these GMP guides are essentially concerned with the technical aspects of the production stage of the industrial cycle only. The important role played by people in the assurance of product quality is stressed in these GMP texts, but they all specify a personnel training programme that is focused on GMP theory which, by definition, is only a component part of the quality assurance system (see Section 4.2.2). Quality control is defined in terms of the traditional inspection and test concept, and most of the GMP guides reviewed during the course of this research do not mention the business and systems responsibilities of the quality

control function for instance. Moreover, quality assurance is seen as being the responsibility of the quality control function, rather than being a companywide and plantwide activity. Quality is itself defined in terms of the "fitness for use" doctrine only, and not as a strategic business concept; this is most likely due to the fact that compliance with statutory requirements relating to product quality is such a dominant consideration within the pharmaceutical industry.

Despite these criticisms, it cannot be gainsaid that GMP principles have played an important role in the attainment and maintenance of generally very high standards of product quality in the modern pharmaceutical industry. These principles have for instance ensured not only an advanced degree of technical sophistication with regard to incoming material control and certain aspects of process control, but have been instrumental in the creation of a quality awareness amongst shop floor personnel and, to a lesser extent, top-level management as well. Moreover, current GMP principles already contain certain important elements that could be further developed and expanded into a formal system of total quality control. The GMP principle regarding documentation (see Section 4.6.3) for instance

embraces *inter alia* the need for accurate lot and serial number tracking which Feigenbaum (*loc. cit.*, p. 804) describes as being a basic production-quality requirement. The GMP principle regarding complaints and recall procedure (see Section 4.6.7) closely resembles the objective of the special process study activity of a total quality control programme (see Feigenbaum, *ibid.*, p.807). Moreover, the GMP principle regarding self-inspection contains some of the basic elements of the quality audit activity (see Section 4.6.9.1).

In the context of domestic and international trade, GMP principles occupy a strategic position in the relationship between the pharmaceutical industry and the respective regulatory authorities primarily as a result of the legal or *quasi*-legal status accorded to those principles. This may, however, result in GMP principles becoming an end to themselves rather than a means to an end. Moreover, there remains an apparent need to expand in practical terms the organisationwide scope of quality management within the pharmaceutical industry, and for the introduction of modern quality management techniques, in order to acquaint both industry and regulatory authorities with the benefits of a system of total quality. These aspects are addressed in the chapters which follow.

# CHAPTER FIVE: THE APPLICATION OF QUALITY MANAGEMENT PRINCIPLES TO THE PHARMACEUTICAL INDUSTRY

## 5.1 GENERAL

Dale, *et al.* (1990, p. 6) state that one of the most important factors which has stimulated the development of a process of total quality management amongst companies in the United Kingdom, has been the realisation that a quality assurance system does not necessarily, of itself, encourage continual quality improvement; it may mean only that an organisation has quality control procedures in place. Crosby (1984, p. 6) notes that it is by not doing what they already know they should do, that companies get into trouble over quality. Feigenbaum (1986, pp. 78 - 79) draws attention to the fact that customer quality satisfaction cannot be achieved by concentrating upon any one area of the plant or company, and that technical activities must be accompanied by the creation of equally powerful managerial and engineering decision making and operating quality systems.

The abovementioned comments are considered to be particularly relevant to the pharmaceutical industry in the light of a possible preoccupation with regulatory demands regarding the quality of pharmaceutical products, rather than with the application of the basic principles of quality management. The scope

of current good manufacturing practice principles, on which the quality control activities of the pharmaceutical industry are largely based (see Chapter 4), is limited by definition to the production function alone.

There is also a danger that the creation of a quality assurance system which is based exclusively on these principles, may be motivated more by the desire to comply with regularatory demands than by a genuine commitment to quality by top management. The same criticism may be levelled at the new design control, incoming material control, product control, and post marketing surveillance requirements of the current regulatory control system (see Chapter 3).

Successful quality management requires not only the establishment and maintenance of a quality control system, but also the continued improvement of that system. This chapter is devoted to an overview of the quality management concepts that would contribute to the achievement of these objectives in the context of the regulatory controls presently applied to the South African pharmaceutical industry.

## 5.2 THE STRATEGIC BUSINESS VALUE OF THE TOTAL QUALITY CONCEPT

Many modern publications on operations management in general and quality management in particular, ascribe

current interest in these specific areas of management to the loss of market share by American and European industries at the hands of Japanese competitors. The pressures of worldwide competition were no doubt exacerbated by the global recession of the late 70's and the early 80's, and its accompanying slow economic growth. Higher quality and higher productivity gained prominence in modern corporate strategies as a result of these trends (Chu, 1988, pp. 30 - 32; Maani, 1989, pp. 11 - 23; and Schroeder, 1985, pp. 8 - 10).

Feigenbaum (*loc. cit.*, pp. 23 - 24) states that experience in recent years has shown quality control programmes to be one of the most important return-on-investment opportunities available to business management today. Fortuna (1990, p. 5) refers to the strong correlation between quality and profitability, which is related to the fact that quality impacts both on the revenue and cost elements of the profit equation. Mortiboys (1990, p. 39) states that the cost of quality mismanagement is typically 15 to 30 per cent of sales revenue. Sound economic reasoning therefore indicates that quality will play an increasingly important strategic role in the modern enterprise.

With reference to the increasing number of companies that have developed or are developing a total quality system in the United Kingdom, Dale, et al. (*loc. cit.*, pp. 3 - 17) advance the following factors as having provoked this interest:

(i) The realisation that compliance with the requirements of a particular quality system is not necessarily a guarantee against producing and shipping nonconforming products This viewpoint is seen as being of particular importance to the pharmaceutical industry, in view of the status accorded to so-called good manufacturing practice (GMP) principles by that industry and the relevant regulatory authorities (see Chapter 4).

(ii) The imposition of stringent quality requirements by major customers. With reference to the pharmaceutical industry, it is submitted that these quality demands would include those made by regulatory authorities on behalf of final consumers of medicinal products (see Chapters 3 and 4).

(iii) National quality campaigns which stress the need for cost-effective quality management systems. The quality systems guidelines known as the SABS ISO 9000 series (SABS, 1987) serve as an example of such a campaign which is applicable to South African industry in general.

(iv) The teachings of internationally respected experts such as Crosby, Demming, Feigenbaum, Ishikawa, Juran, Shingeo and Taguchi.

(v) Published case studies of the benefits achieved through total quality management.

(vi) Loss of market share to competitors.

Feigenbaum (*loc. cit.*, pp. 22 - 23) divides the benefits of total quality control into what he terms "customer satisfaction oriented benefits", and "major economic improvements". He considers the following to be "customer-satisfaction oriented" benefits: Improvement in product quality; product design; production flow; product service; marketplace acceptance; and employee morale and quality-awareness. He lists the following to be "major economic improvements": Reduced operating costs; operating losses; field service costs; and liability exposure.

From the literature it is thus possible to conclude that quality is the cutting edge of successful competition in the modern marketing environment. In fact, Fortuna (*loc. cit.*, p. 3) states that quality is the most important strategic issue facing top

management in the 1990's. Where lives may depend on the predicted functioning of a product, as is the case with a pharmaceutical product for instance, quality becomes an absolute *sine qua non* to participation in international markets.

Due to the fact that quality is a crucial determinant for business success or failure in today's quality performance-orientated markets, it has become a major strategic business area in its own right and a significant factor in what has come to be called strategic business planning. The key is that quality control must be structured explicitly and measurably so as to contribute to business profitability and positive cash flow (Feigenbaum, *loc. cit.*, pp. 17-18). This need for positive managerial leadership in quality underlines the truism that quality is in its essence a way of managing the organisation it is not something that is achieved by chance. Moreover, it underlines the fact that proactive quality management within the modern pharmaceutical enterprise should be considered to be an example of intelligent self-interest, rather than a mere palliative for regulatory demands in that regard.

## 5.3 THE QUALITY CONCEPT DEFINED

Numerous definitions of the quality concept, as it applies to medicines, may be found in the literature.

Benney (1980, p. 1434) quotes the Pharmaceutical Manufacturers Association of the United States of America as stating that quality relates to the degree in which a particular product performs its intended function when used as directed and, futhermore, that product quality is the sum of all factors which contribute directly or indirectly to the safety, effectiveness and acceptability of that product.

For the purposes of this dissertation, however, the quality of a pharmaceutical product will be expressed in terms of how closely that product conforms to specified standards, as judged by the consumer's actual experience with an affordable product which satisfies the consumer's requirements. This approach to the quality concept is relied upon firstly because it emphasises the need for a product to conform to predetermined specifications and, secondly, the need to satisfy the requirements of the final consumer. Moreover, this particular interpretation of the quality concept is in line with that which is applicable to industry in general.

Terms such as "safety" and "therapeutic efficacy", as used in Subsection 1(3) of the Medicines and Related Substances Control Act (South Africa, 1965) to describe the criteria against which the availability of a medicine shall be considered to be in the public

interest, are seen being individual characteristics which make up the composite of product quality (see Feigenbaum, *loc. cit.*, p. 7). The terms "safety", "effectiveness", and "acceptability" of a medicinal product, as quoted by Benney (*loc. cit.*,), may be interpreted in similar fashion. This viewpoint is supported by Evans & Cunliffe (1987, pp. 12 and 18), according to whom product quality is considered to be synonymous with safety and efficacy in terms of the statutory controls applied to medicines in Great Britian.

Fortuna (*loc. cit.*, pp. 4 - 5) highlights an important aspect by expanding on the "fitness for use" definition of quality originally attributed to Juran, and which is based on the parameters of quality of design and quality of conformance, by including additional design-dependant elements such as reliability, durability, and relative cost. This viewpoint is considered to be important in the present context because the concepts of quality and quality control in the pharmaceutical industry have traditionally been associated mainly with the production function (see Chapter 4). Moreover, due to the nature of the regulatory control system applied to the South African pharmaceutical industry (see Chapter 3), the issue of quality of design has traditionally gained prominence more as a regulatory, rather than a quality

issue. Fortuna's viewpoint corresponds to that of the total quality philosophy which is based, *inter alia*, upon the fact that quality is affected at every stage of the industrial cycle, including the product design stage (see Section 5.5).

## 5.4 CONTROL AS A MANAGEMENT, NOT A TECHNICAL, FUNCTION

Control is one of the basic functions of management. According to Rädel & Reynders (1980, p. 281), control constitutes the rounding-off of the management function and also forms the basis for planning and action. Feigenbaum (loc. cit., p. 10) defines the meaning of "control", in the industrial context, as being a process for delegating responsibility and authority for a management activity while retaining the means of assuring satisfactory results.

He describes this process as consisting of the following four steps:

(i) Setting standards. In the context of quality control, this step will involve setting the appropriate cost-quality; performance-quality; safety- quality; and reliability-quality standards for the product concerned.

(ii) Appraising conformance; i.e. monitoring conformance to the standards set.

(iii) Acting when necessary; i.e. correcting problems and their causes throughout the full range of marketing, design, engineering, production, and maintenance factors which influence user satisfaction.

(iv) Planning for improvements; i.e. developing a continuing programme to improve standards of cost, performance, safety and reliability.

This viewpoint contrasts with that found in the technical literature relating to industrial pharmacy, where control is often viewed as consisting of individual (not necessarily inter-related) technical functions. Benney (*loc. cit.*, pp. 1434 - 1437) for instance describes the following separate and distinct activities as constituting control functions in the pharmaceutical industry:

(i) The analysis function. This relates to the performance of appropriate physical, chemical and biological tests prior to or upon completion of a significant phase in the production process of a particular batch of product.

(ii) The monitoring function. This relates to the in-process control or monitoring function applied to materials while they are being processed, and includes an environmental monitoring function where necessary (e.g. during the production of a sterile product).

(iii) The record review and release function. Many documents are routinely used to guide and record the pharmaceutical manufacturing process (see Section 4.6.3). Batch manufacturing records are used to document a product's entire manufacturing history, particularly with regard to the completion of the necessary activities relating to control and production processes. As part of the final product release function, a detailed audit is performed on the relevant batch manufacturing records to verify the completeness and accuracy of those records.

(iv) The quality audit function. Benney (*ibid.*) describes the quality audit as being designed to detect areas where standard operating procedures (SOP's) relating to the research, development, production, control, purchasing and distribution functions, are not being followed. These SOP's are based on current good manufacturing practice (GMP) principles (see Chapter 4). According to Benney (*ibid.*, p. 1436), the quality control audit is performed by an individual or by a multidisciplinary team which is "frequently" headed by personnel from the quality control function. Deviations should be reported to the relevant supervisors, whereas uncorrected deviations found during follow-up audits should be "periodically" reported to higher management for resolution"

The viewpoint put forward by Benney (*supra*) serves as an example of the functional approach to quality control which is generally adopted in the technical literature. This approach in effect results in top management being involved only in an incidental manner in quality issues, because the functional activities described above are not necessarily directly connected to the managerial decision making process. One of the primary objectives of this research is in fact to demonstrate the relevance to the pharmaceutical industry of the principle that quality is a result of the way in which an enterprise is managed, and the consequent need to revise present day concepts of quality control which are based upon purely technical philosophies.

## 5.5 THE TOTAL QUALITY CONCEPT

Numerous definitions and acronyms associated with the term "total quality control" are to be found in the literature. The reason for this surfeit appears to be related to the fact that often only selected aspects of the quality paradigm are addressed by each.

The approach adopted by Feigenbaum and also that of Hohner were found to be particularly useful for the purposes of this research. Feigenbaum (*loc. cit.*, p. 6) defines the concept of total quality as follows:

> "(Total quality) is an effective system for integrating the quality-development, quality-maintenance, and quality-improvement efforts of the various groups in an organisation so as to enable marketing, engineering, production, and service at the most economical levels which allow for full customer satisfaction".

Hohner (1988, p.43) describes total quality as being a management philosophy which incorporates technical skills at all levels of the organisation. He emphasises in particular the broad functional scope of total quality control (which encompasses all manufacturing, engineering, marketing and sales functions); a commitment towards continuous quality improvement; and the achievement of reliability and consistency in the delivered product.

The total quality concept may also be defined in terms of an orientation to the following principles, which are based on Feigenbaum (*loc. cit.*, p. 94), and Fortuna (*loc. cit.*, pp. 11-12):

(i) Basic quality responsibility rests with top management; quality control is a management tool which enables top management to fulfil a leadership role with regard to product quality.

(ii) The formulation and communication of specific quality policies and objectives which have a customer-first orientation.

(iii) Organisationwide integration of all the activities necessary to achieve company quality policies and objectives.

(iv) Provision of ongoing quality education and training to all employees in order to promote quality-mindedness and organisationwide quality motivation.

(v) Active involvement of all employees in the quality establishment, maintenance, and improvement process.

(vi) Defined and effective quality information flow, processing, and control.

(vii) Continuous feedforward and feedback of information relating to measurements and standards of organisation-wide quality performance, including quality cost data.

(viii) Periodic audit of quality system activities.

(ix) A structured approach towards timeous and effective corrective action with regard to quality problems.

(x) A focus on continuous improvement.

(xi) Reduction of product and process variation.

(xii) Emphasis on the prevention of quality deviations, rather than their detection.

(xiii) Extension of quality control activities beyond the (internal) organisation itself to include, for instance, vendor-control and post-marketing surveillance activities.

## 5.6 THE CONCEPTUAL EVOLUTION OF QUALITY CONTROL IN THE PHARMACEUTICAL INDUSTRY

The industrialisation of the pharmaceutical industry followed a pattern similar to that of industry in general, but on a slightly different time scale. The extemporaneous dispensing of medicine by individual apothecaries before the twentieth century gradually gave way to mass production techniques, and the pharmaceutical industry as it is known today came into being as recently as the Second World War. The postwar period has in turn been characterised by extremely rapid technological change, as evidenced by the technologically highly complex nature of modern pharmaceuticals (South Africa, 1978, pp. 4 - 5).

Sharp (1990, pp. 296 - 299) classifies the conceptual evolution of quality control in the pharmaceutical industry to date as consisting of the following three distinct phases:

(i) The initial phase, during which emphasis was placed entirely upon preparative methods (as exemplified by the professional apothecary).

(ii) The second phase, during which end-product testing was considered to be all important (e.g. compliance with specifications detailed in official pharmacopoeias).

(iii) The third phase, to which he refers as the "modern view" that true assurance of quality can only be achieved when end-product testing is integrated within "a more general framework of a detailed understanding and appraisal of the conditions of manufacture". He is furthermore of the opinion that current good manufacturing practice (GMP) principles provide such a framework.

The good manufacturing practice concept is by definition concerned with manufacturing and quality control procedures only (see Chapter 4). The quality assurance concept, on the other hand, is described in the techinical literature as relating to good manufacturing practice as well as other (undefined) factors outside the production function which influence product quality.

It may therefore be concluded from the literature that a purely technical approach to the control of pharmaceutical product quality does not place emphasis on factors such as basic responsibility for quality resting with top management; the organisationwide integration of quality activities; continuous evaluation of quality performance (including quality cost analyses); a structured approach to corrective action relating to quality problems; the quest for continuous improvement; and the importance of prevention rather than detection of quality deviations. Moreover, it may be concluded from the literature that the total quality concept does have a clear orientation to these specific aspects of product quality.

