Annexure B

REPORT OF THE MINISTERIAL TASK TEAM ON THE RESTRUCTURING OF THE MEDICINES REGULATORY AFFAIRS AND MEDICINES CONTROL COUNCIL

AND

RECOMMENDATIONS FOR THE NEW REGULATORY AUTHORITY FOR HEALTH PRODUCTS OF SOUTH AFRICA

25 FEBRUARY 2008

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ACRONMYS

ATM	African Traditional Medicines
CEO	Chief Executive Officer
CTC	Clinical Trials Committee
CTDF	Common Technical Document Format
DG	Director General
ECTD	Electronic Common Technical Document
EG	For example
EMEA	European Medical Agency
EO	Ex Officio
FDA	Food And Drug Administration of the United States of America
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GDP	Gross Domestic Product
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GWP	Good Wholesaling Practice
HIV	Human Immuno- Deficiency Virus
ICH	International Conference on Harmonisation
INCD	International Network for Cultural Diversity
IP	Intellectual Property
ITG	Industry Technical Group
MCC	Medicines Control Council
MHRA	Medical and Health Products Authority, United Kingdom
MOU	Memorandum of Understanding
MRA	Medicines Regulatory Authority
MTEF	Medium Term Expenditure Framework
MTT	Ministerial Task Team
NAFDAC	National Agency for Food, Drug Administration and Control
NCE	New Chemical Entities
NHI	National Health Insurance
NRA	New Regulatory Authority
PDF	Portable Document Format

PIC	Pharmaceutical Inspection Convention
PSUR	Product Safety Update Report
SADC	Southern African Development Countries
SAHRA	South African Health Regulatory Authority
SDA	State Drug Administration, of The Peoples Republic of China
SFDA	State Food & Drug Administration, of The Peoples Republic of China
SLA	Service Level Agreement
SOP	Standard Operation Practice
TCM	Traditional Chinese Medicine/s
TGA	Therapeutic Goods Administration, Australia
WHO	World Health Organisation
WTO	World Trade Organisation

EXECUTIVE SUMMARY

The Ministerial Task Team fulfilled its mandate in accordance with the terms of reference granted to it by the Minister of Health, to review the current Medicines Control Council and to make recommendations. Cabinet resolved in January 2006 that the current MCC be reviewed and recommendations made for a new Regulatory Authority.

The current MCC commenced in 1965. The changed scientific and management environment, complexity of Health Products and the marked increase in the workload have engulfed the MCC. The backlog has resulted in it not being able to continue to function efficiently and effectively. Globally it has been recognised that regulatory authorities for health products should be reviewed every five years. The backlog of the current MCC with regards to the evaluation of pharmaceuticals, the major problems with the evaluation of clinical trials, the failure to work within time scales and meet deadlines, HR gross shortages, funding shortages, lack of electronic system have all compounded the challenges of the current MCC. All these have fuelled the imperative to review the MCC. Mature regulatory authorities have conducted or are conducting reviews to address similar issues.

The review of the MCC by the Task Team was in-depth and included meetings with the MCC, with the MRA, with Industry, with Academics and also other role-players. Regulatory authorities in selected countries, globally were studied and from this detailed search and study it became apparent that the current MCC needed to be replaced. This will ensure that South Africa will be able to address all regulatory needs for health products for the present and for the future.

The Ministerial Task Team has made detailed recommendations for the new regulatory authority. This regulatory authority will be an all embracing on for all health products for human and for animals use. This is the global trend. The recommendation is compatible with other mature and credible health product regulatory authorities.

A new South African Regulatory Authority for Health Products is recommended, as an Agency within the Department of Health. The full time Head of the regulatory authority, as the CEO will be the Accounting Officer, subject to the PFMA and will report directly to the Minister of Health. The regulatory authority will regulate all Health Products through independent operating divisions or components. The regulatory authority will consider the harmonisation where relevant with International standards and also look at a programme for harmonisation at regional level. Efficiency in the evaluation of dossiers will be increased through sharing of information with other regulatory authorities.

The Agency will allow the effective recruitment and retention of highly trained technical and professional staff, by the flexibility in their employment. These scarce skills are an imperative for the functioning of the regulatory authority. This is a challenge experienced by regulatory authorities globally. They have countered the challenge by various models of employment which has ensured the successful recruitment and retention of these scarce resources that are critical for the nature of the complex work.

A partial cost recovery from fees is recommended. The MTT recommends a 50% cost recovery. This will ensure a reduced pressure on the fiscus, enable affordability, cost effectiveness and sustainability. The projected financial assumptions detailed in Chapters 12 and 15 show that this is feasible but the calculations will be firmed up should the recommendations be approved.

The budget will ensure adequate funding of the SAHRA, which will in turn ensure the adequate allocation for the Human Resource needs, the Capex and the Opex. The full recommendations are outlined and are based on the thorough study undertaken of selected models of regulatory authorities provided in the Report.

The recommended structure of the SAHRA is provided in Chapter 8. This will be an independent umbrella body, in keeping with the global trend because of the complexity and interrelatedness of health products and their regulation. It

will include animal health products, which will protect animal health and reduce the residue effects of health products.

Concurrence of the Minister of Health, Minister of Agriculture and the Minister of Environmental Affairs and Tourism is recommended where there is a straddle across the Departments. This will ensure that the products marketed or manufactured in the Country are safe, efficacious and of quality while at the same time protecting human and animal health and at the same time protect the environment by ensuring correct handling and disposal.

The legal implications necessary for the implementation of the SAHRA are outlined in the Report. There are no constitutional implications of the recommendations. There will be a need for amendments of certain Acts and adjustment and / or drafting of regulations. The details are provided in Chapter 13.

Chapter 9 outlines the principles for the SAHRA. These will ensure good governance, successful delivery within prescribed timescales and management according to best practice business principles. An Office of Business Transformation and Administration is recommended with the reasons for it. The new SAHRA will be able to prove its integrity, professionalism, efficiency and value as a successful regulatory authority.

The roles of SAHRA are spelt out. Its relationships with identified internal and external bodies is provided in Chapter 11 specifically, but also intimated in other parts of the report. The need for MOU's with other regulatory authorities is discussed. The need for service level agreements, performance agreements and consideration of harmonisation are highlighted in the report. The importance of relating with the SADC and AU regulatory authorities is identified.

Special Issues such as Conflict of Interests, Declarations, Appeals are dealt within the report.

The Report has identified the need for curriculum reviews to enhance needed output skills of Health Professionals in the regulatory environment. This is based on current deficiencies identified. In-service training is also imperative.

Unintended consequences of the report have identified a need for a Safe Products Body in South Africa, the need to contain the spiralling costs of health care in a comprehensive manner by possibly an NHI, the need for an Ethical Code of Marketing Practice by the Health Product Industry and a need for a Comprehensive Industrial Policy for the Health Product Industry. The MTT did not go into detail as it was not their brief but considered it imperative that they document these issues.

The recommendations are classified into Strategic and Operational. An implementation plan will be formulated if the recommendations are approved. It will recognise the urgency, have defined timescales and be in two synergistic parts, i.e. to effect remedial measures and to usher in the new SAHRA.

The Report provides supporting argument and documentation in the report and annexure for the recommendations offered.

The new SAHRA will take over from the current MCC, which has served its time but now needs to be replaced. This new SAHRA is required, as vast scientific advances have occurred since 1965, when the current MCC was conceived. It is now the practice of mature regulatory authorities to be reviewed every 5 years; it is recommended that this new SAHRA be reviewed in 5 years following conception in order to keep pace with scientific, management, and other advances that impinge on the regulation of health products and best practices.

The Report is structured into Chapters and concludes with recommendations, a conclusion and acknowledgements.

CHAPTER 1

INTRODUCTION AND BACKGROUND

1. Regulation Of Medicines In South Africa to date.

Human medicines have been regulated in South Africa for the past 41 years and over 38 000 medicines have been registered during this time. Currently there are 11 387 registered medicines in addition to 9 500 old medicines. The latter are medicines that were marketed prior 1965. Veterinary medicines have been regulated since 1947 but were only brought under the ambit of the medicines regulatory authority in 1979 after the definition of a medicine was amended to include veterinary medicines. Stock remedies are still regulated separately under Act 36 of 1947. The Department of Agriculture oversees the latter.