Dale,*et al.*, (*loc. cit.*, pp. 3 - 17) distinguish between four distinct stages in the progression from inspection activities to total quality management, namely inspection; quality control; quality assurance; and total quality management. The first stage relates to a simple inspection-based system which is in effect an after-the-fact screening procedure that is carried out on incoming materials, in-process materials, and finished product. The system has no prevention content other than the possible identification of suppliers, workers, or processes that are producing substandard products. The second stage

refers to a system of quality control, which is described as including some form of elementary new design control, raw material- and intermediate product testing, self-inspection by operators, logging of elementary process performance data, and the feedback of process information to supervisors. The third stage of the evolutionary process relates to a system of quality assurance, which is described as featuring the use of a comprehensive quality manual, the (limited) use of quality costs, and the use of statistical process control and quality systems. What is more important, however, for the purposes of this research is the view that a system of quality assurance incorporates a shift in emphasis from mere detection towards the actual prevention of non-conformance. Dale, *et al.*, (*ibid.*) also make the interesting comment that this particular stage of the evolutionary process is likely to have third party approval from a recognised authority (see Chapter 4 of this dissertation regarding the regulatory status of the so-called good manufacturing practice principles used by the pharmaceutical industry).

The fourth, and highest, level of the evolutionary process relates to the application of quality management principles on an organisationwide basis. Individual departmental standards may be no higher than for a "quality assurance"-level of quality management, but will pervade the entire organisation

(not only the production function), and would in fact extend beyond the organisation itself to include "partnerships" with suppliers and consumers.

Mr Sharp (*loc. cit.*, pp. 296-299) is described in that publication as being a widely experienced Industrial Pharmaceutical Consultant, and it may therefore have been anticipated that he would be a proponent of the movement towards a higher level of the evolutionary process relating to quality control; namely total quality management. However, he describes any suggestion of such a movement away from GMP towards what he terms "total quality assurance", or "quality management", as involving "no more than mere semantics". Moreover, he refers to concepts such as quality management, total quality systems, and just-in-time as "current hot topics" and "buzz-words" (*sic*).

The opinions expressed by Sharp (*supra*) may be better understood when seen in the broader context of yet another characteristic of the evolutionary development of the pharmaceutical industry; namely the propensity for quality problems within that industry to elicit highly publicised, and often very emotional, public response. Because of the fact that human (and animal) lives may be at stake, it stands to reason that quality issues such as adverse drug reac-

tions, mislabelling, product mix-ups, adulteration, and contamination are more likely to elicit such public (and political) responses than would be the case involving a product where the risks of failure are not as serious. Government agencies have responded to public and political demands for protection against these potential dangers by imposing various regulatory controls on the pharmaceutical industry (see Section 2.3.3). The need for some form of regulatory control over the manufacture and sale of pharmaceutical products has historically been shown to be a generally accepted principle (see Section 1.1). The modern history of the pharmaceutical industry has in fact been characterised by sporadic quality-related "disasters", of which the thalidomide disaster, which occured during the early Sixties, is the classic example (see Section 2.4.2.1).

Every such "disaster" is usually followed by public protest and demands for more stringent regulatory controls. The argument against what is often considered to be excessive regulation has been put forward mainly by the pharmaceutical industry, on the basis of an alleged prejudice to both public and national interests, as well as increased financial risk to the industry itself. The industry has also on occasion managed to mobilize opinion within the medical profession on the grounds that the physician's freedom to prescribe is endangered by regulatory trends.

The international debate concerning the regulatory controversy has swung pendulum-fashion from one extreme to the other, depending on events. In the wake of the thalidomide incident, for instance, there was overwhelming support for greater regulatory control. This event was, however, followed by a decade without major drug dramas, and arguments in favour of relaxing regulatory controls were increasingly heard. In 1974, problems surrounding the drug practolol again swung the debate in the opposite direction, only to be followed by a new wave of protest against regulation which reached a climax around 1979 and 1980. During the four years that followed, a series of major drug incidents involving, amongst other, benoxaprofen, controled release indomethacin ("Osmosin" and "Indosmos"), oxyphenbutazone, and phenylbutazone, caused opinion to again swing in favour of more extensive regulatory controls (Dukes, 1985, pp. 24 - 30).

The period following the thalidomide affair may therefore be said to have been characterised by the fact that the pharmaceutical industry has increasingly been involved in fighting a rearguard action against what is perceived to be excessive or inappropriate regulatory demands. Sharp (*loc. cit.*, p. 296) in fact is of the opinion that there have been no important conceptual or technical developments in the control of quality in the pharmaceutical industry in Europe since the establishment of GMP principles, and

that the most important developments in this regard have occured in the field of what he describes as the "formalisation" or "bureaucratization" of quality issues.

This preoccupation with regulatory demands and the confrontational nature of the ensuming debate (wether such confrontation is intended or not), is likely to continue for as long as total quality management and related concepts are considered to be an exercise in semantics or mere "buzz-words". Moreover, the viewpoint that good manufacturing practice (GMP) principles represent the ultimate framework for a modern quality assurance system cannot be supported from a business economic perspective, particularly insofar as the emphasis on defect prevention (rather than detection) and the organisationwide scope of quality management (rather than a technical orientation to the production function only) is concerned.

## 5.7 THE INTEGRATION OF A QUALITY SYSTEM INTO PRODUCTION CONTROL SYSTEMS

The technical orientation of the good manufacturing practice (GMP) principles currently applied to pharmaceutical production, was discussed in Chapter 4. From a business economic point of view, the relationship between GMP principles and any particular

production control system is therefore of an incidental nature only. On the other hand, there exists a strong inter-dependence between the total quality approach and JIT production systems. Hohner (*loc. cit.*, p.42) for instance describes a quality commitment to be the pivotal point of a JIT programme's success, and he considers the implementation of a total quality methodology to be a crucial step in the establishment of a successful JIT production system. Ray (1990, pp. 179 - 190) refers to the need to focus upon a fundamental improvement in the capability and reliability of the total production system as a prerequisite for the successful implementation of a JIT production control system, and notes that these preconditions are in essence quality issues.

Many of the elements inherent in the JIT production philosophy are directly applicable to the pharmaceutical production process. The emphasis that is placed upon the identification and elimination of the root causes which create the demand for inventory and the resultant improvement in the capability and reliability of the total production system; the achievement of a high degree of process capability; the achievement of tooling and equipment reliability; the immediate feedback and response to quality problems; the achievement of reduced set-up times for equipment; and the establishment of a carefully eval-

uated supplier base, are for instance entirely compatible with the quality objectives of pharmaceutical production as exemplified by the GMP principles currently applied within the industry. The "do it right first time" philosophy is an integral part of both JIT/total quality and GMP principles; however, whereas GMP methods seek to achieve this by prescriptive means JIT/total quality systems rely instead upon the self-actualisation of the worker through participatory problem solving techniques and a discipline that is inherent in the system itself. Moreover, the JIT/total quality system feeds back information which is relevant to the managerial decision making process, whereas GMP principles are concerned primarily with technical data only. Galomski (1987, p. 230) criticises the latter approach by noting that American executives in general have lost control of the management of quality because they have delegated that activity to quality specialists who are mainly interested in the technical aspects of products and processes.

A major difficulty with the application of JIT production techniques to pharmaceutical manufacture however appears to be the fact that JIT production requires a stable master schedule which is uniform from day to day and even hour to hour (Schroeder, *loc. cit.*, pp. 485 - 486). In other words, the use of JIT techniques is essentially restricted to repetitive

production (i.e. the production of standardised or discrete products in high volume) such as is the case in the automotive, electronics, machinery, and household appliance industries. Batch manufacturing production, as applied in the pharmaceutical industry, on the other hand relies on a highly variable master schedule. Work centres or flow lines must generally be capable of handling a wide variety of products, dosage forms, and pack sizes. Moreover, demand for finished products may be seasonal or very erratic. Cough and cold remedies for instance experience peak demand in winter and virtually no demand during summer whereas expected demand may be severely distorted by an influenza epidemic.

The materials requirements planning (MRPI, II and III) system of production planning and control appears to be more suited to pharmaceutical production than the JIT system, due mainly to the fact that it allows the use of a highly variable master schedule. In the context of pharmaceutical production, the MRP system however appears to have weaknesses or potential weaknesses in important areas.

According to Schroeder (*ibid.*, p. 485), the MRP approach to quality is based upon a policy which tolerates a degree of wastage through scrap, and which places greater emphasis on the prediction of scrap-losses than their prevention. The MRP system in fact stands accused of neglecting quality (Anon, 1989a, pp. 95-96). JIT production, on the other hand, aims for zero defects because if quality is not one hundred per cent, production is in jeopardy due to the starvation of work centres further down the line.

According to Schroeder (*loc. cit.*, pp. 485 - 486), the MRP approach to workers may be characterised as "management by edict", whereas the JIT approach is based on "management by consensus". MRP is basically a planning philosphy which requires workers merely to follow the plan, whereas the JIT approach encourages worker participation in problem solving in order to continually improve quality and productivity. The strategic role played by people in the pharmaceutical production process is generally recognised in the technical literature. Sharp (1986, p. 45) for instance states that science and technology are, relatively speaking, the easy part of pharmaceutical production, and that "people problems" are the really difficult part. It is therefore important to take note of this particular criticism of the MRP concept by Schroeder (*supra*), especially in the context of pharmaceutical manufacture.

From the above discussion it may be concluded that both the JIT and MRP production control systems contain elements which may be successfully applied to pharmaceutical production, but that both systems also contain important elements that are not entirely compatible with the specific requirements of the pharmaceutical production process. The JIT and MRP systems however appear to complement each other in these areas of possible weakness, and it would therefore seem logical to suggest that the two systems should be used in combination with one another.

Goodrich (1989, pp. 46 - 48) is of the opinion that JIT and MRP systems are not only compatible, but that the benefits derived from each are greatly increased when the two systems are used together. The rationale behind this viewpoint becomes apparent when MRP is viewed as the planning half of the operation, and JIT as the execution half (Boccard, 1990, pp. 39 - 40). Duncan (1989, p. 84) states in this regard that a sound requirements plan is especially important to the manufacturer of complex products, i.e. products with multiple components having different properties, processes, resource requirements, and lead times (as is the case in pharmaceutical production), and that MRP is in fact a prerequisite to JIT implementation under these circumstances. Discenza & McFadden (1988, pp. 49 - 53) describe the integration of MRP II and

JIT systems through software unification in companies where MRP is used as the planning system while JIT is used as the execution system.

Heiko (1989, pp. 62 - 63) regards the integration of JIT with MRP as one of the four basic principles on which the practical implementation of a JIT system depends; together with the need to streamline manufacturing operations, the implementation of total quality, and group improvement activities which encourage worker creativity.

Yamaha Motors has developed a system termed Synchro-MRP, which combines the features of MRP and the Kanban subsystem of JIT, and which is intended for use in a high-volume manufacturing company with a broad line of products (Esparragio, 1988, pp. 9 - 10). The system appears to be flexible enough for application to pharmaceutical production.

It is concluded from the above discussion that the implementation of a system of total quality may enable management in the pharmaceutical industry to effectively integrate its quality control system with modern production planning and control systems. It is furthemore concluded that the total quality concept may be uniquely suited to such integration because it forms an integral part of JIT/MRP systems. Due to its purely technical orientation, the GMP principles cur-

rently applied within the pharmaceutical industry have only limited application in this regard.

## 5.8 QUALITY COSTS

Maani (*loc. cit.*, p. 18) states that quality costs are costs of waste; in other words, the cost of "not doing it right first time". Feigenbaum (*loc. cit.*, p. 109) agrees with this viewpoint, and equates unsatisfactory quality to unsatisfactory resource utilisation due to wastage of material, labour, and equipment time, which lead to higher costs. Batson (1988, pp. 61 - 64) refers to the following definition of quality costs by Montgomery: "(Quality costs are) those categories of cost associated with producing, identifying, avoiding or repairing products that do not meet requirements". Plunkett & Dale (1990, pp. 167 - 168) refer to the following definition of quality costs: "(Quality costs relate to) the expenditure incurred in defect prevention and appraisal activities and the losses due to internal and external failure of a product or service through failure to meet agreed specifications". Campanella & Corcoran (1987, p. 210) draw attention to the fact that quality costs should not be viewed as consisting of the expenses of the quality control function of the enterprise.

For the purposes of this research, the various categories of quality costs will be classified according to the system suggested by Feigenbaum (*loc. cit.*, pp. 109 - 145). He divides quality costs into two principal categories; namely the cost of control, and the cost of failure to control.

He refers to these costs collectively as operating quality costs. The cost of control may furthermore be subdivided into prevention costs and appraisal costs, whereas the cost of failure to control may be subdivised into internal failure costs and external failure costs.

Insofar as quality costs in general are concerned, the basic objective of management is to reduce total quality cost to a minimum while at the same time maintaining the required levels of quality. With reference to the pharmaceutical industry in particular, quality costs are central to the current debate concerning the possible revision and relaxation of the regulatory controls currently applied to that industry. It is for instance argued that present-day regulatory requirements may cause a decline in the industry's return on investment to a point where its very survival will be at risk (Dukes, *loc. cit.*, pp. 4 - 25). This particular aspect of the regulatory debate may be said to centre around the determination of the optimum balance between the cost of quality and the value of quality.

The purely technical approach to quality control which is embodied in current principles of good pharmaceutical manufacturing practice (see Chapter 4) encourages an inspection and test approach to quality control. This traditional approach typically emphasises expenditure on appraisal costs (rather than prevention costs), thereby ignoring the effect on total quality costs; total quality costs remain virtually unchanged due to the decrease in external failure costs being offset by the increase in appraisal costs and internal failure costs (Quinn & Bhatty, 1987, p. 217). These good manufacturing practice principles cannot therefore be expected to positively contribute to the debate on the cost of quality. Similarly, the present focus on quality costs as an expense, rather than an investment, will result in the positive contribution of a quality control system to the industry's return on investment being overlooked.

The total quality concept, on the other hand, encourages increased expenditure on prevention activities; this results in the reduction of internal and external failure costs. Apprasal costs may also decrease, due to the need for routine inspection and test activities being reduced. The net result is an improvement in the level of quality with a concomitant decrease in the total cost of quality up to the point

of optimal cost of quality (Quinn & Bhatty *ibid.*, p. 218). Moreover, Feigenbaum (*loc. cit.*, pp. 112 - 114) points out that the major part of the savings generated from a reduction in total quality costs goes into profit improvement. He is of the opinion that this makes the total quality system one of the most attractive return on investment apportunities available. Dukes (*loc. cit.*, pp. 21 - 30) refers to the fact that the current regulatory control debate is often conducted at a very unsophisticated and sometimes emotional level. It may therefore be concluded that the availability of accurate quality cost data will make an important contribution to this debate.

Plunkett & Dale (*loc. cit.*, pp. 165 - 182) note that quality costs may be regarded as a criterion of quality performance only if valid comparisons can be made between different sets of cost data. Consequently, defining the various cost categories and the various elements of each category is of fundamental importance to such a comparison, both within the individual enterprise as well as the industry within which it operates. Differentiating between costs that are quality-related and those that are not, is however often a matter for individual judgement, and many grey areas exist.

It may for instance be debated whether test procedures relating to the identification and assay of incoming materials, or in-process controls such as those relating to tablet mass, uniformity, and friability, are indeed peripheral quality activities, or should rather be considered to be an integral part of the pharmaceutical manufacturing process. If the manufacturer of a sterile product cannot be certain of making a product which is fit for its intended use without first having conducted a test for product sterility on every batch produced, should the cost of the test be considered to be quality-related or process-related?

Plunkett & Dale (*ibid.*, p. 169) are of the opinion that it is not possible to offer general solutions in this regard other than to suggest that if there is serious doubt, the cost should not be defined as being quality-related where it is unlikely to be amenable to change by quality management. Pharmaceutical production is however characterised by the fact that quality costs may have to be incurred at the insistence of an external regulatory control authority (see Chapter 3). Should company management choose not to comply with regulatory demands in this regard, the South African Medicines Control Council is empowered by law to cancel the marketing authorisation (product registration) of a violative product, and/or to recall

any such product from the marketplace. In terms of the approach advocated by Plunkett & Dale (*supra*) it may therefore be argued that quality costs thus incurred are part of process costs, and not quality costs, because quality management is not autonomous in that regard.

It should, however, be borne in mind that the South African regulatory authorities have adopted an approach which relies to a large extent upon consultation with the industry as part of their own decision making procedure. This approach, which is based upon the *audi alterem partem* rule of natural justice, is exemplified by the Medicines Control Council's application of so-called current good manufacturing practice (GMP) priciples to the pharmaceutical industry; the requirements relating to the quality objective(s) to be achieved in this regard are clearly stated, but the actual method whereby those objectives are achieved is left to the discretion of individual company management (see Chapter 4). Moreover, a person or company affected by a decision of the Medicines Control Council has a right of appeal against that decision (see Section 3.5). Company management may therefore be considered able to participate, albeit to a limited extent, in the establishment and implementation of quality goals. When viewed from this perspective, it is submitted that the validity of the approach advocated by Plunkett & Dale (*supra.*) is not

affected by the statutory relationship between the Medicines Control Council and the pharmaceutical industry in South Africa. The fact that this relationship complicates the process of differentiating between costs that are quality-related and those that are not, can however not be gainsaid.

Plunkett & Dale (*ibid.*, p. 165) state that quality-related costs commonly range from five to 25 per cent of company turnover, depending on the industry and the way in which quality is managed by the company, with appraisal and failure costs traditionally making out 95 per cent of this total. The prevention-orientated focus of the total quality concept makes significant savings in quality costs possible; Plunkett & Dale in fact believe that quality costs may be reduced to one third of their level prior to the introduction of cost effective quality management systems. This research revealed no reference in the literature to support such an opinion relevant to the South African pharmaceutical industry. The companywide scope of the total quality concept, and its application to the entire industrial cycle, does however suggest that its inherent potential to achieve such savings must be accepted as being superior to that of the current good manufacturing practice (GMP) principles presently employed by that industry. Moreover, the total quality concept embraces the identification, collec-

tion and reporting of empirical cost data, whereas the application of GMP principles does not supply management with this type of information.

## 5.9 FORMULATION OF QUALITY POLICY

The management policy for any area within an organisation relates to the aggregate of management decisions necessary to achieve stated operational objectives. In particular, a quality policy is established to stipulate the limits within which all quality-related management decisions are taken in order to meet quality objectives. The quality policy should be designed for use as a delineation of the quality objectives and quality policy of a company and is considered to be a prerequisite to the implementation of a total quality programme (Caplan, 1980, pp. 8 - 9; and Feigenbaum, *loc. cit.*, pp. 237 - 240). According to Feigenbaum, the process of quality policy formulation involves the identification of quality-related decisions at each step of the industrial cycle; the identification and analysis of all quality-related problems experienced with the product during the entire industrial cycle; and the documentation of quality policy in order to communicate the quality policy to all functionaries throughout the organisation.

With reference to the identification of quality-related decsions, the MBR1 registration dossier (see Section 3.6) may be viewed as a valuable guideline during this particular phase of quality policy formulation. Regulatory requirements such as the appointment of a pharmacist as managing director in terms of section 22(c) of the Pharmacy Act (South Africa, 1974) and Medicines Control Council requirements relating to major changes (as defined) to the method of manufacture (MCC, 1988, Circular to applicants ref. 13/88), may therefore have a substantial influence on the formulation of quality policy in the pharmaceutical industry. These requirements may however be viewed as merely providing a framework for policy formulation in certain particularly critical areas without entirely removing the discretion of management to define the parameters within which alternative decisions or courses of action may be taken to achieve the stated quality objectives.

The current regulatory control system assures the efficient identification of (technical) quality-related problems and their (physical) analysis. No regulatory guidelines are, however, given regarding the identification and analysis of non-technical quality- related problems. In terms of the total quality concept, this phase of quality policy formulation is approached from a broader (not

exclusively technical) perspective, and is a sustained process which is aimed at achieving continual quality improvement (see Feigenbaum, *loc. cit.*, p. 239).

Caplan (*loc. cit.*, pp. 8 - 9) views the process of communicating a quality policy to all functionaries throughout an organisation as consisting of an inter-linked chain of documents at four levels. The first level comprises the broad statement of quality policy. The second level of documents addresses more specific aspects of the quality system, such as new design control or product control. The third level of documents are termed procedures, which indicate how policy is to be carried out; who does it; when it has to be done; and under what circumstances it is to be done. The fourth level of documents comprises instructions, which are detailed and very specific statements regarding the performance of individual tasks.

The use of formal documentary methods of communication and documentary control measures to verify adherence to policies, procedures and instructions, is one of the basic principles of current good manufacturing practice (GMP) routinely applied in the South African pharmaceutical industry (see Section 4.6.3). It will be noted however that the working documents that are required in terms of current GMP principles relate to

tactical decision making only, i.e. the day-to-day control of quality. No specific reference is made in current GMP theory of strategic quality decision making, either with reference to the orientation of top management in terms of the GMP principle regarding quality management (see Section 4.6.1), or the orientation of employees in terms of the GMP principle regarding personnel and training (see Section 4.6.2). Feigenbaum (*loc. cit.*, pp. 237 - 238) considers the communication of quality policy to be a valuable instrument whereby management can emphasise quality as being an important strategic business concept, and with which to highlight the vital role played by individual attitudes, knowledge and skills in the achievement of the corporate quality objective.

## 5.10 ORGANISING FOR QUALITY

In order to attain the objectives identified by its quality policy, it is necessary for management to co-ordinate the actions of people, machines and information flow across all functional boundaries within the enterprise. Feigenbaum (*ibid.*, p. 149) bases the development of such an organisational framework on three considerations: Firstly, the identification of key organisationwide quality responsibilities and authorities; secondly, the identification of the key quality control responsibilities and authorities of

the quality control function itself; and thirdly, the leadership role of management in the establishment and maintenance of a quality organisation. A discussion of these aspects, as they relate to pharmaceutical manufacture, follows.

5.10.1 Key Organisationwide Quality Responsibilities and Authorities

The MBR1 registration dossier (see Section 3.6) may be viewed as a valuable guideline regarding certain primary quality responsibilities of the product engineering function. These responsibilities would for example relate to the original product design or formulation as detailed under Annexure 2 of the MBR1 dossier (see Section 3.6.3); the establishment of specifications for raw materials, final containers, and finished product as detailed under Annexures 4, 7A and 8A of the MBR1 dossier (see Sections 3.6.7, 3.6.10 and 3.6.12 respectively); the determination of product stability under anticipated conditions of use, as detailed under Annexure 10 of the MBR1 dossier (see Section 3.6.16); pre-clinical and clinical studies to demonstrate the safety and therapeutic efficacy of the proposed product design, as detailed under Annexures 14A to 15C of the MBR1 dossier (see Sections 3.6.20 to 3.6.24); obtaining and collating experimental data relating to the pharmaceutical and biological availability characteristics of the product in support of

the claims made with regard to product safety and efficacy, as detailed under Annexure 13 of the MBR1 dossier (see Section 3.6.19); and establishing and maintaining all working documents relating to product development, as summarised under Annexure 16 of the MBRI dossier (see Section 3.6.25).

Similarly, current good manufacturing practice (GMP) guidelines may be viewed as providing valuable guidelines concerning certain of the primary quality responsibilities of the production engineering function. For example, the selection of suitable processing equipment; the establishment of optimum environmental conditions for the manufacturing process; the planned maintenance of production equipment and facilities; the establishment of step-by-step operating instructions for each item of equipment; the establishment of step-by-step processing instructions; and the establishment of the necessary in-process controls, are aspects of pharmaceutical production that are specifically addressed in current GMP guidelines.

It may therefore be concluded that the current regulatory control system identifies many of the key quality responsibilities associated with pharmaceutical production. However, this system does not specifically address the formal organisationwide identification of key quality responsibilities and

authorities and can at best be considered to provide certain basic guidelines in this regard. It is also important to note that the South African regulatory control system is prescriptive only with regard to minimum quality requirements, and that the onus is therefore on the industry to take any additional steps that it may deem necessary to assure product quality (see Snyman, 1972, pp. 280 - 287). The use of a relationship chart in conjunction with a product's MBR1 dossier, the relevant process flow diagram, and the organogram of the plant concerned, may be a particularly valuable technique in this regard.

### 5.10.2 Key Responsibilities of the Quality Control Function

Feigenbaum (*loc. cit.*, pp. 159 - 160) is of the opinion that, in terms of the modern quality management concept, two basic authorities should be assigned to the quality control function; namely to fulfil a leadership role in the attainment of the company quality objectives and, secondly, to assist in assuring optimum quality costs for the company's products. In order to accomplish this, he is of the opinion that three principal responsibilities must be assigned to the quality control function; namely a business responsibility, a systems responsibility, and a technical responsibility. From the discussion of the conceptual evolution of quality control in the

pharmaceutical industry (see Section 5.6) it may be concluded that, in terms of current good manufacturing practice principles, the quality control function is assigned technical quality responsibility only. A discussion of the main features of the approach suggested by Feigenbaum follows.

5.10.2.1 The Business Responsibility of the Quality Control Function

According to Feigenbaum (*ibid.*, pp. 17-19), the principal characteristic of orienting quality as a primary business strategy is that the quality control programme must foster sound business growth. It must be structured explicitly and measurably so as to contribute to business profitability, and to provide a major competitive advantage to the company.

Current good manufacturing practices applied by the South African phamaceutical industry (see Chapter 4) do not focus on aspects such as efficient operations management systems, ongoing productivity enhancement, and quality cost management for instance. This approach to quality instead centres around a desire to comply with the legal and regulatory requirements pertaining to the pharmaceutical industry. In terms of the total quality concept, on the other hand, the quality control function must make a direct contribution to strategic business planning as part of its business responsibility (see Feigenbaum, *ibid.*, p. 160).

### 5.10.2.2 The Systems Responsibility of the Quality Control Function

In terms of the total quality concept the quality control function provides the primary leadership for the rational structuring of effective people; machine; and information quality systems, as well as the administrative process of assuring the effective and improved operation of the quality system. In other words, in terms of the total quality approach, the quality control function is given the responsibility for leading the integrated quality activities throughout the organisation (see Feigenbaum, *ibid.*, pp. 84 - 85, and p. 160).

It is noted in Chapter 4 of this dissertation that current good manufacturing practice (GMP) principles are generally silent with regard to the systems responsibility of the quality control function in the pharmaceutical industry (see Section 4.6.9.2). Moreover, whereas GMP principles are by definition limited in scope to the production function only, the systems responsibilities assigned to the quality control function in terms of the total quality philosophy emphasises the need for a co-ordinated, organisation-wide approach to quality management during the entire industrial cycle.

5.10.2.3 The Technical Responsibility of the Quality Control Function

In terms of current good manufacturing practice principles, the various functions of the quality control department relate primarily to inspection and test procedures (see Section 4.2.3). The current regulatory control system requires that the technical quality responsibilities of the quality control function must include the following aspects:

i) Development of the raw material control procedures that have to be carried out to determine whether or not raw materials comply with the relevant specification parameters. These procedures may be of an analytical or technical nature, full details of which must be disclosed under Annexure 5 of the MRB1 registration dossier (see Section 3.6.8).

ii) Determination of those control procedures that are to be carried out on raw materials as a batch to batch release requirement, details of which must be disclosed under Annexure 6 of the MBR1 dossier (see Section 3.6.9). These are the tests and procedures that are selected from those listed under Annexure 5 (*supra*) to be used as a raw material batch release requirement.

iii) Development of the final product control procedures that have to be carried out to verify compliance with the final product specifications, and which are disclosed under Annexure 7B of the MBR1 dossier (see Section 3.6.11).

iv) Determination of those control procedures that are to be carried out as a lot release requirement for the final product, as detailed under Annexure 9A of the MBR1 dossier (see Section 3.6.14).

v) Development of the control procedures that are to be applied to the container which is in direct contact with the product, to verify compliance with container specifications. These control procedures are described under Annexure 8B of the MBR1 dossier (see Section 3.6.13).

vi) Determination of the specific control procedures that are to be carried out as a lot release requirement for final container supplies, as detailed under Annexure 9B of the MBR 1 dossier (see Section 4.6.15).

vii) Establishment of the in-process controls which are to be performed during manufacturing and packaging operations, as detailed under Annexure 11 of the MBR 1 dossier (see Section 3.6.17).

From the literature it may therefore be concluded that both the total quality approach as well as the current pharmaceutical regulatory control system recognise the technical responsibility of the quality control function. The difference between these two approaches however lies in the fact that, in terms of the total quality concept, this is not considered to be the only function of the quality control department (see Feigenbaum, *ibid.*, p. 149).

### 5.10.3 The leadership role of management

Mortiboys (*loc. cit.*, pp. 33-43) succinctly states that quality management starts at board level; all directors and managers must therefore be committed to effective leadership and cost-effective qaulity management. The changes which must be made to traditional managerial structures are so fundamental and far-reaching, that they cannot be made simply by the adoption of new techniques or by working harder. Nor will it suffice to appoint or designate a single person or group to manage quality as part of the traditional managerial structure. It is in fact necessary to create a new organisational culture, and the board must take the lead in its establishment. Executives need to change their management style from that of maintaining personal control (i.e. reacting to events as and when they occur), and "fire- fighting" (i.e. forever trying to rectify what has gone wrong),

to that of "planning to the job right first time". The objective of cost-effective quality management is achieved when every employee (including top management) does his job right the first time.

According to Mortiboys (*ibid.*, pp. 37-38), the implementation of a management style which is based upon evaluation and planning to do the job right the first time will involve four activities:

(i) Identifying the situation to be managed, and clearly defining management's objectives. Reference was made in Section 5.9 to the clear delineation of quality objectives as part of the process of quality policy formulation.

(ii) Planning the achievement of these objectives by identifying and providing the necessary resources; communicating the plan; and obtaining the commitment of all concerned. Feigenbaum (*loc. cit.*, pp. 160 - 161) considers the quality organisational structure to be the conduit along which the formally documented quality policy of management is achieved in practice. It enables the communication of quality responsibilities to all employees; the identification of the principal areas of teamwork and co-operation; and the co-ordination of companywide and plantwide quality relationships between individuals and groups.

(iii) Implementing the plan and monitoring its progress. Mortiboys (*loc. cit.*, p.41) notes that appropriate information should not only be passed down through the organisational structure, but that employees should also be encouraged to pass information up through that structure. Badiru (1990, pp. 33 - 36) emphasises the value of communication, co-operation and co-ordination as being fundamental to the total quality concept.

(iv) Taking corrective action when necessary, either by helping people to perform better; by modifying the plan; or even by changing the objectives where appropriate. The accent is therefore upon the continuous improvement of quality standards.

From the literature it may therefore be concluded that, in terms of the total quality concept, top management is required to be actively and continuously involved in guiding the quality efforts of all employees. The commitment to quality by top management is expressed in terms of a formal quality policy which is communicated to all functionaries within the enterprise, and also to vendors and customers outside the enterprise. Moreover, rather than seeking to provide a "checklist" of quality control principles (i.e. a so-called "cookbook-approach" to quality control), top

management is required to seek the active and constructive participation of all employees to continually improve their quality efforts. The positive feedforward and feedback of quality-related information, within the parameters delineated by the quality policy, is an essential component of this process of continuous improvement.

## 5.12 SUMMARY

A review of the literature relating to the total quality concept reveals a number of quality management principles which may be applied within the framework of regulatory controls pertaining to the pharmaceutical industry. It is concluded that the total quality approach may be considered to be a valuable adjunct to the current pharmaceutical regulatory control system particularly in the following areas:

(i) Defining quality and the control of quality. The total quality concept defines quality not only in technical terms (i.e. adherence to specifications), but also in terms of consumer satisfaction (i.e. the satisfaction of consumer needs). Quality is furthermore defined to include related parameters such as safety, reliability, durability and effectiveness. The total quality philosophy also views quality to be affected at every stage of the industrial cycle, not just the production stage.

The business economic approach to the quality concept presented in Section 5.3 differs in all the above respects from the approach inherent in the current regulatory control system. From the discussion of the regulatory perspective in Section 4.2 it may be concluded that this approach to quality and quality control is limited to technical aspects only, and that good manufacturing practice principles are limited by definition to the production phase of the industrial cycle.

(ii) The strategic business value of quality. Quality is today a crucial determinant for business success or failure in modern performance-orientated markets (see Section 5.2). In terms of the total quality concept, top management will resolutely pursue a quality policy aimed at maximising the benefits that may be achieved from a quality control programme. These benefits are of a strategic business nature and include the improvement of the enterprise's competitive position, increased productivity, and increased profitability.

This approach may be contrasted with the requirements of the current regulatory control system which disregards the strategic value of quality. Regulatory requirements relate exclusively to the adherence by the enterprise to certain technical aspects of quality control as a pre-condition to manufacturing and

marketing authorisation. Adherence to these requirements are therefore conditional to the enterprise gaining access to a particular market; under these circumstances, the strategic business value of quality is of a purely coincidental nature.

(iii) The conceptual evolution of quality control. The total quality concept emphasises the need for defect prevention as apposed to an emphasis on defect detection, such as that which is inherent in the current regulatory control system. Moreover, the total quality concept emphasises the organisationwide scope of quality management, whereas current good pharmaceutical manufacturing practice principles in particular are technically oriented and relate primarily to the production function only (see Section 5.6)

(iv) The leadership role of management. The evolution of quality control in the pharmaceutical industry may be said to have been largely "disaster-driven" (see Section 5.6). The commitment to quality by top management under these circumstances may consequently be expected to be dominated by considerations related to compliance with regulatory requirements, rather than a market orientation or the need for optimum resource utilisation. In terms of the total quality approach, on the other hand, it is considered necessary for top management to take the lead in the active creation of a new organisational culture of "doing the job right the first time (see Section 5.10.3).

Moreover, in terms of the total quality concept, management must actively control quality just as it controls any other function of the enterprise. This would involve the delegation of quality responsibilities and authorities throughout the enterprise while retaining the means of assuring that the results achieved match the standards required (see Section 5.4). This viewpoint contrasts with that found in the technical literature; namely that control consists of individual (not necessarily interrelated) technical functions.

(v) Formulation of quality policy. The current regulatory control system provides an incomplete framework for quality policy formulation in certain critical areas; it places emphasis only on the identification of technical quality-related problems and their physical analysis. Current GMP principles emphasise the documentation of quality policy insofar as the use of policies, procedures and instructions are concerned; however, these working documents relate mainly to tactical decision making and not to strategic quality decision making (see Section 5.9).