2. Policy And Legislative Framework For The Current MCC.

Regulation of medicines in South Africa is premised primarily on the National Drug Policy whose aim it is, to ensure that medicines reaching the public and animals are safe, effective and meet the approved standards and specifications through strengthening the MCC, rationalising drug registration, controlling the registration of practitioners and licensing of premises, enhancing the inspectorate and laboratory functions, and promoting other quality measures e.g. GCP, GMP, GWP, GLP, and GDP.

The Medicines and Related Substances Act 101 of 1965 as amended guides registration or market authorisation. This Act and its related regulation govern the manufacture, distribution, sale and marketing of medicines intended for human and animal use. The prescribing and dispensing of medicines is controlled through the determination of schedules for various medicines and substances. The Act provides for the establishment of a Medicines Control Council (MCC). The Minister of Health appoints members (not exceeding 24) of the MCC for a term of five years, renewable but limited to 2 terms. The Minister designates the chairperson and the vice-chairperson of the MCC. The

latter acts as chairperson in the absence of the chairperson. Members are drawn from University Faculties of Medicine, Pharmacy, Veterinary Science and Research Institutions.

3. Roles And Responsibilities

The Minister has overall responsibility for the health of all South Africans. The Minister appoints the MCC and the Appeal Committee that investigates any appeal against the decision of MCC. The Minister of Health, is responsible for the Promulgation of Regulations after consultation with the Council, appoints the Registrar and Deputy Registrar/s, grants exemptions from the operation of some provisions of Act 101 in consultation with the Council [1]and determines the fees payable to the Council in consultation with the Minister of Finance.

The Director General of Health is responsible for the release of information, issuing of permits for psychotropics and narcotics, appointment of law enforcement inspectors, appointment of the secretariat to the MCC and collection of fees. South Africa is a signatory to the INCB and the Director General of Health ensures that all reporting requirements are met.

The MCC's mandate is the following:

- Registration of medicines (human and animal) based on quality safety and efficacy.
- Control of medical devices (covered in the Act but not provided for in regulations)
- Approval and monitoring of clinical trials.
- Monitoring of safety.
- Response to signals.
- Licensing of manufacturers, wholesalers and distributors.

The MCC's obligations include: -

[1] *The Minister may, on the unanimous recommendation of the members present at any meeting of council, by notice in the Gazette exclude, subject to such conditions as he may determine, exclude any medicine from the operation of any or all the provisions of this Act, and may in like manner amend or withdraw such notice.*

- Ensuring public safety.
- Ensuring public protection.
- Ensuring transparency in its processes.
- Accountability to the public, the clients (industry and providers) and the public.
- Responsiveness to the environment.
- Risk assessment i.e. minimisation of harm and maximization of benefit.

The Registrar keeps the medicines register and exercises any duties assigned to him or her by the Council, the Minister and the Director General. The Registrar supervises the secretariat and is responsible for the efficient operation of the MCC and MRA.

4. Legal Provisions On How The MCC Works.

The MCC is obliged to hold at least one meeting every three months. The Minister may hold additional special meetings at the discretion of the Chairperson, on a written request by at least three members of the MCC, or on request. The MCC makes decisions by majority vote except when Section 36 (Exclusion of any drug from operation of the Act) is invoked when a unanimous decision is required. Section 36 states:

The MCC may, subject to the approval of the minister, appoint

- An Executive Committee from amongst its members.
- Other ad hoc committees to investigate and report to it any matter within the mandate of council in terms of the Act.
- Members of technical expert committees, largely drawn from academic institutions, research institutions and practitioners. Members of council are also eligible to be members of the technical expert committees.
- The Executive Committee may exercise all the powers of the Council in between full council meetings, subject to ratification at the first ensuing meeting of council to facilitate execution of urgent matters. The

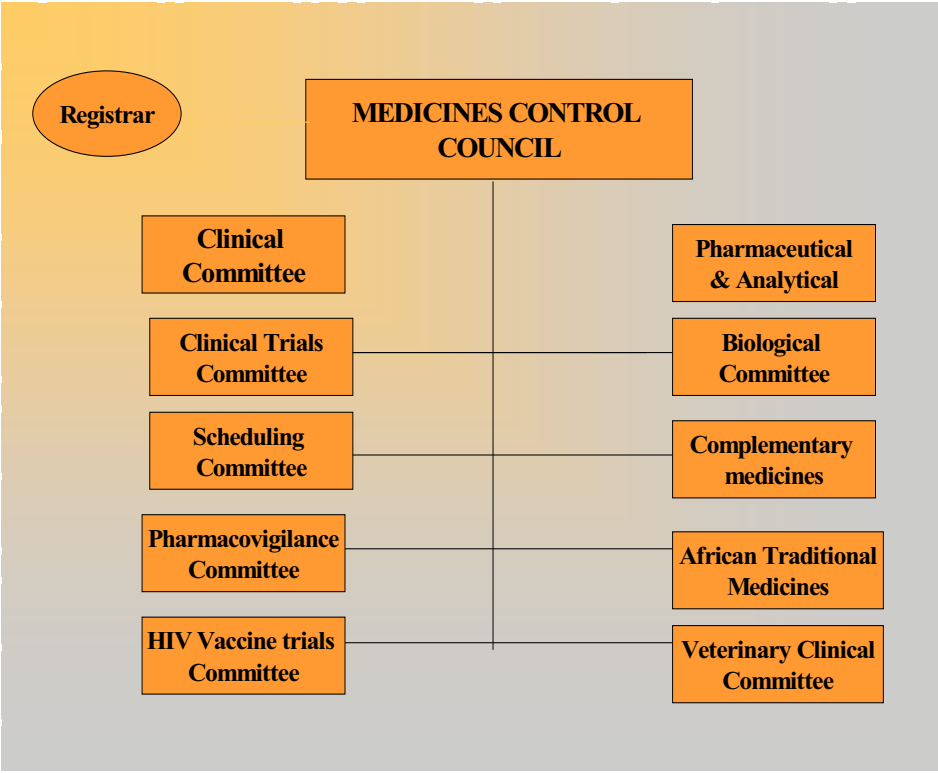
Executive Committee comprises chairpersons of technical Expert Committees, the Vice –Chairperson and the chairperson of council.[2]

The Act provides for an appeal against the decision of the MCC. The Minister appoints an Appeal Committee comprising of not less than three members for the purposes of the appeal concerned. The chairperson of such an Appeal Committee will have a background in law and the skills of the other members will be relevant to the case at hand. The Appeal Committee may confirm, set aside or vary the decision of Council or direct Council to execute the decision of the Appeal Committee. The decision of the Appeal Committee is furnished to both the appellant and the Council. The MCC may contest the decision of the Appeal Committee. Likewise, the Act provides for appeal against any decision of the Director General. In this case, the Minister shall, after considering representations, confirm, set aside or vary the decision of the Director General of Health.

The MCC works through ten standing expert committees as illustrated in figure 1 below.

[2] *The Executive Committee may, subject to the directions of council, exercise all powers and perform all the functions of council during periods between meetings of the council, but shall not have power, save in so far as council directs otherwise, to set aside or vary any decision of the council, and any action taken or decision made by the executive committee shall be subject to review at the first ensuing meeting of the council.*

Figure 1



The MCC and its committees comprise 145 members whose skills are written in law. They include expertise in toxicology and medicine safety, clinical pharmacology, biotechnology, pharmaceutics, internal medicine, virology, pharmaceutical chemistry, neonatology, pediatrics, immunology, veterinary science, complementary medicines and law. A number of experts serve in more than one expert committee.

The Pharmaceutical and Analytical Committee has 16 members. This committee also peer reviews GMP inspectors' reports.

The Scheduling and Names Committee has 7 members.

The Clinical Trials Committee has 22 members.

The Clinical Committee has 18 members.