(vi) Organising for quality. The current regulatory control system does not specifically address the formal identification of key quality responsibilities and authorities; it only provides certain basic

guidelines in this regard. Use of a relationship chart together with the relevant MBR 1 product registration dossier and the process flow diagram of the manufacturing plant, may be a useful technique in this regard (see Section 5.10).

(vii) Integration of the quality control system into production control systems. The total quality concept forms an integral part of modern production control systems such as just in time (JIT), material requirements planning (MRP), or Synchro-MRP (see Section 5.7). Current good manufacturing practice (GMP) principles, which are considered to be the benchmark against which pharmaceutical quality control systems are to be measured, are exclusively technically oriented and consequently of limited use from a quality management perspective (see Chapter 4).

(viii) Quality cost management. The only criteria applied in the current regulatory control system relate to product safety, quality and therapeutic efficacy (see Section 3.3); the system does not focus on quality cost management. Moreover, the inspection and test approach to quality control which is inherent in current GMP principles typically emphasises expenditure on appraisal costs, rather than prevention costs, thereby ignoring the effect on the total cost of quality. The total quality concept, on the other

hand, emphasises the value of expenditure on prevention (rather than appraisal) activities in terms of the reduction of the total cost of quality. In terms of this approach quality costs are viewed to be an investment, rather than an expense (see Section 5.8)

The relevance of these aspects to the control of quality in the pharmaceutical industry were tested by means of a survey questionnaire. The results of this research are summarised in Chapter 6.

# CHAPTER SIX: THE RESEARCH METHODOLOGY, RESULTS AND CONCLUSIONS

## 6.1 GENERAL

A review of the literature reveals several quality management principles which could find general application within the pharmaceutical industry. These principles relate to a specific approach to quality and quality management; the strategic business value of quality; the leadership role of management; the formulation of quality policy; organising for quality; the integration of production and quality control systems; and quality cost management (see Chapter 5). The relevance of these quality management principles to the pharmaceutical industry was tested by means of structured interviews with individual pharmaceutical companies.

## 6.2 DEVELOPMENT OF THE QUESTIONNAIRE

A structured questionnaire was developed for use during personal interviews with randomly selected pharmaceutical companies in the Cape Province and Transvaal. Both open-ended and structured questions were used. Where necessary, prompts were included as an aid to clarifying the questions asked. The questionnaire (see Annexure 1) consists of the following sections:

### 6.2.1 A company profile

This section is designed to capture information required with a view to possible future contact with the company concerned. Data relating to ownership, organisational structure, size and product mix were captured with a view to establishing possible links between these aspects and the company's approach to quality. The company's wishes regarding the feedback of research results and the maintenance of confidentiality due to the possibly sensitive nature of data obtained during the interview, were also recorded in this section of the questionnaire.

### 6.2.2 The company's quality philosophy

This section contains six questions which are designed to test the company's approach to quality and quality management, against the background of current regulatory requirements in this regard. These questions are structured as follows:

(i) *"What is the purpose of your company's quality assurance system?"* This open-ended question is intended to determine whether the respondent would focus on technical; regulatory; and/or strategic business factors.

(ii) *"How would you define product quality?"* This open-ended question is intended to determine whether the respondent would focus on technical and regulatory aspects, or aspects relating primarily to the final consumer.

(iii) *"Who takes final responsibility for product quality in your company?"* This open-ended question is intended to test for a functional; regulatory; or total quality orientation to quality management.

(iv) *"Do you apply the same quality assurance system to registered and unregistered products?"* This structured question is aimed specifically at those companies whose product mix includes registerable products (i.e. products which by law are subject to regulatory controls) and unregistered products (such as cosmetics and health foods) which are not subject to the same controls. The question is intended to test for parallel standards in the quality control systems that are applied to registered and unregistered products, i.e. a quality commitment dictated by regulatory requirements rather than a genuine conviction on the part of top management.

(v) *"Does the scope of your quality assurance system differ from that of GMP principles?"* This structured question is intended to determine whether or not the respondent supports the viewpoint found in the technical literature that good manufacturing practice (GMP) principles represent the ultimate framework for a modern pharmaceutical quality assurance system, in terms of an organisationwide scope and in terms of the entire industrial cycle.

(vi) *"Do you see the quality improvement process as being separate from the quality control activity?"*

This structured question is intended to test the respondent's support for the business economic viewpoint that quality should be actively managed just as any other function of the enterprise (i.e. quality improvement efforts should be integrated with other organisational improvement activities), and that the quality improvement process should not be driven only by defects detected by inspection and test activities.

6.2.3 The company's quality policy

This section of the questionnaire contains seven questions which are designed to test the respondent's approach to quality policy formulation, communication, and revision. These questions are structured as follows:

(i) *"Does your company have a quality policy?"* This structured question is intended to distinguish between those companies who have a formal quality policy and those who do not.

(ii) *Is the company's quality policy statement available in writing?"* This open-ended question is intended to determine the availability and format of the company's quality policy statement.

(iii) *"Who finally approves the company's quality policy?"* This open-ended question is intended to determine the managerial level at which the company's quality policy is initiated.

(iv) *"How is your company's quality policy communicated?"* This open-ended question is intended to determine the nature of the internal and external communication routes used by management to communicate company quality policy.

(v) *"When formulating or revising your quality policy, do you identify quality-related decisions at each step of the industrial cycle?"* This open-ended question is intended to determine whether or not the company adopts a multi-functional, organisationwide approach to quality policy formulation and revision in which specific functional areas of application are identified and quality responsibilities assigned.

(vi) *"When formulating or revising your quality policy, do you identify and analyse quality-related problems that may be or have been experienced during the entire industrial cycle?"* This open-ended question is intended to test for a multi-functional approach which incorporates the entire industrial cycle and which includes a structured approach to the possible need to adapt quality policy guidelines.

(vii) *"How frequently do you revise your quality policy?"* This structured question is intended to give an indication of the company's commitment to the quality improvement process.

6.2.4 Organising for quality

This section of the questionnaire contains three questions that are designed to test the respondent's approach to creating the organisational structure needed to implement the company's quality policy. These questions are structured as follows:

(i) *"How do you identify the key organisationwide quality responsiblities and authorities in your company?"* This question is designed to test for the use of regulatory guidelines, the process flow diagram, the company organogram, or any other aspect that could possibly be used in a relationship chart to identify key organisation-wide quality responsibilities and authorities within a pharmaceutical company.

(ii) *"How are your personnel, marketing and finance departments involved in your quality assurance system?"* This question is designed to test the extent of the organisationwide integration of the quality effort.

(iii) *"What key responsibilities have been formally delegated to the quality control function in your organisation?"* This open-ended question is designed to determine the extent to which technical responsibilities; systems responsibility; and/or a business responsibility has been formally delegated to the quality control (or quality assurance) function of the enterprise.

6.2.5 Production control

This section of the questionnaire contains four questions that are designed to determine the suitability of just-in-time (JIT) and materials requirements planning (MRP) production control systems to pharmaceutical production, with specific reference to the contribution made to the assurance of product quality. These questions are structured as follows:

(i) *"Does your company apply JIT principles of production control?"* This structured question is designed to determine the compatibility of JIT principles with pharmaceutical production.

(ii) *"Do you see a connection between JIT principles and your quality assurance system?"* This open-ended question is intended to determine whether or not JIT is seen as more than just an inventory management system.

(iii) *"Does your company use an MRP system of production planning and control?"* This structured question is intended to determine the compatibility of the MRPI,II or III systems with pharmaceutical production.

(iv) *"Does the MRP system complement your quality assurance system in any way?"* This open-ended question is designed to determine whether or not the MRP system is seen as a production planning and control tool only; and in particular wether or not a degree of synergy is seen to exist between MRP and JIT by those companies who make use of both systems, with specific reference to the quality assurance effort.

6.2.6 Quality costs

This section of the questionnaire contains five questions that are designed to determine the nature and extent of quality cost management in the pharmaceutical industry. These questions are structured as follows:

(i) *"Do you measure and report quality costs?"* This structured question is intended to test for the presence of a formal quality cost measurement and reporting system.

(ii) *"What cost categories or cost elements have you defined?"* This open-ended question is designed to determine the nature of the quality cost categories used to collect

quality cost data, and in particular to determine the level of sophistication in distinguishing between quality costs and production costs.

(iii) *"Who receives the quality cost reports?"* This open-ended question is intended to determine the managerial level of involvement and organisationwide scope of the quality cost management system.

(iv) *"Who decides to take action on quality costs when this becomes necessary?"* This open-ended question is intended to determine the managerial level of involvement in the quality cost management system.

(v) *"What percentage of total sales is attributable to total quality costs in your company?"* This structured question is intended to gather empirical data concerning individual companies for possible comparison on an industry-wide basis.

## 6.3 THE RESEARCH METHODOLOGY

The Register of Pharmacies prepared by the South African Pharmacy Council (1993) was used to identify the names and addresses of pharmaceutical manufacturing facilities in South Africa. For logistical reasons, only companies

situated in the Cape Province and Transvaal were considered for the purposes of the survey. With the help of the Directorate Medicines Control and Registration of the Department of Health (van Heerden, 1994) a randomly selected list was made of companies who own their own manufacturing facilities, and who design, manufacture and distribute their own products.

A mailing list of 29 companies was thus compiled; nine of these companies are situated in the Cape Province and twenty companies in the Transvaal. A letter requesting an hour-long interview was addressed to the quality assurance manager of each of these companies, together with a reply-paid form for indicating the willingness of the company to participate in the research as well as a date and time for the proposed interview.

Twenty-two replies were received, nineteen of which were positive, two negative, and one which was positive but which arrived too late to be included in the sample. Seven companies did not respond to the request for an interview. Of the nineteen companies who indicated their willingness to participate in the research, four were situated in the Eastern Cape, four in the Western Cape, and eleven in the Transvaal. All appointments were confirmed telephonically.

Each interview was conducted according to the structured questionnaire described in Section 6.2. The prompts included in the questionnaire (see Annexure 1) were used where necessary to clarify the relevant question or to elicit a response on an aspect not covered in the repondent's reply. The entire interview was recorded on audio tape.

Each audio tape was transcribed by summarising the respondent's replies. Where prompts were used, this was indicated when noting the respondent's reply. In view of the fact that every company interviewed preferred the data gathered during the interview to be treated as confidential, the participating companies were coded alphabetically (i.e Company "A" to "S") and the different fields under each section of the questionnaire were coded numerically. Information not readily obtainable during the interview, or the release of which had first to be cleared with top management, was forwarded by post and included in the summary of results upon receipt (e.g. extracts from quality manuals).

## 6.4 THE RESEARCH RESULTS AND THEIR ANALYSIS

The following is a summary of the results obtained with the use of the survey questionnaire described in Section 6.2:

### 6.4.1 The company's approach to quality

The following aspects were researched:

#### 6.4.1.1 The purpose of the company's quality assurance system

The majority of respondents (nine) consider the purpose of their quality assurance systems to be the assurance that the finished product will conform to specifications, or will comply with regulatory or ethical requirements. However, a significant number of respondents (eight) consider the purpose of their quality assurance systems to be consumer-oriented. Terms such as consumer safety, consumer needs and fitness for use criteria were considered important in this regard. More- over, four of the latter companies see a direct link between their quality assurance systems and strategic factors such as profitability and risk management (lia- bility exposure) in particular.

#### 6.4.1.2 The definition of product quality

The majority of respondents (fourteen) defined quality in terms of a consumer-orientation. Aspects such as assuring consumer satisfaction, satisfying consumer needs, assuring consumer safety and fitness for use or conformance to specifications as judged by the consumer, were highlighted in this regard. Five of the companies who defined the purpose of their quality assurance system in technical terms (see Section 6.4.1.1), defined product quality in

terms of a consumer-orientation. Only four of the respondents defined quality in terms of a technical of regulatory orientation (e.g. conformance to specifications, as determined by the MBR1 product registration dossier).

6.4.1.3 Responsibility for product quality

One respondent stated that responsibility for product quality is vested exclusively in the company's board of directors. Nine respondents nominated specific members of their company's board of directors as being ultimately responsible for product quality; four of these nominated the chief executive officer as being the responsible person; four respondents named the managing director; and one respondent named the company medical director. Eight respondents stated that the quality assurance manager assumes responsibility for product quality, although three of these respondents saw this as being a delegated responsibility with ultimate responsibility being vested in the company board of directors, and another three respondents saw this as being the situation in practice, whereas the managing director assumes legal responsibility for product quality in terms of current legislation. One respondent vests responsibility for product quality with a "quality surveillance committee" consisting of the divisional head, the managing director, the quality assurance manager and the head of the medical division; this committee reports directly to corporate headquarters (overseas).

6.4.1.4 The application of parallel systems of quality assurance

All but five of the companies interviewed manufacture both registered products (i.e. products subject to the pharmaceutical regulatory control system), and unregistered products (i.e. products not subject to those regulatory controls). Unregistered products thus manufactured include cosmetics (nine companies); health foods and vitamins (six companies); veterinary products (four companies); medicated animal feeds (one company); and toiletries, pulp products, adhesives and woven products (one company).

Each of the companies who manufactures both registered and unregistered products, applies exactly the same quality assurance system to both types of product. In most cases specifications are, however, not as extensive as is the case with registered pharmaceutical products. Some of the reasons given for not applying parallel systems of quality control to registered and unregistered products include the need to "keep employees focussed" on a specific system; to prevent possible confusion between differing quality assurance procedures; to prevent "corruption of the standard set"; and to give the "same level of confidence" in all products produced.

6.4.1.5 The scope of the quality assurance system

Only six respondents were of the opinion that the scope of their quality assurance (QA) systems differed from that of

pharmaceutical good manufacturing practice principles (GMP). Thirteen respondents stated that there was no difference in the scope of their QA systems and GMP principles; one of these respondents stated that a QA system reinforces GMP but does not broaden its scope; others stated that the one is "part and parcel" of the other and that they differed from one another only in respect of a few minor (technical) details.

Of the six respondents who did see a difference in scope between the concepts of QA and GMP, all agreed that a QA system was broader in scope both in terms of its organisationwide purview and its application to the entire industrial cycle. Eleven of the thirteen respondents who initially equated the scope of their QA systems to GMP principles conceded that their QA systems were in fact broader in scope, once prompted. Two of these thirteen respondents would, however, not agree with the suggestion that GMP principles were limited in scope to mainly the production function only.

6.4.1.6 Management of the quality improvement process

Twelve respondents were of the opinion that the quality improvement process is indeed separate from the quality control activity; five respondents stated that this was not the case; and two respondents had no opinion in this regard. Of the above-mentioned twelve respondents who

conduct a separate quality improvement programme, four stated that top management had no involvement in the programme which was being driven at a middle management multidisciplinary (technical) level (three respondents) or at a supervisory/department head level (one respondent).

Eight of the respondents who conduct a separate quality improvement programme stated that top management was directly involved in this. This involvement came either directly from the chief executive officer or board of directors. A number of these companies gave specific names to their quality improvement programmes, such as "(Company) Team Excellence," "Green Areas," "The (Company) Way," and the "Simply Better" programme. Many of these programmes had been established with the help of outside consultants or with the help of corporate headquarters. Multinational companies, however, do not always receive such support from corporate headquarters; one (multinational) respondent stated that top (corporate) management did not always give the same status to quality as they did to other functions of the enterprise. This problem had been recognised in this particular company and is being addressed at present.

### 6.4.2 The company's quality policy

The following aspects were researched:

6.4.2.1 The existence of a quality policy

All the respondents interviewed stated that their company does have a quality policy.

6.4.2.2 The existence of a written quality policy

Thirteen of the nineteen respondents interviewed indicated that their company quality policies are available in writing. However, a number of the documents examined could better be described as mission statements, with no direct link to quality policies and procedures.

Six of the nineteen respondents interviewed indicated that their quality policies were not immediately available in writing; for the purpose of this research, these documents were considered to be unavailable as an immediate source of reference. Two of these six respondents referred to their quality policy as being based on an informal understanding amongst management.

6.4.2.3 Final approval of the company's quality policy

Sixteen of the nineteen respondents stated that their company quality policy had been finally approved by their chief executive officer and/or board of directors. Four of the multinational companies interviewed, stated that

their chief executive officer was located overseas at the corporate headquarters. One of the nineteen respondents stated that the managing director approved company quality policy without the board of directors being involved. Two of the nineteen respondents interviewed have no formal quality policy (see Section 6.4.2.2); for the purposes of this research this question was considered not to be applicable to these companies.

6.4.2.4 Communication of the company's quality policy

Seven of the nineteen respondents interviewed either do not communicate company quality policy externally or did not refer to such external communication in their response to the question (see Section 6.2.3.4). Three of the nineteen respondents stated that no deliberate attempt was being made to incorporate a quality message into advertisements and/or public relations communications. Nine of the nineteen respondents interviewed stated that they did actively communicate quality policy outside of the company through advertising and/or public relations communications; follow-up on customer surveys; guided tours of the plant; and formal vendor contact programmes.

Seventeen of the nineteen respondents interviewed stated that they do communicate their quality policy internally; most respondents mentioned verbal and written internal communications (mainly standard operating procedures), and

training programmes, as being the methods used. Formal internal communications programmes, that promote teamwork and a collective approach to quality authorities and responsibilities, were also mentioned as being methods employed in this regard. One respondent saw internal auditing programmes to be an important medium for communicating quality policy within the company, whereas two respondents referred to the display of mission statements on company noticeboards as being important in this regard.

6.4.2.5 Identifying quality-related decisions

The majority of respondents (eleven) indicated that a multifunctional approach is used to identify quality-related decisions at each step of the industrial cycle during the formulation or revision of quality policy. In one of the companies interviewed, this process would for instance involve a formal review by a technical committee composed of managers from the quality assurance; production; product development; engineering; information systems; distribution; and safety and security departments. In another company, all aspects relating to the product's industrial cycle are summarised in a "product fact file", which is then circularised to every functional department for comment and formal approval or change to the existing quality policy.

In contrast to this mainly technical approach to quality policy formulation or revision, one company stated that its entire board of directors is involved in this process. The quality assurance manager of this company is also a member of the board. The board's first step would be to determine wether or not quality objectives have changed or need to be changed; whether the organisational structure and the assignment of responsiblities have changed; verification of the resources available; the assesment of internal quality audit results; and ammendments introduced or requested by the regulatory control authorities. Moreover, the review will include the quality system in general and control procedures; third party contract reviews; a product design review; document reviews; document (change) modification; environmental controls; and equipment qualification. All (sterile) manufacturing processes are validated twice a year; any changes to be made are submitted to the board for formal approval.

6.4.2.6 Identifying and analysing quality-related problems

The respondents interviewed appeared to be better attuned to formally responding to quality-related problems than to the formal identification of quality-related decisions during the entire industrial cycle. Fifteen of the nineteen respondents stated that quality-related problems were reviewed by means of a structured multifunctional system, whereas eleven respondents indicated that such an approach

was used to identify quality-related decisions (see Section 6.4.2.5). Two companies stated that they have no formal guidelines for analysing quality-related problems, but relied instead on personal experience and regulatory guidelines in this regard.

The multifunctional approaches encountered varied from a mainly technical (production) emphasis to more broadly-based (organisationwide) committees. In some companies the relevant failure costs are calculated and reported (see Section 6.4.5.1). One company mentioned that it relied heavily on a very comprehensive system of product history documentation when analysing quality-related problems; such product history files consist of a record of the prototype work, including laboratory and pilot-scale production; the process validation protocol; equipment qualification protocols; product stability trials; transportation and packaging trials, product complaints, and all other relevant data. These data are documented per product, and are used when analysing problems or designing new products of a similar design.

### 6.4.2.7 Quality policy revision intervals

Four respondents stated that their company quality policy is revised at least once a year. The majority of respondents (eleven) stated that they revise their quality policies on an ongoing basis; two of these companies

stated that this would be done at least once in three years, while another one of these companies set the limit for revision at two years. One respondent stated that the policy review process would be triggered by regulatory requirements (e.g. updating of the MBR1 dossier) or by problems being experienced.

### 6.4.3 The company's organisational approach to quality

The following aspects were researched:

#### 6.4.3.1 Identification of quality responsibilities and authorities

Four respondents mentioned regulatory guidelines (in particular the MBR1 registration dossier) as playing an important role in the identification of organisationwide quality authorities and responsibilities. One of these respondents views the MBR1 dossier (see section 3.6) as being the starting point. This particular company then uses the guidelines provided by the ISO 9000 system to identify and analyse key organisationwide areas of quality responsibilities and authorities throughout the entire industrial cycle, by making use of aids such as a comprehensive organogram (including detailed job descriptions) and process flow charts.

Three respondents use the company organogram as the primary source for identifying organisationwide quality

responsibilities and authorities. Two respondents view the process flow chart as being a primary aid in this regard, in combination with the company organogram. One respondent views the "professionalism" of the pharmacist who is in direct control of all critical areas relating to quality, as being the single most important aspect in this regard.

When prompted, most respondents agreed that a product MBR1 dossier and process flow chart, together with the company organogram, could be used to identify the relevant organisationwide quality authorities and responsibilities. One respondent made the interesting remark that instead of targeting specific key areas in this regard, his company prefers to adopt an approach which is based on a shared (organisationwide) responsibility for quality.

Most of the respondents view the MBR1 dossier as being a valuable guideline regarding (the technical aspects of) quality assurance. Two respondents, however, pointed out that changes sometimes have to be made to the specifications contained in the MBR1 dossier as part of the quality improvement process, and that the regulatory control system is often too slow and cumbersome to allow those changes to be implemented timeously thereby limiting the value of the MBR1 dossier as a quality management tool. Certain changes to the MBR1 dossier may only be made with the prior approval of the Medicines Control Council (MCC, 1988, Circular to applicants ref. 13/88).

These repondents felt that "professional decisions" should be given more freedom and authority in this regard.

6.4.3.2 Multifunctional involvement in the quality assurance system

Nine of the nineteen respondents stated that their personnel; marketing; and finance functions were not formally involved in the formulation of quality policy. In those companies where multifunctional participation in problem solving and decision making does occur, it was found that such involvement was in most cases triggered by specific quality problems on an *ad hoc* basis.

Three of the nineteen respondents interviewed stated that the organisationwide integration of their company's quality effort occurs at board level. Six other respondents referred to an organisationwide, multi-disciplinary approach to quality problem solving, decision making and policy formulation. Many different approaches were encountered in this regard, including the following:

(i) The use of a multidisciplinary "project team"

(ii) Formal, scheduled management meetings to discuss the results of internal quality audits and customer complaints for instance, and to recommend quality policy changes where necessary.

(iii) Emphasis on multifunctional teamwork and multiskilled training as part of creating a new quality "culture" within the company aimed at achieving "world class supplier" status.

(iv) A quality policy which refers to specific quality objectives for every individual functional department and all levels of management, as well as documented routines for the inter-functional co-ordination of activities which influence quality.

(v) In terms of the management responsibilities identified with the aid of the ISO 9000 system, key responsibilities and detailed job descriptions are detailed in an organogram which depicts the formal integration of organisationwide quality responsibilities and authorities.

6.4.3.3 <u>The key responsibilities of the quality control function</u>

All of the respondents interviewed referred to the technical (inspection and test) responsibilities of their quality control function. With reference to a systems responsibility, the quality control function is seen by most respondents to play an important role in personnel training and internal auditing programmes. External audits involving vendors; the reciprocal auditing of different plants within the same organisation; and process validation programmes are also seen as being part of the routine systems responsibility of the quality control

function by most respondents. One quality assurance manager stated that he has no boundaries in terms of his involvement with quality issues within the organisation, and that he routinely participates as a member of a multi-functional team in this regard.

Most respondents referred to the business responsibility of the quality control function only after having been prompted in that regard. Many respondents stated that this is an implied or informally delegated responsibility. Five respondents referred to management control systems that are used to directly or indirectly evaluate the performance of the quality control function in this regard; these include:

(i) Asset management performance measurement (return on investment).
(ii) Reduction in wastage due to quality-related problems.
(iii) Achieving throughput targets (in terms of approved product output).
(iv) A monthly productivity report.
(v) Achieving targeted operating quality costs.
(vi) Cost deviation reports.

Only one respondent referred to quality as a method of achieving a competitive advantage.

### 6.4.4 The integration of quality control and production control systems

The following aspects were researched:

6.4.4.1 The application of JIT principles of production control

Fourteen of the nineteen respondents stated that they do apply just-in-time (JIT) principles; however, most of these respondents stated that these principles are applied "selectively" in order to cope with the variable lead times associated with the importation of a large percentage (70 per cent in one case) of starting materials from overseas. Another problem mentioned was that of the unpredictable ordering patterns of stock by large consumers such as government departments, which necessitates keeping buffer stocks of (sometimes strategic) finished products or raw materials. The very large minimum order quantities imposed by certain local vendors also presents a problem to some respondents, whereas one respondent stated that their company has been particularly successful in implementing a JIT programme in partnership with local vendors.

The majority of those respondents who do apply JIT principles of production control, do so in all manufacturing departments. These respondents manufacture a wide range of products, including sterile liquids and semi-solids; all non-sterile dosage forms; products containing potentially toxic or hazardous materials such as hormones, penicillins and cephalosporins; and products which are unregistered and therefore not subject to the medicines regulatory control system.

None of the five respondents who do not apply JIT production control principles cited problems with a highly variable master schedule as being the reason for this. Problems with variable lead times of imported materials, and the unreliability, as well as the very large minimum order quantities of certain local suppliers, were cited as being the main reasons for them not applying JIT principles. Of those respondents who do apply JIT principles, the majority considered their variable master schedule not to be a problem.

One respondent mentioned that the first five days of that company's production schedule is "set in concrete"; the next five days are however negotiable and it is during this period that unforseen changes will be accommodated. Another respondent stated that the design of highly flexible production lines, which allows items of equipment to be removed from the line and replaced as complete units, enables that company (a manufacturer of small volume parenteral products) to react to a change in master production schedule within 24 hours.

6.4.4.2 The benefits of JIT production control

Seven of the nineteen respondents either do not apply JIT principles or do not see a connection between JIT and their quality assurance system. Four of these respondents stated that the main purpose of JIT is to reduce inventory levels.

Twelve of the nineteen respondents do see JIT as contributing to their quality assurance systems. Most respondents (seven) referred to the contribution made by JIT to the creation of a "right first time" culture of continuous improvement within the organisation. One respondent stated that his company measures the success of their JIT system in terms of work order delivery rate (i.e the time elapsed between commencement of production and delivery of the finished product). At the time of the interview this company was operating at above 98 per cent of the forecasted work order delivery rate.

The contribution made by the JIT system towards improving vendor relations and vendor contact was referred to by four respondents. The motivation of vendors to aspire to higher levels of quality, and the shifting of inspection and test activities from the purchaser to the supplier, are aspects that were highlighted in this regard.

The rapid feedback and response to quality problems facilitated by a JIT system were mentioned by three respondents. The fact that a JIT system regulates production at a predetermined workrate which in turn takes the pressure off the inspection and test functions of the quality assurance system, was referred to by three respondents. All those respondents who were prompted, agreed that JIT principles contribute to improved production capacity and production reliability as well as all the aspects mentioned above.

6.4.4.3 The use of MRP systems for production planning and control

Seventeen of the nineteen respondents interviewed stated that they employ MRPII systems for production planning and control, or equivalent systems (which provide for a feedback loop between orders and the master production schedule). The two smallest companies interviewed (with an annual turnover below R20 million) do not operate such a system.

6.4.4.4 The benefits of MRP production planning and control

Most respondents (eight) referred to the discipline imposed by their MRP system as being its main contribution to the quality assurance system. It is felt, in particular, that the system ensures that quality is not compromised due to a rushed production schedule.

One respondent highlighted the fact that this discipline results from the fact that the system demands (right first time) compliance, and that it does not allow anybody to work outside that system. It should be noted that this particular company operates its MRP system on a "realtime" basis, and does not follow the practice of "backflushing" or batch processing of data, thereby enhancing the discipline inherent in the system.

The role of an MRP system in the tracking of materials and yields were referred to by two respondents. One respondent also saw it as an aid to the rapid identification of quality problems. All but one of the respondent's, when prompted, were of the opinion that there is a synergy between their MRP and JIT systems.

Three respondents viewed their MRP system as being primarily a production planning tool which has no direct influence on their quality assurance system; when prompted, one of these respondents did however refer to the fact that MRP does assist the company's quality assurance discipline.

When prompted about the criticism that the MRP system tolerates a degree of waste (contrary to the objectives of a quality assurance system), two respondents made the interesting remark that this depended on the standards designed into the system by the user himself. Taking production yield as an example, a zero-based standard would require a 100% yield. The system does however allow the user to set a budgeted yield of, say 85%, to allow for the unavoidable loss of product as a result of the flushing of transfer lines for instance, thus enabling the attainment of a 100% theoretical yield while in practice allowing for a 15% "wastage".

### 6.4.5 Quality cost management

The following aspects were researched:

#### 6.4.5.1 The measurement and reporting of quality costs

Thirteen of the nineteen respondents interviewed stated that they do measure quality costs. One of these companies, which has an annual turnover of approximately R27 million, stated that this reporting system had been installed only very recently. Most companies report on quality costs on a monthly basis; some generate a quarterly trend analysis or a weekly deviation report, in addition to the monthly report.

Six of the nineteen respondents interviewed stated that they either do not measure and report quality costs, or do so on an informal basis only. Those companies using an informal system would do so as part of the monthly production report or as part of the routine accounting system.

#### 6.4.5.2 Defining quality cost categories

A wide variety of quality cost categories was encountered during the research. Most respondents (twelve) measure the cost of waste, which includes both internal and external failure costs (one company measures internal

failure costs only). Examples given include scrap, the cost of rework and unplanned line stoppages or machine downtime.

Nine respondents consider the cost of product yield variation (i.e. the difference between actual and budgeted or theoretical product yield) to be part of their quality costs. One respondent defines a quality cost as being the cost of anything which does not meet the relevant standard set by the company i.e. the cost of non-conformance; this company has found the "classical" method of quality cost classification as suggested by Feigenbaum (1986, pp. 110-112), to be "cumbersome" and to offer no advantage in terms of the information provided to management. Three respondents to however apply the "classical" system of quality cost measurement (see Section 6.4.5.5).

One company expresses quality costs as being the difference between the budgeted and actual costs for each cost category, calculated per production department. The "saving" on internal failure costs is for instance calculated as being the difference between actual and budgeted costs, based on historical data. Similarly, the "saving" on quality assurance department overheads (which is considered to be a quality cost) is expressed as being the difference between actual and budgeted expenditure.

A considerable divergence of opinion was also encountered regarding the distinction between quality costs and production costs. One company for instance considers the cost of both rework and internal scrap to be production costs. Another company is of the opinion that all (quality) costs should be considered to be production costs. A surprisingly large number of respondents (eleven) view the overhead expenses of their quality assurance departments as being a quality cost.

6.4.5.3 The recipients of quality cost reports

The majority of respondents stated that company quality cost reports are submitted to the board of directors or top management (usually the chief executive officer). Some companies "filter" the quality cost report through technical/functional management first; in one company, for instance, departmental heads report to the quality assurance manager who then submits the report to the chief executive officer. In another company, the quality cost report (which in this case focusses on issues such as internal/external failures, yield variation and the operating costs of the quality assurance function) is discussed during a weekly meeting between the chief executive officer, the plant manager, the quality assurance manager, and the purchasing manager. In yet another company, quality cost data are discussed at a

technical committee meeting and also at a factory management meeting. The financial director, who prepares the formal report which is submitted to top management, is a member of the latter committee.

The technical director (or operations manager) also features prominently in the reporting structures of some companies. One company for instance measures "quality costs", but reports only "excessive" yield variation data to the technical director.

6.4.5.4 Taking action regarding quality costs

Most of the respondents stated that the company's board of directors or chief executive officer would decide wether or not to take action on quality costs. Technical personnel, however, feature strongly in this decision making process; one company for instance stated that either the technical manager or the chief executive officer would make the decision, depending on the seriousness of the problem at hand. Another company stated that the decision would be made by the managing director, the factory manager, and the quality assurance manager without the board of directors itself being involved.

6.4.5.5 Quality costs as a percentage of sales

Five of the nineteen respondents interviewed had no quality cost data at their disposal; another four re-

spondents had only estimated figures available; and one respondent would not disclose these data for reasons of confidentiality.

Due to the widely divergent cost categories and methods of measurement used by those respondents who do measure quality costs, it is not possible to make direct comparisons between the results obtained by each company. However, it may be deduced from the results obtained that some companies have better control over their quality costs than others. One company for instance calculates its current (total) operating quality costs to be 0,25 per cent of sales, and has set itself the objective of reducing this figure to 0,1 per cent (calculated as the total cost of non-conformance).

Another company reports "internal failure" costs of 0,25 per cent and "external failure" costs of 0,04 per cent, but these cost categories are again vaguely defined in that "external failure" costs are for instance calculated to include only goods returned to the plant due to damage in transit or despatch errors. This company also includes product yield variation in its figure of 0,25 per cent "internal failure" costs, whereas a number of companies estimate loss on yield alone to be as high as 15 to 20 per cent of sales. Moreover, this company includes the total overhead costs of its quality assurance function in the figure for "internal failure" costs, whereas another company puts this figure alone at 17,3 per cent of sales.

The above-mentioned figures of 0,25 per cent and 0,04 per cent therefore appear to be abnormally low, especially in view of the fact that the comparative figures were supplied by companies engaged in the manufacture of a similar range of products. It is therefore not possible to make an empirically-based conclusion in this regard, other than to state that some companies are either more accurate in the measurement of quality costs, or more successful in their management of quality costs, than others.