Biological Committee has 12 members

Complementary Medicines Committee has 8 members

Pharmacovigilance Committee has 9 members

African Traditional Medicines Committee has 10 members

HIV Vaccine Trials Committee has 12 members (Now incorporated into Clinical Trials Committee)

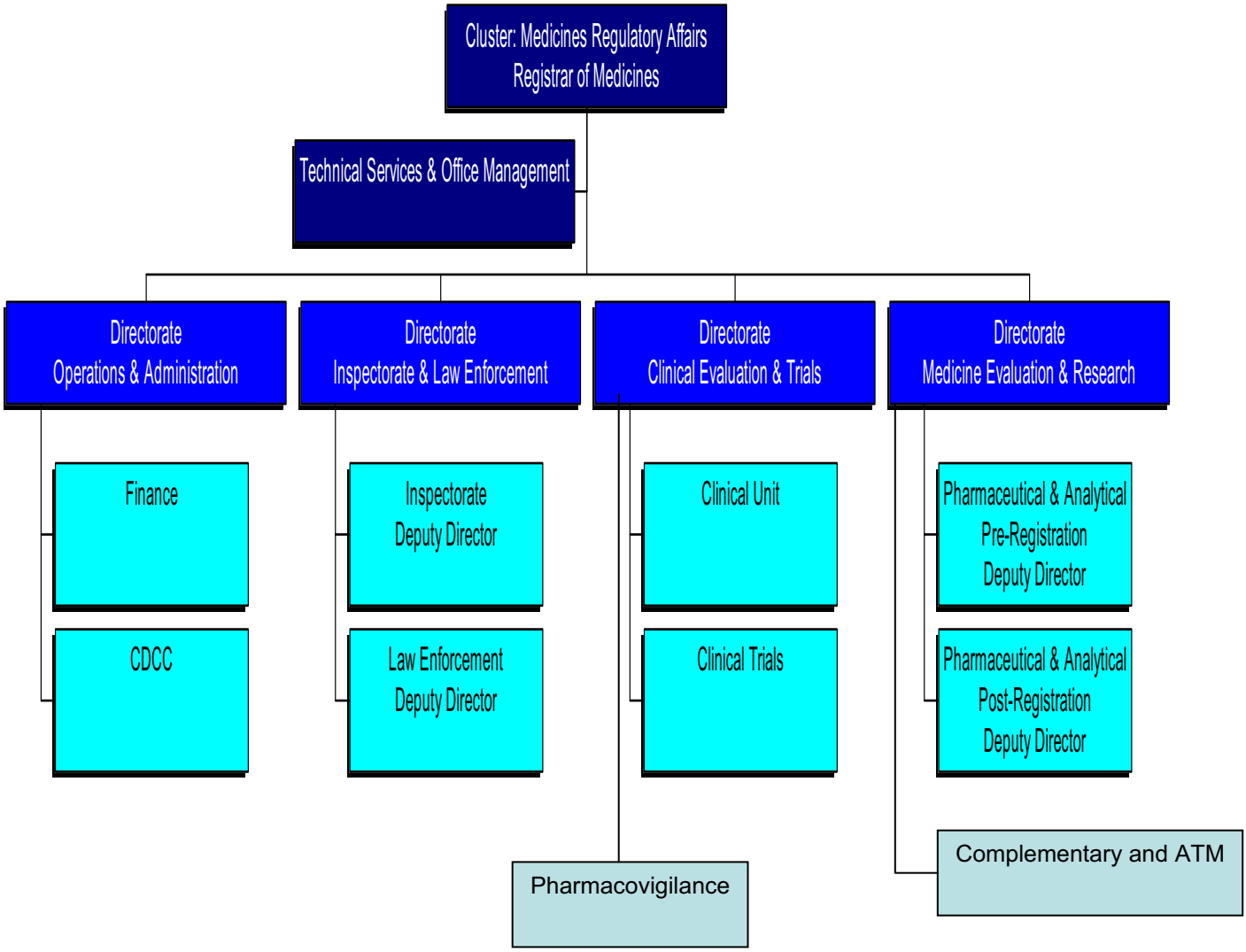
Veterinary Clinical Committee has 12 members

5. Cluster: Medicines Regulatory Affairs (MRA)

The Cluster: Medicines Regulatory Affairs (MRA) serves as the secretariat to the MCC. The Registrar is the cluster manager of this unit. All personnel of the MRA are employed by the Department of Health and are accountable to the Director General. The cluster comprises four Directorates, viz Medicines Evaluation and Research, Clinical Evaluations and Clinical Trials, Inspectorate and Law Enforcement and Operations and Administration. The high level organogram is illustrated in Figure 2 below.

FIGURE 2

Medicines Regulatory Affairs Organogram



The cluster has a staff complement of 138, comprising 74 technical officials (health related), 1 law expert, 1 information technology expert and 62 administrative supports. Of the 74 technical officials, two are at doctorate level, three MD and 11 Masters level,

6. Process Of Evaluation

MCC has published a number of guidelines on the information required for evaluation of dossiers for different categories of medicines and also on the process Council and its committees will follow. These are published on the website mccza.com and are continually updated when necessary.

Amendments are published for comment before ratification. Workshops are held from time to time with manufacturers to update them on amendments to guidelines, new guidelines and processes. There is a forum viz ITG comprising industry regulators and MRA technical staff that meet to discuss common operational issues (this has not met recently). There is however no pre-evaluation meeting with applicants.

Applications are received by the MRA (Directorate Operations and Administration), allocated a reference number and are screened for administrative and technical completeness. The applicant is notified of the outcome of screening. An application is either accepted or put on hold if there are shortcomings. The applicant should be advised to correct shortcomings within 7 –10 days. Screening should take 10 working days. If screening is successful, the applicant is notified to submit the full dossier. The latter is allocated to the different directorates for allocation to evaluators for scientific assessment with a time frame. There may be queuing for allocation depending on the number of dossiers, the required technical expertise and the availability of evaluators.

An evaluator may raise questions, which are forwarded to the applicant by the secretariat, and responses are forwarded back to the evaluator. The evaluator then submits a report to the relevant committee for peer review. Questions to the sponsor may be raised at this stage and the evaluator may be required to continue with the assessment. When the committee is satisfied with the evidence on safety, efficacy and quality, it will make a recommendation to MCC for registration. Each technical committee works independently and all work concurrently on a particular product. Technical staff from the MRA provides support to the committees and attend committee meetings. This

arrangement is however not always efficient as committees do not sign off reviews at the same time. Reports from the Clinical Committee are usually finalised after the other Committees' reports are finished.

External reviewers evaluate new chemical entities. A certain amount of technical evaluation of generic medicines is performed in-house. Evaluation reports prepared by internal reviewers are also subject to peer review by the relevant expert committee.

Members review all recommendations to MCC and the expert committee chairs table recommendations and respond to any questions raised. The MRA Directorate Managers attend meetings of the MCC and provide the requisite support, respond to questions and note directives from Council.

Each Directorate supports a committee or committees of Council with both technical and administrative support. Technical screening of applications, development if standard package inserts for generics, pharmaceutical and analytical evaluation of generics, bioequivalence evaluation of generics, post registration minor amendments are done in-house.

The Director General appoints Law enforcement inspectors. There are three GCP inspectors and eight GMP inspectors. MRA has applied for PICs membership, has been inspected and now granted membership. This unit also inspects wholesalers and distributors for good Wholesaling Practice and good Distribution Practice.

The law enforcement arm's functions include ensuring compliance by all practitioners and the public with the provisions of the Medicines and Related Substances Act, border control, processing of narcotics permits for imports and exports, compliance with INCB requirements and co-operation and liaison with other law enforcement agencies with regard to prosecution. Law enforcement inspectors have powers to enter premises, search and seize suspect medicines, take samples and conduct tests on such samples. They do not have powers to arrest and prosecute and rely on other law enforcement agencies for these functions. The inspection of manufacturing

sites occurs both locally and internationally. There are more than 200 licensed manufacturers, importers and exporters locally and another 180 sites inspected abroad. There are 117 licensed wholesalers/distributors and another 700 to be inspected.

MCC performs a full evaluation and does not consider approval by another regulatory authority as proof of registrability. There are memoranda of agreements however with some of the mature regulatory authorities e.g. FDA, Swissmedic, TGA, MHRA with the usual provisos on confidentiality. When necessary, an evaluation report is sought from another agency. These are however do not influence the evaluation and are only used at the end of the review for quality assurance.

Each committee has developed standard operating procedures. There is however no formal Good Review Practice policy or code to ensure timeliness, predictability and consistency.

Legislation provides for fast -track evaluation of all items on the Essential Drugs List and for innovative medicines for which there is no registered product that meets that particular health need. There is also provision for allowing the importation and use of unregistered medicines on compassionate grounds. The Minister has delegated this function to the MCC. MRA processes these applications by delegation, solicits support from the MCC when necessary and reports to council on all exemptions granted. This delegation is necessary so as not to deprive the public of timely access to medication. This exemption (Section 21of the Act) is also used to enable importation and use of unregistered medicines in clinical trials.

An illustration of human medicine registrations processed over the last four years is tabulated in Table 1 below.

TABLE 1 (a)

Year	2003	2004	2005	2006
Applications ^received*	586*	707*	603*	940
(i) NCE	31	62	40	49
(ii) Generic	555	645	563	860
(iv) Fast track**	77	290	125	191
Registered***	440	290	769	551

* Excludes veterinary products
**Fast track = expedited registration

*****The totals supplied for products registered are those registered in the particular year, and do not necessarily include applications received in that year (e.g. of the 440 products registered in 2003 only some are of the 586 submitted in 2003, the majority still from previous years)**

An illustration of registrations of all medicines reflecting the backlog

Table 1 (b)

Registration Information as at 08-01-2008

Applications	[1]Received (final)	[3]*Not registered end 2007*	*Percentage not registered*	[2]Registered	NCEs (molecules)	
					Received	Registered
2003						
Human	580	*163*		418	16	20
Veterinary	15	*4*		16		
Total	**595**	***167***	**28 %**	**434**		
Generics	508			318		
2004						
Human	590	*215*		281	25	17
Veterinary	12	*6*		8	2	
Total	**702**	***221***	**31 %**	**289**		
Generics	563			213		
2005						
Human	590	*309*		746	18	20
Veterinary	10	*8*		20		
Total	**600**	***317***	**53 %**	**766**		
Generics	490			633		
2006						
Human	923	*737*		546	18	19
Veterinary	16	*16*		6	3	
Total	**939**	***753***	**80 %**	**552**		
Generics	801			468		
2007 (01/01/2007 – 30/11/2007)						
Human	883	*866*		386	22	9
Veterinary	12	*12*		1		
Total	**895**	***878***	**98 %**	**387**		
Generics	765			342		
Total				**[5]2 428**		
	[4]3 731	**[4]2 336**	**63 %**	**[4]1 395**		

[1]Applications received: Number of **final** applications received, i.e. those that passed screening

[2]Applications registered: The number indicated as registered in a particular year does not indicate the number received AND registered in the *same* year, but indicates the total number registered in that year and includes applications from previous years

[3]Applications not registered: The numbers indicate the number of applications of those submitted in the particular year not yet registered to date.
[4]Of the 3 731 applications received for the period 2003 to 2007, 1 395 were registered and 2 336 have not yet been registered.
[5] 2 428 applications were registered in the period 2003 to 2007, i.e. 1 395 of the applications submitted in that period and 1 033 from the period before 2003.

7. Clinical Trials

The Medicines and Related Substances Act 101 and the National Health Act 61 of 2003 govern conduct of clinical trials. All clinical trials of both non-registered and registered medicinal substances in humans must be approved by the MCC prior to commencement. Sponsors must register all South African based trials on the South African Clinical Trials Register, managed by the Department of Health. The National Health Act mandates the establishment of National Research Ethics Council that ensures compliance of all Research Ethics Committees to the relevant legislation, regulations and guidelines. Research ethics committees ensure the protection of, and respect the rights, safety and well being of study participants. The GCP Guideline 2006 edition is the guidance document. It was developed and aligned to ICH and WHO GCP guidelines. The MCC evaluates the study design, the competency of the Principal Investigator, compliance with GCP. The MCC issues a certificate that authorises the importation of the study drug or grants exemption from the registration conditions of a registered drug when the trial is for example investigating a new indication.

GCP inspectors conduct inspections to verify compliance with GCP guidelines to ensure that clinical studies follow scientific and ethical requirements. They also verify that the informed consent processes particularly for vulnerable populations and for obtaining biological samples for genetic studies meet GCP, regulatory and ethical standards. Most studies are performed to support new drug development, a few vaccines and there are an increasing number of bioequivalence studies. The majority of sponsors are research-based industries. The MRA screens applications. There must be a national Principal Investigator. The current workload of investigators and their time commitments to clinical trial work are declared. If a trial is to be conducted in

South Africa and not in the host country of the applicant or sponsor, an explanation with reasons has to be provided. If applicable, all details of and the reasons for trials being halted by other regulatory authorities or ethics committees are required.

The number of studies reviewed over the last three plus years is tabulated in Table 2 below: -

Reviewed Clinical Trials

TABLE 2

	2004	2005	2006	2007
January	41	41	63	0
February	0	32	45	0
March	0	0	0	69
April	44	47	0	0
May	0	1	44	54
June	50	34	45	37
July	0	0	0	0
August	49	51	35	51
September	74	0	0	0
October	0	63	42	82
TOTAL	**258**	**269**	**274**	**293**

- The lead- time from the date of application to the date of approval on average is 12 to 16 weeks.

- Some of the limitations that have been noted are GMP and GCP related e.g. non-adherence to GMP standards for investigator drug, particularly with non- industry sponsored trials, lack of SOPs, poor record keeping, lack of appointment of monitors, etc. MCC/MRA also do not proactively monitor trials very closely after approval. There are only 3 GCP inspectors.

8. Laboratories

Laboratory services are outsourced to two laboratories, based at the Universities of Free State and North West. The latter conducts pharmaceutical analyses and the former conducts batch analyses of biologicals. Pharmaceutical analyses are mainly requested for post- marketing surveillance.

9. Medical Devices

Only medical devices that are impregnated with medicines are evaluated, and even so only for the medicine component. The quality and safety of the device itself is regulated under the Directorate Health Technology. Medical devices are classified into three classes on the basis of risk, viz:

- Class I – Low risk to patient and no contact or interaction with body
- Class IIa – Medium risk- invasive, but limited to natural body orifices and wound management
- Class IIb – Medium risk, partially or totally implantable, may modify biological or chemical composition of body fluids
- Class III- high risk- affect functioning of vital organs and ‘ or life support systems.

The Radiation Control unit licenses radiation emitting devices and equipment. Currently devices that are imported must comply with a designated ISO standard, be registered in the country of origin (the CE mark and FDA approval are recognized) and for locally produced ones, standards SANAS develops standards. There is a global network that reports adverse events and South Africa is a participant. South Africa is a net importer of devices.

10. Complementary Medicines

These are not yet regulated. Council is still finalizing regulations. They were supposed to be finalised by November 2007 but have not yet been finalised. The Medicines and Related Substances Act defines medicine in a manner that includes **all** medicines. There are many in the market already. A call up notice was issued by MCC and applicants are still submitting products for noting. The intention is to phase in regulation of these products. Prioritization will be based on risk. Claims range from enhancing body functioning, risk reduction and cure. Ingredients (medicinal and non medicinal), recommended conditions for use, safety and efficacy information, GMP, level of evidence are some of the areas that will be covered in regulatory evaluation.

11. African Traditional Medicines

Herbal medicines are challenging as they contain a number of bioactive chemicals. Standardization implies that the preparation contains a designated percentage of chemical component or a range thereof, to be therapeutically active. With botanicals, the compounds responsible for therapeutic activity are usually unknown.

On the other hand, natural products have been sources of leads to synthetically produced molecules that are developed as allopathic medicines. Some natural products however seem to be more efficacious in their native state, the reason often being the stability of the molecule.

- They are not yet regulated. Council is drawing up guidelines for evaluation thereof. It is envisaged there will be three broad groups of products viz: -
    - Those that have been used for ages mainly for minor and self-limiting ailments. The focus will be mainly hygiene, as efficacy will have been established. The proviso is they would be used in the traditional way, which mainly extemporaneous.

- Those that have been used over ages but are commercialized and packaged as capsules, tablets, elixirs etc. Quality and safety will have to be established. Manufacturers would have to comply with GMP, labeling standards and be licensed. Wholesalers would comply with GWP and GDP etc. and be licensed.
- Those claiming cure for more serious conditions e.g. HIV and AIDS, diabetes, hypertension, communicable diseases etc. Efficacy, safety and quality will have to be established through clinical trials, GMP etc. as with allopathic medicines.

The challenge though is to find appropriate tools for establishing evidence. Clearly defined criteria to describe the amount and type of data required evaluating products for safety, quality and efficacy are necessary. An expert group of MCC is currently investigating this issue.

12. Medicines And Food

MCC has appointed a Task Team to investigate the interface between medicines and food. This team is working with a representative from the Food Control Directorate. The purpose is to develop a risk based methodology that will define at which levels food components become medicines in accordance with International norms. Mature Regulatory Authorities are addressing the same issue.