Three companies (company "I", company "M", and company "S") were found to have employed the "classical" system of quality cost determination i.e. the determination of the cost of control and the cost of failure to control. However, in the case of company "I" these data had been collected for a period of four months only, the system having been introduced by the company that recently. In the case of company "M", the figures quoted had been based on a once-off survey based on historical data. The figures relating to company "S" are considered to be the most accurate of these three companies. These figures are as follows:

| | Company "I" | "M" | "S" |
|---|---|---|---|
| Failure costs; internal: | 2,5% } | 3,6% } | 1,7% |
| Failure costs; external: | 1,0% } | } | |
| Prevention costs: | 2% | 1,7% | 0,2% |
| Appraisal costs: | 6% | 2,8% | 3,2% |
| Total as a percentage of sales | 11,5 | 8,1 | 5,1 |

With reference to the composition of company "S's" (total) operating quality costs, it is noted that internal/external failure costs comprise 33,3 per cent of the total; appraisal costs 63,3 per cent; and prevention costs 3,4 per cent.

## 6.5 THE HYPOTHESES REVIEWED

The following hypotheses were developed from the literature, and from personal observation.

6.5.1 The existing system of regulatory control will be enhanced by a quality management approach to the problem of assuring the quality of pharmaceutical products.

6.5.2 The establishment of a total quality system will result in an operations management system superior to that provided by the good manufacturing practice principles currently in use.

6.5.3 Quality management principles may be used to develop a structured approach to the problem of delegating quality authorities and responsibilities within the pharmaceutical industry.

6.5.4 There is a need for more accurate quality cost data in the pharmaceutical industry.

## 6.6 THE FINDINGS REVIEWED

The survey questionnaire which is described in Section 6.2 was used to test the practical value of a total quality system in the context of the pharmaceutical industry, with reference to the following aspects in particular.

### 6.6.1 The quality philosophy and its strategic implications

The traditional quality culture in the pharmaceutical industry is driven by the regulatory process of product registration or marketing authorisation (see Chapter 3), and the so-called Good Manufacturing Practice (GMP) principles on which regulatory manufacturing authorisation is based (see Chapter 4). In terms of this traditional approach, quality is defined with reference to products that meet registration and compendial specifications and are produced according to currently accepted GMP principles (Kieffer & Nally, 1991, p.131).

The traditional approach to quality and quality management may therefore be expected to emphasise issues relating to the production function, and also the quality of product design. This is confirmed by the narrow scope of GMP principles which by definition focus on the production function (see Section 4.2.2), and the emphasis placed on issues such as product safety and therapeutic efficacy by the product registration process. Pharmaceutical product

quality may consequently be expected to be viewed from a mainly technical perspective. Moreover, the industry's approach to quality management may be expected to be determined by regulatory guidelines, particularly in view of the legal or *quasi*-legal status of those guidelines (see Section 4.5).

The finding that the majority of respondents interviewed consider the purpose of their quality assurance system to be the assurance that the finished product will conform to specifications (see Section 6.4.1.1), is consistent with this traditional approach to quality in the pharmaceutical industry. Similarly, the finding that the majority of respondents interviewed saw no difference between the scope of their quality assurance systems and GMP principles (see Section 6.4.1.5) is consistent with this traditional approach. The finding that strategies for the external communication of quality policy are relatively underdeveloped (see Section 6.4.2.4) may also be related to a lack of appreciation of the strategic business value of quality, in accordance with the traditional (technically-oriented) approach to quality.

It is, however, now being recognised even in the technical literature that good pharmaceutical manufacturing practice is attained only when technical expertise is combined with the necessary management skills (see Begg, 1984, pp. 31-32). Moreover, the strategic business value of quality is now also being recognised in the technical literature.

Kieffer & Nally (loc. cit., p. 131) for instance highlight the pharmaceutical industry's current environment of global competition, rising health care costs, customer demand for better products and services, and the changing expectations of employees. They then point to the benefits of adopting a total quality philosophy in terms of enhanced customer satisfaction, better products and services, improved productivity, increased profits, and the achievement of a competitive advantage.

This fundamental shift away from the traditional, purely technical, approach to quality is reflected in some of the results obtained during this research. For instance, a significant number of respondents interviewed consider the purpose of their quality assurance systems to be consumer-oriented, and some of these respondents see a direct link between their quality assurance systems and strategic business factors such as profitability and risk management in particular (see Section 6.4.1.1). Moreover, the majority of respondents defined quality in terms of a customer-orientation, while only four out of nineteen respondents defined quality purely in terms of a technical or regulatory orientation (see Section 6.4.1.2). The majority of respondents were also of the opinion that the quality improvement process is separate from the quality control activity, and a number of companies were found to have implemented high profile in-house programmes in this regard (see Section 6.4.1.6). All those companies who manufacture both registered and unregistered products were

found to apply the same quality assurance system to all products as that which is required in terms of the regulatory controls pertaining to (registered) pharmaceutical products (see Section 6.4.1.4). This is seen as another example of the current philosophical shift away from the traditional approach to quality and quality management in the pharmaceutical industry.

### 6.6.2 Quality policy and the leadership role of management

The majority of respondents stated that their company quality policies were available in writing and are revised on an ongoing basis. In some cases it was however difficult to establish a direct link between the policy document and quality objectives and procedures; particularly in cases where the policy document took the form of a so-called "mission statement" (see Sections 6.4.2.1, 6.4.2.2 and 6.4.2.7). In these companies, and also in those companies who do not have a written quality policy, no clear delineation of quality objectives exists. The leadership role of top management is thus only vaguely defined.

Many companies were found to rely on written standard operating procedures and job descriptions to communicate quality policy internally. In cases where this communications system is based on pharmaceutical good manufacturing practice (GMP) principles, the effective feedforward and feedback of quality information may be a problem.

This is related to the fact that the working documents which are created in terms of GMP requirements, relate mainly to tactical (i.e day-to-day) decision making rather than to strategic quality decision making (see Section 5.9). This may for instance explain why many of the quality assurance managers interviewed cited technical, rather than strategic, aspects as being the rationale for their company's quality assurance system (see Section 6.4.1.1.). The strategic business elements of a company's quality policy may thus be overshadowed by technical considerations related to GMP compliance.

Reference is made in Section 6.4.1.6 to a number of quality improvement programmes encountered amongst the companies researched. This would serve to indicate an awareness within the pharmaceutical industry of the need for top management to initiate such programmes. Moreover, these programmes are characterised by a high degree of employee involvement; the "Green Areas" programme of one company for instance involves daily discussions by a workteam of issues relating to quality, safety, equipment and housekeeping. Suggestions for improvements in any of these areas are formally recorded and followed up with the active involvement of senior and top management. Careful planning of employee education in areas such as the dynamics of the modern enterprise, and the development of inter-personal communications skills, preceded the introduction of the "Green Areas" programme in this company.

This company's programme is however at present applied in selected functional areas only; namely the shop floor, purchasing department, planning department, and distribution department.

One of the companies interviewed during the research mentioned that their attempt at introducing the "Green Areas" concept had met with a great deal of resistance from certain shop floor personnel. These employees saw the scheme as being an imposition by management, rather than an attempt at obtaining their constructive involvement. This experience would seem to suggest that careful planning and appropriate training is required before introducing the "Green Areas" concept, and that it should certainly not be seen by management to be a "quick-fix" method of achieving a commitment to continuous quality improvement. The development of interpersonal communication skills, and an appreciation for the strategic business value of quality are seen to be important prerequisites in this regard; but the key to the sucess of such a programme appears to lie in effective planning, a sustained involvement, and a genuine commitment on the part of top management.

Another company which participated in the research bases its quality organisational structure on five broad principles: (i) Leadership; which is defined with reference to management's responsibility for giving direction and providing employees with the necessary information,

training, resources and authority, and for employees themselves to demonstrate leadership by finding better ways to do their work. (ii) Total involvement; which refers to the organisationwide involvement of everybody in quality improvement activities and a shared responsibility for quality. (iii) Customer focus; which refers to the goal of meeting or exceeding customer requirements, including those of internal customers. (iv) Measurement; which refers to the need for monitoring quality performance as compared to stated quality goals. (v) Continuous improvement; with specific reference to prevention and innovation activities. Top management sees this programme as providing a "values-based" approach to each task performed in that the entire programme is based on the core values of people (customer/employee), integrity, and excellence. Top management also actively communicates the programme as providing the "tools and processes" needed to support the company's business strategies; in other words, the strategic business value of the programme is accentuated.

Deming, quoted by Greenwood (1988, pp. 36-37), warns that slogans and exhortations serve only to frustrate workers. He notes that most problems originate from within the management system itself and that management requires the help of the workers to improve this system. The elimination of empty slogans, and the frustration which it causes, is consequently considered to be one of top

management's "system obligations". One of the companies interviewed during this research feels so strongly about this particular aspect that it cites this as being the reason for the company not having a written quality policy at all. Not having a clearly delineated quality policy to guide decision making at all levels within the organisation may however result in precisely those frustrations and inefficiencies which this company is attempting to avoid.

Of the nineteen companies who participated in this research, one stands out as having the most clearly articulated quality policy and quality management system. This company's quality policy consists of a short three-paragraph written statement by the chief executive officer in which he formally commits the company to a policy of total quality management; formally delegates responsibility for its implementation (to a particular plant manager on this case); and states the quality policy objective to be the assurance that all goods and services supplied by the company will meet the critical performance criteria set out in the company's "mission", "values" and "objectives".

This company's "mission" is stated as striving to be a leading South African pharmaceutical company in terms of both volume and value growth; and to market, produce and distribute quality products to the health care professions. The mission statement furthermore declares that these objectives will be achieved firstly by producing

high quality cost effective medicines which shall be made available to the entire population of South Africa; and secondly, by virtue of the efforts of competent employees who are encouraged to continually improve their work knowledge, skills and performance through "free and open communication, training, self discipline and being completely committed to living the company's values and achieving the company's quality objectives".

This company furthermore formally relates its competitive strategy to the following core values:

(i) A customer orientation; i.e. striving to provide products and services of superior quality and value in order to meet the expectations of internal and external customers.

(ii) A commitment to innovation; i.e. encouraging employees to continually strive to be creative and innovative in order to produce new and better quality ideas for improved organisationwide performance.

(iii) The maintenance of personal and corporate integrity; i.e. conduct based on openness and honesty in order to engender trust and be able to pass the test of public and internal scrutiny at all times.

(iv) Teamwork; i.e. the value of teamwork and open communication in enabling employees to work together as partners in pursuit of the company's "mission", "values" and business strategy.

(v) A performance orientation; i.e. a focus on results achieved, and continuous improvement in organisationwide activities. Top management has also introduced a formal programme of continuous improvement which is based on

these core values. This "Simply Better" programme of continuous improvement includes guidelines for putting into practice the above-mentioned values, and for setting an example for others to follow.

The "objectives" referred to in this company's quality policy are summarised as follows:

(i) To provide high quality products and services to satisfy all internal and external customers.

(ii) To encourage and maintain a high level of quality awareness amongst all employees.

(iii) To continually improve and monitor operating competency.

These broadly-stated objectives are supplemented by specific quality objectives for a particular twelve-month period. For example, the quality objectives for 1994 include the reduction of total failure costs by a specified percentage as compared to the average monthly total failure costs for 1993. Similar objectives have been set for the current year in the areas of quality awareness and improved operating competency.

A predominantly technical approach to the identification of quality-related decisions was however encountered amongst some of the companies who participated in the research (see Section 6.4.2.5). Moreover, most of these companies were found to be better attuned to the identification and analysis of quality-related problems than they were regarding quality-related decisions (see

Section 6.4.2.6). This is seen to be the result of technically-orientated regulatory demands in this regard, rather than as part of a structured approach to quality policy formulation.

### 6.6.3 Organising for quality

It was found that the relevant MBR1 registration dossier; the company organogram and job descriptions; and the relevant process flow-chart are used to a greater or lesser extent by most companies as a management tool for the identification of organisationwide quality authorities and responsibilities. The MBR1 dossier was highlighted by some respondents as being a valuable guideline regarding the technical aspects of quality assurance in particular.

The opinion was expressed that delays caused by the regulatory requirement of first having to obtain the formal approval of the Medicines Control Council to make certain changes to the MBR1 dossier, limits the practical value of the MBR1 dossier in this regard (see section 6.4.3.1). This criticism is accepted with some reservation. Annexure 16 of the MBR1 dossier requires a summary of experimental data from which final product specifications, analytical methods, manufacturing procedures, the product stability profile, and pharmaceutical and bioavailability characteristics are derived (see section 3.6.2.5). The requirement is therefore for a thoroughly structured series of new design control activities which, if performed properly, should yield a

product and manufacturing processes that are unlikely to require major adjustment at a later stage. This approach by the regulatory authorities in fact underscores the total quality principle that the assurance of customer quality satisfaction must begin during new product design and development (see Feigenbaum, *loc. cit.*, p. 617). Moreover, a thorough approach to machine qualification and process validation to determine the process variables and acceptable limits for those variables, is now accepted even in the technical literature as being fundamental to pharmaceutical manufacture (see Nally & Kieffer, 1993, pp. 25-30). Provided the pharmaceutical development of the product (as summarised under Annexure 16 of the MBR1 dossier) is conducted in accordance with the above-mentioned principles, the MBR1 dossier could therefore be considered to be a valuable aid in identifying the technical aspects of organisationwide quality responsibilities and authorities.

Quality problems transcend individual functional organisational boundaries within companies (Feigenbaum, *loc. cit.*, p. 150). Multifunctional participation in quality problem solving and decision making is therefore a fundamental requirement for the organisationwide integration of the quality effort. Many of the companies interviewed during the research either have no formal multifunctional involvement in their quality assurance system, or adopt an *ad hoc* approach to such involvement (see Section 6.4.3.2). Feigenbaum (*ibid.*, pp. 150-152)

draws attention to the fact than more than 80 per cent of fundamental quality problems requiring improvement today are outside the scope of traditional quality control departments. It may therefore be predicted that many of the abovementioned companies might have difficulty in effectively responding to quality problems and in achieving sustained improvement in quality.

It was found that most respondents view the key responsibilities of the quality control function in terms of technical and systems responsibilities (see Section 6.4.3.3). This is consistent with the traditional quality culture in the pharmaceutical industry. Reference is however made in Section 6.6.1 to the finding that many respondents adopt a consumer-orientation to quality; recognise the need to actively manage the quality improvement process; apply a unitary system of quality assurance to all products, wether they be subject to regulatory control or not; and display an understanding the relationship between product quality and strategic business factors such as profitability and risk management. It may therefore be concluded that a business responsibility has in fact been delegated by top management to the quality assurance functions of the companies researched, but that this responsibility has in many cases been delegated informally.

Details relating to the organisational structure of fourteen pharmaceutical manufacturing companies were obtained

during the research. In all of the companies researched the quality assurance manager either reports directly to a member of the board, or is himself a member of the board of directors. This organisational structure would suggest that quality is managed in the same way as major functions such as finance, marketing, human resources, public relations and production. A more detailed examination of these organisational structures however shows that this is not necessarily the case.

The quality assurance manager is often placed at the same managerial level as the managers of the production planning, engineering, logistics, technical training, distribution and loss control departments for instance. These functionaries would typically report to a technical or operations director, who is a board member. It is also quite common for the quality assurance manager to have a "dotted line" link with the chief executive officer of the company which enables him to communicate directly with top management on matters regarding product quality. In some of the multinational companies, this structure extends up to corporate headquarters (overseas), thereby providing the quality assurance manager with a direct link with top management in the event of a possible internal dispute over a quality issue.

Reference is made in Chapter 4 of the functions that have to be performed by a quality assurance manager in terms of current pharmaceutical GMP principles (see Section 4.6.2).

One of the basic tenets in this regard is that the quality assurance manager should function independently from the production manager. Moreover, in terms of the provisions of section 22 read with section 29 of the Pharmacy Act (South Africa, 1974) a pharmacist, who is the managing director of the company, shall assume legal responsibility for product quality. With reference to the organisational structure of most of the companies included in this research, it was found that a significant number of companies conduct quality problem solving, decision making and quality policy formulation activities at a technical level (see Section 6.4.3.2). It would appear that the position of the quality assurance manager in the organisational hierarchy may be determined by current regulatory requirements rather than a conviction that quality is a strategic business function within the modern enterprise.

### 6.6.4 Quality and production control systems

Most of the respondents who do apply JIT principles of production control stated that they do so on a "selective" basis, due to problems experienced with the variable lead times of materials sourced from overseas suppliers and the unpredictable ordering patterns of certain large (public sector) consumers in particular (see Section 6.4.4.1). This may be interpreted to mean that these respondents view JIT as being synonymous with zero inventories and pull

production, rather than being a philosophy based on the principles of continuous improvement and the elimination of any activity which does not add value to the product (see Ray, 1990, pp. 179-180). Most of the respondents see JIT as contributing positively to their quality assurance systems and in particular to the creation of a "right first time" culture within the organisation (see Section 6.4.4.2). The results obtained during the research however point to a predisposition within the pharmaceutical industry towards viewing JIT more as an inventory management tool than as the core component of manufacturing excellence (see Ray, *ibid.*, p. 180).

This viewpoint may change under the increasing pressures of cost constraints brought to bear on the industry through the introduction of generic substitution and other macro-environmental factors (see Section 2.2.2). The reference that was made by four respondents to the role played by JIT in improving vendor relations and vendor contact is considered to be particularly significant in this regard (see Section 6.4.4.2). Ray (*ibid.*, pp. 187-188) refers to the extension of the concepts of manufacturing excellence to vendors and their own vendors, and states that in the ideal JIT environment vendors deliver directly to the production line. From the research results obtained, it appears that there is already a movement towards this goal in the pharmaceutical industry; this would herald the need for a fundamental change in the approach to incoming material control by the regulatory authorities.