13. Challenges

Human Resources

- The Regulatory Authority relies heavily on a small pool of external reviewers who have other responsibilities in their primary jobs at Tertiary Educational Institutions, Hospitals etc. Some reviewers serve in more than one committee. There are no service level agreements or contracts that bind them to agreed to time lines for reviews. This compromises transparency and responsiveness to clients' questions on when reviews are likely to be finished. This also results in long lead

times, on average 24 to 36 months for new chemical entities and 18 to 24 months for generics, 12 to16 weeks for approval of clinical trials etc. there are no service level agreements.

- Clinical evaluation skills are developed and built through practice and mentorship. There are few young evaluators in the expert groups and even at MCC. This poses a serious threat to sustainability and succession planning.

- In- house, the high turn –over of staff particularly in the clinical trials and clinical unit poses a challenge. Experienced staff migrates to the private sector and to other units within the department for better salaries. There are challenges both in terms of recruiting and retaining sufficient numbers and skills. Competencies and numbers of in-house staff need to be assessed. This may require more flexibility in employment conditions, creative incentives to enable and training.

Infrastructure

- The electronic systems used are disparate and managed by each directorate. The SIAMED system used as a registration system does not enable easy tracking of submissions across committees and directorates. It also does not enable efficient allocation of work to reviewers and monitoring of outputs. An electronic document management system is currently being sourced.

Finance

- Both the MCC and the MRA are funded totally through the departmental budget. Any increases are within the MTEF structure. Though fees are collected from applicants, these funds do not accrue

to the MCC/MRA but rather to the Treasury. The fee structure is as follows:-

CURRENT FEE STRUCTURE

TABLE 3

NEW CHEMICAL ENTITY	R30 000
GENERIC	R 12 500
MAJOR LINE EXTENSIONS	R20 000
MINOR VARIATIONS	R230
LICENSING	R3 600
RETENTION FEES	R550
SCREENING	R1050
FAST TRACK APPLICATIONS	R5 000
REGISTRATION	R600
EXEMPTIONS (unregistered drugs)	R200

Quality

- Though there are SOPs that guide reviewers quality systems need improvement. There is also no structured plan for capacity building except for GMP and GCP inspectors.

Conflict Of Interest

- As South Africa is a small country, external evaluators used by the MCC may also perform investigational work for the pharmaceutical industry. There is a potential for conflict of interest with both MCC and MRA staff. Though declaration of interest forms that are signed at every meeting, this strategy however does not go far enough. Risk analysis and management is minimal.

Orphan Drugs

- This area needs attention and there is no provision in the legislation for facilitating access. There are many older medicines that are still required for developing country needs. Another area of concern is the

regulation of radiopharmaceuticals. The latter has a very small market in South Africa and there has been reluctance on the side of manufacturers to register them. The other challenge is the interface between the radiation control units in regulating these.

Juristic Person

- The legislation provides for a regulatory authority that is a juristic person. An interrogation of what this means is necessary. Currently, the Regulatory Authority has “autonomy” in scientific evaluation. It does not have staff and cannot hire and fire. It cannot negotiate remuneration that is for example linked to productivity. Technical experts are remunerated on the basis of tariffs set up by the Treasury for recommendations committees.

Regional Mandates

- This relates to co-operation and harmonization of regulation within SADC. Counterfeits and resistance to antibiotics stemming from sub-optimal use have no boundaries. Many of the countries in the region have weaker regulatory systems. There is however willingness in general to strengthen medicine regulation. An analysis of the strategic role of South Africa in SADC is necessary. Local production of pharmaceuticals, particularly those that address conditions prevalent in developing countries has been identified as a priority by the African Union. This implies the regulatory authority must be strategically positioned to respond to this need.

Co-Operation With Mature Regulatory Authorities

- South Africa needs to assess whether benefits derived from co-operative agreements with more mature regulatory authorities are fully maximized. This will become more crucial as evaluations for new biotechnologies becomes necessary. Expertise for these is still limited

the world over. The country may need to identify different tools and methodologies to address these.

Veterinary Medicines

- Two departments regulate these. The distinction is that MCC regulates those medicines that have potential to impact on the health of humans e.g. antibiotics. The Directorate Food Control regulates maximum residue levels in pesticides. Stock remedies (including pesticides) are regulated under Act 36 administered by the Department of Agriculture. The intention of this Act is to enable farmers to access animal medicines that they can administer themselves without the intervention of a veterinarian. This is necessary, as some conditions need immediate attention. The challenge arises when farmers use antibiotics and other medicines, inclusive of hormones, in feeding troughs to promote growth. This has a direct impact on antibiotic resistance in humans. Residue levels also need to be monitored for safety in humans. This dual regulation opens loopholes, as standards applied by the two departments are not similar. Clearer guidelines are necessary. Animal health stakeholders have indicated they would prefer regulation under one regulatory authority.

Timelines & Transparency

- Registration timelines are sub-optimal. Service level agreements with evaluators are necessary. Delays are however not only caused by the MRA/MCC. Some of the dossiers or clinical trial applications are substandard.

- The Electronic Document management system being implemented will enable the MRA to track documentation, the efficiency of both officials and evaluators, facilitate assignment and re-assignment of dossiers, and facilitate communication amongst experts. It is envisaged

submissions will be electronic and each applicant will have access to their own dossier movement and can respond quickly to any questions raised during the evaluation.

- It is envisaged it will also make it easier to share information intended for providers (e.g. issues of Pharmacovigilance, cautions, warnings), and the public.

Post Marketing Surveillance

- This area needs to be strengthened. The capacity of the MRA and linkages with universities are sub- optimal.

Pharmacovigilance

- The challenge in this area is the volume of reports received by the MRA.

Fast Track Provisions For Generics

- Legislation provides for fast track evaluation of all medicines on the Essential Drugs List. This was intended to facilitate access to medicines that address the most prevalent conditions in the country. The majority of items on the EDL are generics. While competition is desirable in making medicines affordable, there is no cost reduction until the number of generics reaches four or five. EDL generics applications tend to clog the regulation system, delaying evaluation of other products thus compromising timely access thereto. This policy directive may have to be revisited, ensuring the original intention is preserved, but more efficiently.

How To Enhance Efficiency

- Appraisal of the workload of evaluators and the introduction of SLA
- Setting up standards to ensure consistency of evaluation

- Project management of evaluation process including allocation, and timeline management
- Setting up of a performance management system linked to incentives and penalties (internal)
- Strengthen in-house capacity to evaluate generics.
- Fast tracking of the implementation of the electronic document management system
- Enhanced communications with the industry to ensure the transfer of information in both directions

CHAPTER 2

MINISTERIAL TASK TEAM TERMS OF REFERENCE

The Ministerial Task Team was appointed to conduct and review of the current MCC and MRA and to make recommendation for a new regulator authority for health products in South Africa. The terms of reference of the Task Team were to:

- Undertake a detailed background study and conduct a current situation analysis of the past and current Medicines Control Council (MCC) and Medicines Regulatory Affairs (MRA) and study all available resource documentation.

- Conduct a legal scan of the legislation regarding the MCC and the MRA of South Africa and of selected other related regulatory bodies globally.

- Investigate the roles and relationships of the MCC and the MRA and / or similar regulatory bodies.

- Undertake an analysis of regulatory bodies globally in terms of their organisational structures, functions, relationships and effectiveness. This must include bodies of various formations in selected countries including those in Africa.

- Study the organisational structure and operations of the selected bodies reviewed.

- Determine possible models for a regulatory authority inclusive of their formation, organisational structure, situation, function, outputs and efficiency.

- Consider the details of the regulation of Health Technology, Medical Technology and Medical Devices, and make recommendations for a single or a separate regulatory authority with regard to medicine and these technologies.

- Consider additional terms of reference as decided by the Minister and the Director-General and any further issues that may arise in the work of the task team during its work.

- Make recommendations with regard to a efficient regulatory authority body for Medicines and Health Technology, Medical Technology and Medical Devices for consideration by the Minister.

CHAPTER 3

PROBLEM STATEMENT/ ISSUES OF CONCERN

The current regulatory authority (MCC) dates back to 1965 and needed a systemic review in order to perform its functions in the current environment in which significant, scientific advances have occurred, globalisation has had a strong effect, workload has increased enormously and regulatory affairs in health products are advancing fast. There has been concern expressed about the efficiency of the current MCC due to resource and capacity constraints and a structure, which has been outgrown. This is contributing to disadvantageous knock on effects.

CHAPTER 4

VISION AND MISSION

A Vision and Mission Statement for the New Regulatory Authority needs to be developed. The current MCC and MRA do not have a vision and/or a mission statement.

CHAPTER 5

OBJECTIVE

To recommend to the Minister a comprehensive and an independent umbrella New Regulatory Authority that will fulfil its mandate and ensure that all Health Products (Human and Animal) regulated and registered in South Africa meet the standards prescribed and are safe, efficacious, effective and of good quality.

CHAPTER 6

LEGISLATION

LEGAL SCAN OF SPECIFIED COUNTRIES' MEDICINES REGULATORY AUTHORITIES LEGAL FRAMEWORKS

This document provides an outline of the legal frameworks within which specified countries'[3] medicines regulatory authorities operate. It is a brief analysis of the legislation, particularly Acts that regulate such regulatory authorities. It refers, amongst others, to the following in respect of such regulatory authorities:

- Scope of legislation;
- Structures;
- Establishment;
- Composition;
- Powers and functions;
- Registration of medicines;
- Related advisory bodies; and
- Other related matters.

1. BOTSWANA

1.1 *Act*: Drugs and Related Substances Act, 1992

1.2 *Scope of the Act*:

- Medicines;
- Habit forming drugs, as prescribed by the Minister.

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[1] Botswana, Zimbabwe, Tanzania, Nigeria, Singapore, Australia, India, Canada, UK, USA and China.
[2] sec 5
[3] Director of Health Services: Botswana (DG)

1.3 *Structure*: Advisory Board[4]

- Established by the Minister.
- Functions:
  - To advice the Director[5] on:
    i. Whether a drug should be registered or not;
    ii. The conditions subject to which a drug may be registered;
    iii. Whether registration should suspended or revoked.
- Composition and terms of reference determined by the Minister by Notice in the Gazette when appointment is made.
- Term of office: 3 years, eligible for re-appointment.

1.4 *Registration of Medicines*

- Medicines must be registered by the Director before they can be imported into, exported from, manufactured, distributed or sold in Botswana.
- Applications for registration are submitted to the Director.
- The Minister may, in special circumstances, exempt any drug from registration.
- The Director keeps a register of registered drugs.
- The Director may suspend or revoke the registration of a drug.
- Drugs may only be manufactured in establishments licensed under the Industrial Development Act, 1988.

1.5 *Other matters*

- Inspectors are appointed by the Director.
- Persons aggrieved by the decision of the Director may appeal to the Minister.

[4] section3
[5] Section4

2. ZIMBABWE

2.1 *Act*: Medicines and Allied Substances Control Act, 1969

2.2 *Scope of the Act*: medicines and related substances

2.3 *Structure*: Medicines Control Authority

- Established by the Act, a juristic entity.[6]
- Constitution of Authority[7]
    - Not less than 8 but not more than 12 members appointed by the Minister, as follows:
        i. 1 medical practitioner appointed from 3 nominations by the Medical Association;
        ii. 1 Veterinary surgeon appointed from 3 nominations by Council of Veterinary Surgeons;
        iii. 1 pharmacist appointed from 3 nominations by Pharmaceutical Society;
        iv. 1 medical officer of health for a local authority appointed from 3 nominations by Urban Councils Association;
        v. 1 legal practitioner of not less than 5 yrs standing from nominations by Law Society;
        vi. 1 medical practitioner who is a specialist physician;
        vii. 1 person with special knowledge of the action and applications of medicines;
        viii. 1 officer for whom the Ministry is responsible who is either a pharmacist or a medical officer.
    - The Minister designates one member as chairperson and another as vice-chairperson.
    - Term of office, 5 years, members eligible for reappointment.

[6] section 6 (1)(e)
[7] section13
8Section 13A
9 Section 16 (1)

- A person who has a direct or indirect interest in the sale of medicines (manufacturers, wholesalers) disqualified from being a member (not pharmacist / medical practitioner).[8]
- Minister may remove member from office on stated grounds.

- Committees: Authority may establish the following committees:
  - Executive committee
  - Laboratory Committee.
- Funds: Authority has own Funds, fees payable to it and those appropriated[9] and funds are audited by the Auditor-General.
- Annual Report: Authority submits annual report to the Minister on its activities.[10]
- Director-General of Authority: The Authority is headed by the Director-General (DG) who shall:
  - Be the secretary of the Authority;
  - Subject to control of Authority, manage operations of Authority and supervise staff of the Authority.

2.4 *Clinical Trials*

No person shall conduct clinical trials on any medicines without prior authorization of the Authority granted with the approval of the Secretary.[11] Applications are submitted to the DG.

2.5 *Zimbabwe Regional Drug Control Laboratory*

- Functions:
  - Evaluate safety, quality and safety of medicines;
  - Conduct training in the analysis of medicines.
- The Director of the laboratory is appointed by the Authority in consultation with the Minister and the director shall have knowledge of pharmaceutical analysis of medicines.

[8] section 6(1)(e)
[9] section 13
[10] section 13A
[11] section 16(1)

2.6 *Registration of Medicines*

- Applications are made to the DG and the following are taken into account in deciding on the registrability of medicines[12]:
  - Whether availability of that medicines is in the public interest
  - Safety, quality and efficacy
  - Condition of premises, if manufactured in Zimbabwe.
- In cases of medicines manufactured outside Zimbabwe, the application must be accompanied by a certificate confirming registration in the country of manufacture.[13]

2.7 *Registration of Premises*

Applications for registration of premises are made to the DG.[14]

2.8 *Appeals*

Appeals against decisions of the Authority are lodged with the Administrative Court.[15]

2.9 *Inspectors*

Inspectors are appointed by the Authority in consultation with the Minister.[16]

2.10 *Regulations*

The Minister makes regulations. Not in consultation with anyone (including Authority).[17]

2.11 *Exemptions from operation of Act*

The Authority may exempt medicines from operation of Act. Not in consultation with anyone.[18]

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[12] section 30(1)
[13] section 30(2). Interesting because medicine cannot just be manufactured for export to Zimbabwe without registration in country of origin
[14] section 56(1)
[15] section 62
[16] section 65
[17] section 74

3. TANZANIA

3.1 *Act*: The Tanzanian Food, Drugs and Cosmetics Act, 2003

3.2 *Scope of the Act:*

- Food, medicines, medical devices, cosmetics and herbal medicines.

3.3 *Structure*: Tanzanian Food and Drugs Authority[19]

- Established by the Act;
- It is an executive agency:[20]
  - Headed by the CEO referred to as Director-General;
  - The DG is appointed by the Minister on advice of the Civil Service Commission;
  - Commission receives from the Board a list of candidates from whom the DG is appointed;
  - DG is the accounting officer of the Authority;
  - DG appoints and dismisses staff of the Authority.
  - Minister may after consultation with the Commission on the recommendation of the Permanent Secretary[21] dismiss the DG.

3.4 *Responsibilities / powers / functions*

- It is a regulatory body for all the products under the Act;
- It regulates matters of safety and quality;
- Regulates the manufacture, sale and importation of medicines;
- Regulates clinical trials;
- Approves and registers products;
- Issue licenses under the Act;
- Appoints inspectors;
- Maintains registers;
- Responsible for its human resource management and development;

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[18] section 75
[19] sec 4
[20] parastatal / organ of state
[21] head of health (DG in SA context)

- Establishes a Fund for all moneys received by it and disburses such moneys for its activities;
- Appoints technical committees to advise the DG.

3.5 *Ministerial Advisory Board*[22]

- Comprises:
  - Permanent Secretary (chairperson);
  - DG who is the secretary;
  - Not more than 12 persons appointed by the Minister who shall include:
    i. A legally qualified person;
    ii. Chief Medical Officer;
    iii. Director: National Food Security;
    iv. Chief Government Chemist;
    v. Director: Tanzanian Bureau of Standards;
    vi. Representative of local government;
    vii. DG of medical Services: Zanzibar;
    viii. Representative of the Minister responsible for beekeeping and fisheries;
    ix. DG of Tanzanian Atomic Energy Commission;
    x. A person with knowledge of the products who is not a civil servant;
    xi. A person representing the interests of the Authority's stakeholders.
- Notable responsibilities
  - Provides the Civil Service Commission with a list of candidates from whom the DG is appointed.
- What the Board does not do:
  - Advise the Minister on the regulations (the DG does);
  - DG not accountable to it (only the Minister, after consultation with Civil Service Commission, on the recommendation of the Permanent Secretary, can dismiss DG);

[22] sec 8.41

- Appointing analysts and establishing more labs, the Minister is advised by the DG and not the Board).