The research showed that JIT principles are currently being applied in the manufacture of a wide range of pharmaceutical and related products (see Section 6.4.4.1). It may therefore be concluded that JIT production control principles are universally compatible with pharmaceutical production. Most of the respondents interviewed either did not refer to problems with the highly variable master production schedules normally associated with pharmaceutical production, or did not state this to be the rationale for them not using JIT principles of production control (see Section 6.4.4.1).

The MRP II system of production planning and control, which plans and controls inventories and production capacities via a feedback loop between orders and the production master schedule, was found to be used by most of the companies who participated in the research. Only two companies, with an annual turnover of less than R20 million, were found not to operate this sytem (see Section 6.4.4.3).

The ability of the MRP system to ensure a planned workload on the quality assurance laboratory in particular was mentioned by most respondents as being the most important contribution to their quality assurance systems (see Section 6.4.4.4). This would for instance result in incoming material controls, in-process controls and finished product release controls being conducted timeously and without the integrity of the system being compromised due to a rushed production schedule.

The majority of respondents prompted in this regard agree with the viewpoint of Boccard (1990, pp. 39-40); namely that MRP may be viewed as the planning half, and JIT as the execution half, of a production control system which incorporates both MRP and JIT principles. Moreover, when asked about the criticism put forward by Schroeder (1985, p. 485) concerning the ability of the MRP system to tolerate a degree of waste (and hence bad quality), two respondents highlighted the fact that this depended on the standards designed into the system by the user himself (see Section 6.4.4.4). Based on these responses it is concluded that a Synchro-MRP system, as described by Esparragio (1988, pp. 9-10) may be adapted for use in the pharmaceutical industry.

### 6.6.5 Quality cost management

Most of the companies surveyed do measure and report quality costs (see Section 6.4.5.1). This would appear to indicate a general acceptance within the pharmaceutical industry of the value of quality cost management. The wide variety of quality cost categories encountered during the research, and the divergence of opinion that was found to exist regarding the distinction between quality costs and production costs, does however bring into question the level of sophistication of quality cost management in the industry (see Section 6.4.5.2). The majority of respondents stated that quality cost reports are submitted to top management (see Section 6.4.5.3) who then also decide upon what action to take when necessary (see Section 6.4.5.4).

The individual cost categories and combination of cost categories used by most of the companies surveyed is however of such a nature that the value to management of the resultant quality cost data is extremely limited.

The majority of companies surveyed measure internal and external failure costs only. The difficulties encountered with the "classical" prevention-appraisal-failure categorisation of quality costs in the pharmaceutical industry appear to confirm the limitations of this approach, as highlighted by Plunkett & Dale (1990, pp. 165-168). They are of the opinion that the need to identify and measure quality costs across a wider spectrum of company activities has exposed the following limitations in this approach: (i) These quality cost categories do not match well with the cost information most commonly available from accounting systems. (ii) Many grey areas exist regarding quality-related activities, making cost categories difficult. (iii) It often happens in practice that cost categorisation takes place after data collection in accordance with the "received wisdom" on the topic. (iv) This categorisation seems to be of interest only to quality department personnel. (v) It is not an appropriate categorisation for the most common uses of quality cost information; hence companies tend to devise their own elements to suit their own situation or industry. According to Plunkett & Dale (*ibid.*, p. 167), the use of a broader categorisation which measures only the cost of conformance and the cost of non- conformance is gaining favour as an alternative approach to quality cost measurement.

Based on the results obtained during this research, the alternative approach referred to by Plunkett & Dale (*supra*) is accepted with reservation. Firstly, this approach is essentially based on the same broad categorisation of principal operating costs as that which is used by Feigenbaum (*loc. cit.*, pp. 110-112) to develop the "classical" prevention-appraisal-failure method of categorisation, namely the cost of control (i.e. cost of conformance) and the cost of failure of control (i.e. cost of non-conformance). A major problem identified during this research is the inability of companies to distinguish between that which is a quality cost and that which is a production cost (see Section 6.4.5.2). Plunkett & Dale (*loc. cit.*, p. 167) state that the alternative approach in practice requires departments within the company to "identify key-result processes" against which to measure their performance and costs. This approach is not seen as providing a solution to the above-mentioned problem of cost categorisation encountered within the pharmaceutical industry.

Another important criticism of the alternative approach to cost categorisation relates exactly to that which is seen by Plunkett & Dale (*ibid.*, p. 166) as being a weakness of the "classical" method of cost categorisation, namely that it adds nothing to the data's potential for provoking action by management. It is considered fundamental to the quality cost management process that management should be

able to distinguish between the appraisal cost and prevention cost components of the cost of control (cost of conformance) for instance. The reason for this relates to the fact that, without this information, management could be tempted to solve the problem of high failure costs (cost of non-conformance) simply by increasing appraisal costs. In terms of the total quality concept, on the other hand, increased expenditure on prevention costs will reduce failure costs as well as appraisal costs. This results in a reduction in the (total) cost of quality while at the same time increasing the level of quality, productivity and profitability (see Feigenbaum, *loc. cit.*, pp. 112-114).

One of the companies surveyed reported their current operating quality costs to be 0,25 per cent of sales, calculated as the total cost of non-conformance (see Section 6.4.5.5). This figure is in itself most impressive. However, without knowing what that company's cost of appraisal is, it would be impossible to determine wether or not net profit performance may be improved through more efficient quality management. Moreover, without knowing the ratio of appraisal costs to prevention costs, it would not be possible to devise an effective strategy in this regard.

Only three companies were found to have employed the "classical" system of quality cost categorisation, and of these three companies only the figures supplied by one company are considered to be reliable (see Section 6.4.5.5). It is noted that this company's (internal and

external) failure costs comprise 33,3 per cent of total operating quality costs; appraisal costs 63,3 per cent; and prevention costs 3,4 per cent. Based on these figures, it may for instance be recommended that future strategies to reduce total operating quality costs in this company be aimed at increasing expenditure on prevention activities while at the same time reducing expenditure on appraisal.

## 6.7 THE CONCLUSIONS

An interpretation of the results obtained from the research is given in the sections which follow.

### 6.7.1 Conclusions regarding the hypotheses

A comparison between the current regulatory control system which is used to assure the quality of pharmaceutical products in South Africa, and the total quality concept, highlights the following aspects in particular:

#### 6.7.1.1 The field of reference

Current regulatory requirements relating to the granting of marketing authorisation (product registration) incorporate many (but not all) of the new design control; incoming material control; product control; and post-marketing surveillance activities that would routinely be performed in terms of a total quality system (see Chapter 3).

It should be noted however that the components of the South African regulatory control system are exclusively technically-orientated, with no managerial focus. This characteristic in fact underlies the inspection and test approach to quality which is inherent in the current regulatory control system.

The regulatory requirements relating to manufacturing authorisation, and which are embodied in current good manufacturing practice principles, are by definition related only to the production phase of the industrial cycle (see Chapter 4). The total quality concept, on the other hand, forms the foundation for the organisationwide integration of all those activities which have to be performed in order to consistently achieve the quality objectives of the enterprise (see Section 5.5). The organisationwide scope of the total quality concept, and its application to the entire industrial cycle, are seen as its primary distinguishing features when compared to the current regulatory control system.

6.7.1.2 The strategic business value of quality

The possible existence of oligopolistic and even monopolistic therapeutic submarkets in the South African pharmaceutical market, is referred to Section 1.2. The unique features of the South African market for prescription medicines that have thusfar contributed to a low

elasticity of demand, and those macroenvironmental issues which are now challanging the traditional *status quo*, are referred to in Section 2.2.2. Both this research and the technical literature reveals that a fundamental shift away from a purely technical approach to quality is beginning to take place within the pharmaceutical industry. A customer-orientation to quality; the association that is made between quality and profitability; and the high profile which is given to quality improvement programmes based on employee involvement, is evident amongst some of the companies who particpated in the research (see Section 6.6.1). The technical literature now also recognises the strategic business value of quality in terms of such aspects as improved productivity, increased profitability, and the achievement of a competitive advantage (see Kieffer & Nally, *loc. cit.*, pp. 131-138).

This philosophical shift away from a purely technical approach to quality is seen as being influenced by the modern competitive environment of the pharmaceutical industry. This may be due to a realisation that quality is an essential part of the marketing mix; that it enables companies to effectively differentiate their products from those of their competitors, whilst the elimination of waste through improved quality results in the most efficient utilisation of company resources and hence the maximisation of productivity, profitability and competitive advantage. This is in contrast to the traditional approach to quality and quality management, which is related mainly to the need for regulatory compliance.

6.7.1.3 Quality policy formulation

The current regulatory control system does not provide any formal guidelines to quality policy formulation. Section 1(3) of the Medicines Control Act (South Africa, 1965) determines that criteria related to safety, quality and therapeutic efficacy must be met before marketing authorisation may be granted in respect of a pharmaceutical product (see Section 3.3). Besides this broadly stated objective, only the guidelines contained in good manufacturing practice principles, which by definition apply mainly to the production phase of the industrial cycle, serve to guide industry in this regard (see Section 4.3). It is also important to note that the quality objectives described by the regulatory control system are of a technical nature only. This must of necessity result in the strategic business elements of company quality policy being overshadowed by technical considerations related to regulatory compliance.

A formal policy statement, in which a company's quality objectives are clearly defined, is a fundamental component of a total quality system. Similarly, a structured approach to the identification and analysis of quality-related decisions and problems is an integral part of such a system. The current regulatory control system lacks both these elements.

A quality policy is established to formally stipulate the limits within which all quality-related management decisions are to be taken in order to meet stated quality objectives. The quality policy may thus be looked upon as being the first level of communication which is used by management to communicate specific quality objectives. Such communication is specifically aimed at functionaries throughout the organisation (see Section 5.9). In terms of the total quality approach, the nature of such communication will moreover have a strong strategic business content rather than an exclusively technical orientation.

It is felt that the weakly-developed quality policy and communications structures encountered in some companies during this research (see Section 6.6.2) can be improved by means of a total quality approach. Such an approach is also seen as fundamental to the success of many of the quality improvement programmes encountered during the research (see Section 6.4.1.6). Without the firm basis which is provided by a clearly defined quality policy, such programmes may flounder as a result of a lack of co-ordination and organisationwide impact; and a (perceived) lack of involvement by top management.

#### 6.7.1.4 The quality organisational structure

Reference is made in Section 6.6.1 to the fact that the traditional quality culture in the pharmaceutical industry

is influenced by the dual regulatory processes of marketing authorisation and manufacturing authorisation. These two processes may occur independently from one another (see Sections 3.5 and 4.1). It is also possible for marketing authorisation and manufacturing authorisation to be granted in respect of the same product to different parties acting independently from one another; for instance in the case of the holder of a marketing authorisation contracting an authorised third party manufacturer to manufacture a particular product. This may lead to a fragmented or uncoordinated approach to quality control during the industrial cycle of a particular product.

The South African regulatory control system apportions final responsibility for product quality to the managing director of a pharmaceutical company. In terms of the provisions of section 22 of the Pharmacy Act (South Africa, 1974) the managing director must be a pharmacist who is required to "manage the business" of the company. No guidelines are given in this regard other than by section 29 of that Act, which stipulates that the manufacture of a medicine must be supervised by a pharmacist (see Section 4.6.2). The functions of a company managing director are furthermore not defined by South African company law. The duties and powers of a managing director are determined instead by that which is assigned to him by the company's board of directors (Pretorius, et al, 1991, pp. 459 - 462).

This combination of factors has resulted in the somewhat paradoxical situation of the managing director sometimes being a mere figurehead who is appointed only to satisfy regulatory requirements in that regard. At best this creates two internal lines of communication within a large organisation; one dealing with regulatory issues and the other with the management of the actual day-to-day affairs of the company. This is seen as being a potential hindrance to the co-ordination of the quality effort in a pharmaceutical company. An examination of the functions specifically delegated to the quality assurance manager in terms of current GMP principles (see Table 4.1), reveals that these relate mainly to technical responsibilities and some systems responsibilities. The results obtained from the research (see Section 6.4.3.3) appears to confirm that this is indeed the situation in practice. The research did however reflect a realisation amongst respondents of the key role played by the quality assurance function in terms of strategic business factors. The fact that this business responsibility has in many cases been delegated to the quality assurance function in an informal manner only, would appear to indicate that top management may however still not be entirely convinced of the business strategic value of quality; or that considerations related to regulatory demands predominate in this regard.

From the above it may be concluded that the current regulatory control system has had a profound effect on the quality organisational structures within the South African

pharmaceutical industry. This has resulted in a sometimes unco-ordinated approach to quality control during the various stages of a product's industrial cycle; a lack of internal organisationwide co-ordination; and an essentially technical approach to quality, with the emphasis being on regulatory compliance.

It is felt that a total quality approach can be used to complement the current regulatory control system in this regard. The structured approach inherent in the total quality concept with reference to the identification of key organisationwide quality authorities and responsibilities; the identification of the technical, systems, and business authorities and responsibilities of the quality control function itself; and the leadership role of management is seen as offering particularly appropriate solutions to the problems identified (see Section 5.10).

The total quality approach is seen as being complementary to the current regulatory control system not only in the sense that it gives a new dimension to the management of quality, but also due to the fact that certain elements of the regulatory control system will be more fully developed. The relevant MBR1 dossier and process flow-chart, together with the company organogram and job descriptions, may for instance be used to construct a relationship chart with which to identify organisationwide quality authorities and responsibilities. Most of the relevant management

information already exists within the current regulatory control system; a total quality approach provides the basis for co-ordinating and applying this information to maximum effect (see Section 6.6.3).

6.7.1.5 Enhanced operations management

In Section 5.7 the interdependence that exists between the total quality concept and operations management systems such as just-in-time (JIT) and materials requirements planning (MRP), is contrasted with current GMP principles. It may be concluded that, due to the technical orientation of GMP guidelines, those guidelines are of limited use from an operations management perspective.

The research revealed that the application of both JIT and MRP principles of production control are entirely compatible with pharmaceutical manufacture (see Section 6.6.4). From the literature, it appears that a mayor difficulty with the application of JIT production control techniques to pharmaceutical manufacture would relate to the unstable master production schedule that is normally associated with pharmaceutical manufacture. The research however revealed this not to be the case (see Section 6.4.4.1). The research also revealed the widespread use of the MRPII system of production planning and control amongst the companies surveyed (see Section 6.4.4.3); and that the criticism relating to the tolerance of waste by the MRP

system is valid only insofar as the standards designed into the system by the user himself allows for wastage (see Section 6.4.4.4).

Most respondents felt that JIT and MRP systems make some positive contribution to their quality assurance programmes; and the majority of respondents interviewed also felt that these two systems complement one another (see Sections 6.4.4.2 and 6.4.4.4). This would serve to confirm the opinion in the literature that these systems are not only compatible but also enhance the benefits derived from eachother; in particular if MRP is viewed as the planning half and JIT as the execution half of such an integrated system (see Section 5.7). The critical part played by quality issues in the successful application of JIT principles in particular, are furthermore considered to be of paramount importance to this research (see Ray, 1990, pp. 179-190). This is due to the fact that the fundamental role played by quality in the application of JIT/MRP integrated systems will enable the pharmaceutical industry to co-ordinate its quality control and production control systems more effectively than would be the case were it to rely on GMP principles only. The purely technical orientation of GMP principles does not provide a basis for such integration of quality control systems with effective production planning and control systems.

### 6.7.1.6 Management's control over quality costs

A fundamental component of the control function of management relates to monitoring conformance with set standards. Whereas the technical literature often views control as consisting of various individual (technical) functions that are not necessarily interrelated, the business economic viewpoint holds that control consists of the setting of standards; appraisal of conformance; taking corrective action when necessary; and planning for improvements to be made (see Section 5.4). This would serve to emphasise the fact that effective control cannot take place without the effective feedback of relevant information to management. The GMP principles which currently form part of the regulatory control system (see Chapter 4) do not provide for such a structured feedback of information to management.

Managerial decision making cannot be based on technical information only. Quality cost data are an essential component of the quality management process; one of the companies researched applies the dictum: "You cannot manage what you do not measure" in this regard. The surprisingly unsophisticated systems of quality cost management generally encountered amongst the companies surveyed, however points to a possible need within the industry for guidance in this regard.

The total quality concept incorporates the identification and measurement of various quality cost categories. It also assists management in understanding the important interrelationship between these cost categories. In particular it enables management to direct the quality improvement effort into areas that will maximise its contribution to company profitability (see Section 6.6.5).

### 6.7.2 Conclusions regarding the implications

The implications of the research relate to the need for a fundamental change in the philosophical approach to quality and quality management in the pharmaceutical industry. The total quality philosophy embodies characteristics related to the establishment, maintenance, and improvement of quality control systems which have important implications to both the pharmaceutical industry and the regulatory authorities regarding the following aspects in particular:

(i) The need to move away from a purely technical (inspection and test) approach to quality, towards a recognition of the pivotal role played by management skills in the attainment of the quality objective. It is concluded from the discussion in Section 4.5 that both the pharmaceutical industry and regulatory authorities internationally consider good manufacturing practice (GMP) principles to be the benchmark against which any quality assurance system must be measured. This viewpoint ignores the limitations inherent

in GMP principles, which are related to their narrow, production-orientated, focus. Moreover, GMP principles have a purely technical basis (see Chapter 4), whereas the total quality concept is based on the precept that quality is the result of good management; quality control is seen as being a management tool which enables top management to fulfil a leadership role with regard to product quality (see Section 5.5).

The technical (rather than managerial) orientation of the South African regulatory control system, and similar systems elsewhere, is seen as being the inevitable consequence of the fact that this regulatory control system is itself based upon (natural) scientific principles only. The planning, co-ordination and control of those activities necessary to consistently deliver a product of the required quality to the final consumer is thus linked to inspection and test activities based on technical principles only.

The business economic viewpoint, on the other hand, is that quality is in essence a way of managing the enterprise and that managerial control over quality is achieved in exactly the same manner as control over the financial, marketing and other functions of the enterprise. The total quality concept provides the basis for a structured approach to the establishment of a dynamic company-wide managerial structure aimed at consistently achieving a stated quality goal. An understanding of the total quality concept is thus seen as being important to the pharmaceutical industry as well as regulatory quality auditors in particular.

(ii) A recognition of the strategic business value of quality in the modern competitive environment; and in particular the positive contribution to company net profits that can be made by the effective management of quality. Reference is currently being made in the technical literature to the strategic nature of quality in the current environment of global competition in which the pharmaceutical industry operates (see Kieffer & Nally, *loc. cit.*, p. 131). It is furthermore considered significant that the majority of respondents who participated in this research, defined quality in terms of a customer-orientation, and that some of these respondents see a direct link between their quality assurance systems and strategic business factors such as profitability and risk management (see Section 6.6.1). The traditional quality culture in the pharmaceutical industry, which has its roots in requirements relating to the need to comply with (mainly technical) regulatory demands concerning product quality, is however in need of a fundamental re-orientation to the strategic business value of quality. The total quality concept provides the mechanism whereby this may be achieved, with specific reference to aspects such as the improvement of the company's competitive position, increased productivity, and increased profitability.

The aim, with respect to product quality, of both the industry as well as the regulatory authorities, is to best serve the interest of final consumers of medicines. Any

system of quality assurance that not only achieves this objective but at the same time enhances the achievement of business strategic goals, must of necessity receive the wholehearted supported of industry at large. This incentive would serve to increase the commitment to quality within the pharmaceutical industry beyond that which may currently be based largely on regulatory demands only.

(iii) A broadening of the scope of the quality control function beyond issues that relate mainly to product design and production, towards an integrated approach that is focussed on the entire industrial cycle. Reference is made in Section 6.6.1 to the fact that the traditional quality culture in the pharmaceutical industry is influenced by a regulatory control system which is based on a process of marketing authorisation (see Chaper 3) and a process of manufacturing authorisation (see Chapter 4). In practice, these two processes may take place entirely independently from one another, both in terms of timing as well as in terms of the individual companies involved. It is for instance possible for one company to obtain marketing authorisation, and for another company to obtain manufacturing authorisation, in respect of the same product. The regulatory control process by its very nature therefore allows a fragmented appraoch to be adopted to quality control during the industrial cycle. This is done for practical reasons which cannot be avoided.

This fragmented approach to quality control is however exacerbated by the narrow, production-orientated focus of GMP guidelines which form the basis for regulatory manufacturing authorisation. The total quality approach, which highlights the fact that quality is affected at every stage of the industrial cycle, is seen as having the potential for making an important contribution in this regard. From a regulatory point of view in particular, it is important that companies are able to view the interrelationship between the various stages of a product's industrial cycle in the correct perspective.

(iv) The formulation of quality policy. The total quality concept emphasises the need for a clearly-defined quality policy statement in which top management sets out company quality objectives. Such a policy statement is required to relate to integrated policies and procedures which are aimed at ensuring the active involvement and continued commitment of all employees, and of top management, to the quality effort. The current regulatory control system provides an incomplete framework for quality policy formulation. In particular, it places emphasis only on the identification of technical quality-related problems and their (physical) analysis (see Section 5.9). Moreover, the system of documentary control which is an integral part of GMP guidelines (see Section 4.6.3) relates mainly to day-to-day technical decision making without specifically contributing to strategic quality decision making. The finding that it was difficult to establish a direct link

between the policy documents and the quality objectives and procedures of some of the companies who participated in this research (see Section 6.6.2), is seen to be directly related to the above-mentioned characteristics of the current regulatory control system.

(v) The formal co-ordination of the organisationwide quality effort. No generally applied approach to the identification of key organisationwide quality responsibilities and authorities in a pharmaceutical company was revealed by the research (see Section 6.4.3.1). The systems responsibility, and in particular the business responsibility of the quality control function of most of the companies researched were found to be relatively weakly-developed (see Section 6.4.3.3). A review of the evolution of quality control in the pharmaceutical industry moreover suggests that the commitment to quality by top management may be related primarily to regulatory requirements in that regard (see Section 5.6). Evidence was, however, found of a significant awareness within the industry of the need to continually improve quality; particularly in the areas of defect prevention and the need for innovation (see Section 6.6.2). The total quality concept is seen as providing a structured approach to the task of organising for quality in the absence of regulatory guidelines in that regard. The use of a relationship chart which is based on the relevant company organogram; process flow chart; and the

MBR1 product registration dossier, as suggested by Mader (1989, p.24), is seen as an example of the approach to organisationwide co-ordination inherent in the total quality concept.

(vi) The active involvement of all employees in the quality establishment; maintenance; and improvement process. The importance of the activities of people in the assurance of pharmaceutical product quality is well-recognised even in the technical literature. The current regulatory process in general and GMP guidelines in particular, are largely procedure-driven. The danger is that human nature will tend to circumvent standard operating procedures if not convinced about their relevance or value. Moreover, without the active involvement of employees in the quality effort, management will be deprived of the feedback of quality-related information so vital to the decision-making process. The active involvement of all employees is a fundamental component of the total quality concept. Evidence was found of the fact that a number of the companies researched recognise the importance of employee participation in the quality improvement process for instance (see Section 6.4.1.6). Such programmes cannot however be conducted in isolation from the quality establishment-maintenance-improvement process. Their effectiveness and sustainability will be assured only through a formal and structured integration into the quality system, as part of a total quality system.

(vii) The importance, and correct use of quality cost data. In terms of the current regulatory control system the only criteria that are applied during the marketing and manufacturing authorisation processes, are those which relate to product safety, quality, and therapeutic efficacy (see Section 3.3). Moreover, the inspection and test approach to quality control which is inherent in current GMP principles would result in a possible overemphasis of expenditure on appraisal costs, rather than prevention costs, thereby ignoring the effect on the total cost of quality. The wide variety and selective use of quality cost categories which were encountered during the research, and the divergence of opinions regarding the distinction between quality costs and production costs amongst those companies surveyed, points to a relatively unsophisticated level of quality cost management in the pharmaceutical industry (see Section 6.6.5). Control is one of the basic functions of management, and involves the setting of standards; appraising conformance; acting when necessary; and planning for improvements (see Section 5.4). Capturing accurate quality cost data is considered to be an essential component of the management function relating to product quality and of the total quality concept.

The above-mentioned aspects would serve to emphasise that better quality cannot be achieved merely by tightening up regulatory requirements or by moving technical goalposts; nor can it be achieved without a genuine commitment and the

active involvement of company top management. There is nevertheless a great deal of compatibility between total quality methods and philosophies, and the current regulatory control system. This is primarily related to the fact that consumer interest is the focal point of the quality control efforts of both the pharmaceutical industry and the regulatory authorities. The total quality concept is consequently seen as being the next logical step in the evolutionary process of quality control in the pharmaceutical industry.

### 6.7.3 Conclusions regarding further research

The relatively unsophisticated quality cost systems encountered in the pharmaceutical industry during the research, serves to indicate a need for development in that regard. In particular, the establishment of guidelines that will distinguish between quality costs and production costs in the pharmaceutical industry is considered to be an essential component of such further research. It is envisaged that broad principles of quality cost determination may be established and developed to a level of sophistication that will also enable their use by regulatory control auditors as an aid to the identification of specific quality problem areas within a plant, as well as their causes. Potential quality problems may for instance be identified by an upward trend in internal failure costs, and possible causes for this trend may be indicated by

increasing appraisal costs together with static or declining prevention costs. Such research will however have to be based upon a larger sample size than that which was used for the present research.

No reference is made in this research to statistical control methods, despite the fact that these methods constitute an integral part of the total quality concept. This was purposely done in order to focus on the role of the management function in the assurance of pharmaceutical product quality, particularly in the light of the purely technical approach of the current regulatory control system in this regard. Process validation and machine qualification issues are however increasingly regarded as being of crucial importance by South African regulatory authorities (Schlebusch, 1994). It is consequently felt that further research regarding the total quality approach to the use of statistical control methods will be both valuable and opportune. In particular, the effect on quality costs (and net profits) of a pharmaceutical process validation programme is seen as being an important area for further research.

The majority of respondents who participated in this research stated that they do apply just-in-time (JIT) principles of production control (see Section 6.4.4.1). However, reference is made in Section 6.6.4 to the possibility that these respondents in general may view JIT as

being synonymous with zero inventories and pull production, rather than a philosophy which is based on the principles of continuous improvement and the elimination of waste. Further research is required in this regard to determine the validity of this deduction, and its application to the pharmaceutical industry in general.

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**ANNEXURE ONE: SURVEY QUESTIONNAIRE**

This annexure contains details relating to the structured questionnaire which is referred to under Section 6.2.

The questionnaire consists of a section for gathering data required to compile a profile of the company concerned, and sections relating to the company's quality philosophy; the company's quality policy; the company's quality organisational structure; the production control systems being used; and quality cost management. Where necessary, prompts were included in the questionnaire (see boxed areas) as an aid to clarifying the questions being asked. Each interview was recorded on audio tape.

# COMPANY PROFILE

NAME OF COMPANY: .....

POSTAL ADDRESS: .....

TEL.(CODE): ..... (NUMBER): ..... FAX: .....

CONTACT PERSON: .....

MULTINATIONAL ☐ SOUTH AFRICAN ☐

ORGANOGRAM (ATTACHED)

ANNUAL TURNOVER: .....

PRODUCT MIX:

STERILE LIQUIDS ☐
SEMI-SOLIDS ☐
SOLIDS ☐

NON-STERILE LIQUIDS ☐
SEMI-SOLIDS ☐
SOLIDS ☐

TOXIC/HAZARDOUS PRODUCTS:

PENICILLINS ☐
CEPHALOSPORINS ☐
HORMONES ☐
CYTOSTATICS ☐
OTHERS (SPECIFY) ☐

UNREGISTERED PRODUCTS:

HEALTH FOODS/VITAMINS ☐
VETERINARY MEDICINES ☐
COSMETICS ☐
OTHERS (SPECIFY) ☐

.....

.....

FEEDBACK REQUIRED? ☐ YES ☐ NO

CONFIDENTIALITY REQUIRED? ☐ YES ☐ NO

# QUESTIONNAIRE

## 1. COMPANY'S QUALITY PHILOSOPHY

1.1 What is the purpose of your company's quality assurance system?

| |
|---|
| Technical factors : inspection and test, production oriented<br>Regulatory requirements : what is legally required<br>Strategic factors : competitive advantage, productivity, profitability |

1.2 How would you define product quality?

| | |
|---|---|
| Technical orientation : | conformance to specified standards<br>regulatory compliance |
| Customer orientation : | safety<br>therapeutic efficacy<br>affordable product<br>judged by consumer's experience |

1.3 Who takes final responsibility for product quality in your company?

| | |
|---|---|
| Total quality orientation : | top management |
| Regulatory orientation : | managing director (pharmacist) |
| Functional orientation : | QA function<br>production function<br>line supervisors/inspectors |

1.4 Do you apply the same quality assurance system to registered and unregistered products?

| | |
|---|---|
| Medicines registered i.t.o. Act 101 } | parallel standards - |
| Cosmetics/unregistered products } | quality commitment related to regulatory requirements |

1.5 Does the scope of your quality assurance system differ from that of GMP principles?

| | |
|---|---|
| Entire industrial cycle : | new design control<br>incoming material control<br>product control<br>post marketing surveillance |
| Organisation wide scope : | not restricted to manufacturing only. |

/....

1.6 Do you see the quality improvement process as being separate from the quality control activity?

| |
|---|
| Multidisciplinary quality improvement steering committee.<br>Chaired by die C.E.O.<br>Quality improvement integrated with other organisational improvement activities. |

2. COMPANY'S QUALITY POLICY

2.1 Does your company have a quality policy?

2.2 Is the company's quality policy statement available in writing?

| |
|---|
| Copy available?<br>Broad statement. Specific functional areas of application.<br>Procedures (who, how, when). Instructions (step-by-step performance of tasks). |

2.3 Who finallly approves the company's quality policy?

| |
|---|
| Chief Executive Officer<br>Managing Director<br>Quality Manager<br>.....<br>..... |

2.4 How is your company's quality policy communicated?

| | | |
|---|---|---|
| Verbally | } | |
| During personnel training | } | internal communication |
| Via a quality manual | } | |
| ..... | | |
| ..... | | |
| Advertising | } | external |
| Public relations | } | communication |
| ..... | | |

2.5 When formulating or revising your quality policy, do you identify quality-related decisions at each step of the industrial cycle?

| |
|---|
| Multifunctional approach<br>Plan actions, responsibilities, time scales<br>Set operational standards : eg. no errors, no defects<br>Target specific functional areas of application. |

/....

2.6 When formulating or revising your quality policy, do you identify and analyse quality-related problems that may be or have been experienced during the entire industrial cycle?

| | |
|---|---|
| Multifunctional approach | |
| Formal procedure includes : | formulation problems<br>production problems<br>marketing problems<br>product performance problems |
| Structured approach : | how could problem have been prevented?<br>do policy guidelines need to be changed? |

2.7 How frequently do you revise your quality policy?

3. ORGANISING FOR QUALITY

3.1 How do you identify the key organisationwide quality responsibilities and authorities in your company?

| | |
|---|---|
| Pharmacy Act<br>GMP Guidelines | } Regulatory requirements used as the primary guideline. |
| MBR1 dossier<br>Relationship chart | } Based on process flow-chart, organogram. |

3.2 How is your personnel; marketing; and finance departments involved in your quality assurance system?

Quality policy formulation
Involvement in decision making, problem solving and feedback of quality information.
Organisationwide integration of the quality effort.

3.3 What key responsibilities have been formally delegated to the quality control function in your organisation?

Business responsibility: QA programme must foster sound business growth, profitability, competitive advantage.

System responsilibity:(i) Primary leadership i.c.w. quality objectives, training, employee involvement in the quality establishment/maintenance/improvement process, and system design. (ii) Structuring of quality system : Co-ordinate people, machines, information. Define quality information flow, processing and control. (iii) Administrative control of the QA system : Continuous feedforward/feedback of performance data (including quality costs). Periodic internal and external audit of the system.

/....

/....

Technical responsibility: (i) Incoming material control (Annexure 6). (ii) Final product release (Annexure 9A). (iii) Container release (Annexure 9B). (iv) In-process controls (Annexure 11). (v) Product complaints (technical/ adverse drug reactions - Reg. 12).

4. PRODUCTION CONTROL

4.1 Does your company apply JIT principles of production control?

Downstream work centre starved if upstream work centre does not deliver on time?
Highly variable master schedule a problem?
Applied in particular department only?

4.2 Do you see a connection between JIT principles and your quality assurance system?

Improved production capacity
Improved production reliability
Eliminate the causes of inventory
Immediate feedback/response to quality problems
Reduced equipment set-up time
Vendor approval system
"Right first time" philosophy

4.3 Does your company use an MRP system of production planning and control?

MRP I inventory control system generates manufacturing and purchase orders to achieve master production schedule output.

MRP II plans and controls inventories and production capacities; feedback loop between orders and master schedule allows for adjustments according to available capacity.

MRP III plans and controls all manufacturing resources including inventory; cash; personnel; facilities and capital equipment.

4.4 Does the MRP system complement your quality assurance system in any way?

Production planning and control tool only?
Linked to quality via efficient resource utilisation?
Does tolerate a degree of waste?
Only if used in combination with a JIT system (MRP for planning; JIT for execution)?

/....

## 5. QUALITY COSTS

5.1 Do you measure and report quality costs?

5.2 What cost catogories or cost elements have your defined?

| |
|---|
| Quality costs = expenses of the QA function?<br>Quality costs = those costs that are amenable to change by quality management.<br>Cost of control = prevention costs + appraisal costs<br>Cost of failure to control = internal + external failure costs |

5.3 Who receives the quality cost reports?

| |
|---|
| Shopfloor supervisors : e.g. weekly reports of costs of scrap and rework.<br>Departmental managers : e.g. monthly reports of total costs highlighting current problems or progress with quality improvement projects.<br>Top management : e.g. quality costs included in company's cost reporting system, highlighting total costs and costs to be acted upon. |

5.4 Who decides to take action on quality costs when this becomes necessary?

| |
|---|
| Top management<br>Financial management<br>Quality assurance manager<br>Multifunctional committee |

5.5 What percentage of total sales is attributable to total quality costs in your company?

| |
|---|
| 5 - 10 - 15 - 20 - 25 per cent<br>actual figure<br>estimated figure<br>no idea |