3.6 *Tanzanian Food, Drugs Authority Laboratory*

- The laboratory is established by the Act within the Authority.
- The laboratory:
  - Performs quality functions;
  - Conducts analyses;
  - Conducts research / training.
- The Minister may, on advice of the DG, establish other laboratories to assist the main one.
- The Minister may, on advice of the DG, make rules on the functions of/procedures by laboratories.
- The Minister appoints analysts on the advice of the DG.

3.7 *Registration*

- Registration of premises[23]
  - Applications for the registration of premises used for manufacturing are made to and considered by the Authority and if approved, the DG registers the premises.
- Licence to manufacture products[24]
  - Applications made to the Authority;
  - Licence issued by the Authority.
- DG keeps registers of licenses issued in respect of:
  - Manufacturers;
  - Wholesalers;
  - Retailers, et al.

[23] sec 18
[24] sec 20

4. NIGERIA

4.1 *Act / Decree*: Drugs and Related Products (Registration, etc) Decree, 1993

4.2 *Scope of Act*: medicines, cosmetics and medical devices

4.3 *Manufacturing / Importation*

Products may only be manufactured / imported after a permit has been granted for that purpose by the National Agency for Food and Drug Administration and Control.[25]

4.4 *Registration of products*[26]

- An application for registration is made to the Agency and approved / rejected by the Agency.
- Amongst factors taken into account by Agency in deciding whether a drug can be registered is the need for such a drug in Nigeria.
- Registration valid for 5 years.
- Agency may cancel registration of product.
- Agency also considers applications for clinical trials.

4.5 *Drug Registration Committee*[27]

- The Committee evaluates the product and advises the Agency;
- Committee members are appointed by the Agency.

4.6 *Structure*: National Agency for Food and Drug Administration and Control (NAFDAC)

- Established in terms of own decree[28]
- Its Governing Council *comprises:*[29]

[25] section 1
[26] section 2
[27] section 8
[28] National Agency for Food and Drug Administration and Control Decree, 1993. section 1.
[29] Section 2

- Chairman, appointed by the President of Nigeria on the recommendations of the Minister;
- Director-General of Health;
- Director-General of Standards Organisation of Nigeria;
- Chairman of National Drug Law Enforcement Agency;
- Chairman of the Pharmacists Board of Nigeria;
- A person representing the Pharmaceutical Group of Manufacturers Association of Nigeria;
- Person representing the Food Beverage Group of the Manufacturers Association of Nigeria;
- The Director-General of the Agency;
- 3 other persons to represent public interest appointed by the Minister.

- *Term of office*: 4 years eligible for only 1 further term.
- *Removal from office*: a member of the Council may be removed from office by the President of Nigeria on the recommendation of the Governing Council.

4.7 *Functions / Powers of the Governing Council*[30]

- Advises government on general policies on control of products including bottled water and chemicals;
- Makes regulations with approval of Minister;[31]
- Determines quality standards;
- Appoints, develop, train & dismiss staff of Agency;
- Establishes committees for Agency;
- Opens and operate an account for the Agency;
- Determines management system for Agency.

4.8 *The Agency*

- Functions / Powers[32]
  - Regulates / controls drugs, bottled water and chemicals;

[30] section 6
[31] section 29
[32] section 5

- Conducts tests to ensure compliance with standards;
- Conducts investigations / inspections of premises;
- Determines standards and guidelines for production, manufacture, etc;
- Establishes and controls relevant laboratories
- Pronounces of quality and safety;
- Conducts research;
- Sponsors conferences.

- Structure of Agency[33]
  - Administration and Finance section;
  - Planning research and Statistics;
  - Regulatory and Registration;
  - Inspectorate division;
  - Laboratory Services;
  - Headed by Director-General (CEO) appointed by President;
  - Agency juristic person.
- Funds of the Agency

  Agency shall establish Fund for depositing fees charged by Agency.

4.9 *Regulations*

- Regulations are made by the Governing Council with the approval of the Minister.

4.10 *No appeal provisions*. It means other laws relating to review proceedings apply.

[33] section 8

5. SINGAPORE

5.1 *Act:* Medicines Act.

5.2 *Scope of the Act*: Medicines

5.3 *Structure*: Licensing Authority

- Licences and certificates to import, export, supply by sale or wholesale or manufacture or assemble medicines are issued by the licensing authority[34] which is;
    - The Chief Executive of the Authority, and
    - The Director-General: Agri-Food and Veterinary Services in relation to veterinary medicinal products and animals.

5.4 *Appeals*

- Appeals against decisions of licensing authority are lodged with the Minister for Health / Minister for National Development (vet med products and animals). The Minister's decision is final.[35]

5.5 *Exemptions in respect of herbal remedies*

- The requirement for a licence / certificate does not apply to herbal remedies where such remedies:[36]
- Are sold / supplied for administration to a particular person
- Manufactured / assembled at the premises by the occupier of such premises
- The process of producing the remedy consists only of drying or crushing
- The remedy is supplied without any written recommendation (labelling / package insert / leaflet).

[34] sections 4 and 5. Pharmacists and medical practitioners accordingly exempted.
[35] Section 4(3)
[36] section 8

5.6 *Exemptions from provisions of the Act*

- The Minister may, by order, provide for exemptions from the licensing / certificate requirements.[37]

5.7 *Applications for licences*

- Applications for licences are made to the licensing authority and it is the licensing authority that is responsible for keeping a register of medicinal products.[38]

5.8 *Factors relevant to the determination of applications for licences*

- The following factors are taken into account:[39]
- In case of product registration licence
  - Safety, quality and efficacy.
- In case of importation licence
  - An undertaking by manufacturer to permit the premises to be inspected;
  - An undertaking by manufacturer to comply with prescribed conditions;
  - A declaration by manufacturer that applicable laws of country of origin have been complied with.
- In case of manufacturing licence
  - Operations to be carried out;
  - Premises / equipment;
  - Qualifications of persons who will be supervising the operations;
  - Arrangements for safekeeping / maintaining adequate records.
- In case of wholesale licence
  - Premises / equipment for storage and distribution;
  - Arrangements for safekeeping.

5.9 *Patents*

[37] section 9
[38] section 11
[39] Section 12

- In considering an application for a licence, the licensing authority takes into account possible patent right infringement. The applicant is required to furnish a declaration of non-violation of patent rights.[40]

5.10 *Inspections*

- Inspectors are appointed by the licensing authority.[41]

5.11 *Fees*

- Fees payable in terms of the Act to the licensing authority shall be paid to the Authority or Agri-Food and Veterinary Authority.[42]

5.12 *Protection of confidential information on innovation products*[43]

- Where the licensing authority receives an application that contains confidential supporting information on an innovative medicinal product, the authority has an obligation-[44]
  - To keep that information confidential;
  - Not to use that information to grant another licence.
- The information referred to above may be disclosed-
  - With the consent of the applicant;
  - If in opinion of Authority, is necessary to protect health / safety of public.
- The information may be disclosed to the following that shall take steps to ensure information is kept confidential-
  - Other government department / statutory body;
  - Any adviser engaged by Authority;
  - Any advisory committee established under the Act;
  - WHO;
  - Food and Agriculture Organization;
  - Any regulatory agency of WTO country.

[40] Section 12A
[41] section 57
[42] section 72A
[43] section 19A. Sections with capital letters were subsequently inserted.
[44] This is not a secrecy clause that simply requires Authority staff not to disclose information as this is provided for in section 62.

5.13 *Advisory Committees*

- Advisory committees for the Authority are appointed by the Minister[45]

5.14 *Regulations*

The Minister makes regulations.

6. AUSTRALIA

6.1 *Act*: Therapeutic Goods Act, 19892.

6.2 *Scope of the Act*:

- Medicines, medical devices, complementary medicines[46] and other therapeutic products.

6.3 *Appeals*

- Appeals against decisions of the Secretary with regard to registrations are made to the Minister. Appeals against Minister are made to the Administrative Appeals Tribunal.

6.4 *Declaration that goods are / are not therapeutic goods*

- A declaration that goods are / are not therapeutic goods is made by the Secretary and such declaration must be published in the Gazette.[47]

6.5 *Appointment of authorised persons (inspectors)*

- Authorised persons are appointed by the Secretary.[48] These persons exercise powers as conferred under various sections of the Act.

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[45] Section 73
[46] see section 52F and 52G. Section 52G simply establishes complementary medicines evaluation committee whose constitution and functions are prescribed by regulations.
[47] Section 7
[48] section 7A

6.6 *Register of Therapeutic Goods*

- The Secretary keeps a register of therapeutic goods and the register comprises 3 parts i.e. for registered goods, listed goods & medical devices.[49]

6.7 *Determination of standards*

- The Minister, by order published in the Gazette, determines standards for therapeutic goods.[50] It's a criminal offence to import, supply or export therapeutic goods that do not comply with standards.[51] The offence also has civil penalties.[52]

6.8 *Exemption from Registration*

- The Minister may, in writing, exempt from registration certain therapeutic goods if the Minister is satisfied that it is in the national interest to do so in order to stockpile therapeutic goods to deal with potential threat to public
- Health that may be caused by a possible future emergency or emergency that has occurred.[53]
- The Minister must table such exemption before Parliament for information.[54]
- Exemptions for special use for treatment of a person or for experimental purposes is granted by the Secretary.[55]

6.9 *Registration*

- Applications for registration / listing must be delivered to office of Department specified by the Secretary.

[49] section 9A
[50] section 10
[51] section 14
[52] section 14A
[53] section 18A
[54] section 18(11)
[55] section 19

- Factors to be taken into consideration when deciding on the application for registration include:[56]
    - Safety, quality and efficacy;
    - Goods presentation;
    - Standards compliance;
    - Acceptability of quality control standards;
    - Such other matter as the Secretary may consider relevant.

6.10 *Patents*

- A certificate[57] of patent non-violation is required when an application for registration is made.

6.11 *Cancellation of Registration*

- The Secretary may cancel registration if:[58]
- Failure to do so would create imminent risk of death, serious illness / injury;
- Person refused to comply with conditions.

6.12 *GM Therapeutic Goods*

- Applications for the registration of therapeutic goods that are genetically modified or contain genetically modified products must be considered after advice from the Gene Technology Regulator.[59]

6.13 *Manufacturing of Therapeutic Goods*

- Applications for licenses are made to office of the Department specified by the Secretary and where such application satisfies all requirements, licence is granted by the Secretary.[60]
- The Minister determines manufacturing principles and such principles may relate to standards / equipment / premises to be used.[61]

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[56] section 25
[57] section 26B
[58] section 30
[59] 30C
[60] section 37

6.14 *Therapeutic Goods Administration Account*

- Account in which it is deposited amounts received in respect of registrations et al established in terms of section 45 of the Act.

6.15 *Committees*

- The following are some of the Committees established by the Act
- National Drugs and Poisons Schedule Committee;[62]
- Complementary Medicines Evaluation Committee.[63]

7. INDIA

7.1 *Act*: Drugs and Cosmetics Act, 1940

7.2 *Scope of the Act*:[64]

- Medicines, including homeopathic, ayuvedic, unani (for humans / animals)
- Insect repellents and pesticides, as specified
- Substances used on components of medicines, eg empty capsules
- Medical devices, as specified
- Cosmetics

7.3 *Structure*: Drugs Technical Advisory Board[65]

- Appointment: It is appointed by the central government to advise the government on technical matters in relation to the administration of the Act.
- Composition: It comprises-
  - Director-General of Health (chairperson) *ex officio (eo);*
  - Director: Central Drugs Laboratory *eo;*

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[61] section 36
[62] section 52B
[63] section 52G
[64] sec 3
[65] sec 5

- Director: Central Research Institute *eo;*
- Director: Veterinary Research Institute *eo;*
- President: Medical Council *eo;*
- President: Pharmacy Council *eo;*
- Director: Central Drugs Research Institute *eo;*
- 2 officials in charge of drugs control in the states[66] appointed by the central government;
- 1 person elected by the executive committee of the Pharmacy Council from academics in pharmacy / chemistry / pharmacognosy;
- 1 person elected by the executive committee of the Medical Council
- From academics in medicine / therapeutics;
- 1 person appointed by the central government from the pharmacy industry;
- 1 pharmacologist elected by governing body of Council of Medical Research;
- 1 person elected by Central Council of Indian Medical Association;
- 1 person elected by Council of Indian Pharmaceutical Association; and
- 2 government analysts appointed by the central government.

- *Term of office*: members serve for a period of 3 years and are eligible for reappointment / election.
- *Responsibilities / Functions / Powers*: The Board-
  - Determines rules[67] subject to central govt approval, relating to the conduct of its business;
  - Appoints its committees (also from non-members);
  - Central government makes rules on the administration of the Act after consultation with the Board;[68]

[66] in SA context, provinces
[67] in SA context, regulations
[68] sec 12

- Central government determines standards of quality in relation to the manufacture / sale / distribution after consultation with the Board;[69]
- Central government determines functions of the Central Drugs Laboratory after consultation with the Board.

- *Secretary of the Board*: The Board's secretary and staff are appointed by the central government.

7.4 *Central Drugs Laboratory*[70]

- Established by the central government;
- Conducts tests on medicinal products;
- Analyses samples;
- Some functions of the CDL in respect of certain medicines are performed by other institutions, e.g.
  i. Vaccines, toxins, sera, antigens: performed by the Central Research Institute;
  ii. Polio vaccines: Indian Medical Research Council et al;
  iii. Homeopathy: Homeopathy Pharmacopoeia Laboratory.

7.5 *Drugs Consultative Committee*

- Appointed by central the government;
- Comprises 2 representatives of central government and 1 representative per state nominated by such state;
- Advises central government, states and Board to ensure uniformity on the administration of the Act throughout India.

7.6 *Inspectors / analysts*

- Appointed by the central government.

[69] sec 8
[70] sec 6

AYURVEDIC / UNANI DRUGS

7.7 *Ayurvedic / Unani Drugs Technical Advisory Board*[71]

- Appointed by central government;
- Composition:[72]
    - Director-General of health;
    - Drugs Controller India;
    - Official in Ministry of Health dealing with Indian systems medicines;
    - Director: Central Drugs Laboratory;
    - 1 government analyst;
    - 1 pharmagognocist appointed by the government;
    - 1 phyto chemist appointed by the government
    - 4 persons appointed by the government from pharmacopoeia committees;
    - 3 teachers in Indian systems medicines appointed by the central government;
    - Chairperson appointed from amongst members by the central
    - Government;
    - Secretary / support staff appointed by the central government.

7.8 *Separate sections of the Act on ayurvedic / unani drugs dealing with*:

- Standards of quality;
- Analysts (qualified in these systems);
- Inspectors (qualified in these systems);
- The central government makes rules for these systems after consultation with the Board.

7.9 *Registration of medicines*

[71] sec 33B
[72] sec 33C

- An application for licence to manufacture / distribute medicines specified by the central government in the Gazette is considered and approved / rejected by a Central Licence Approving Authority appointed by the central government.[73]
- State governments appoint state licensing authorities to consider applications for licenses to sell, stock, exhibit, offer for sale or distribute medicines.
- Applications for licence to import new drugs considered and issued / rejected by licensing authorities.
- Appeals against decisions of licensing authorities are made to the central government.
- Applications for licences must be considered and finalised within 9 months. In exceptional circumstances, an extended period of 3 months is allowed.
- Persons / applicants aggrieved by delays in the consideration of applications
- Can appeal to the central government.
- The Minister may, on the advice of the DG, make rules on the functions of / procedures by laboratories.
- The Minister appoints analysts on the advice of the DG.

[73] Rule 68A

8. CANADA

8.1 *Act*: Food and Drugs Act, 1985

8.2 *Scope of the Act*: Foods, Drugs, Cosmetics & Devices

8.3 *Manufacturers*

- No person shall sell any drug described in Schedule C or D unless the Minister has indicated that the premises in which the drug was manufactured and the process and conditions of manufacture are suitable to ensure safety of the drug.[74]

8.4 *Inspectors / analysts*

- The Minister appoints inspectors and analysts.[75]

8.5 *Exports*

- The Act does not apply to drugs that are not manufactured for consumption in Canada and not sold for consumption in Canada if the package is marked with the word “Export” / “Exportation” and a certificate that the package does not contravene any known requirement of the law of the country to which it is destined.[76] The certificate is signed and issued by the exporter.[77]

8.6 *Clinical Trials*

- Applications for authorisation to sell / import a medicine for clinical trials are made to and approved by the Minister.[78]

8.7 *Regulations*[79]

- The Governor in Council makes the regulations

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[74] Section 12
[75] section 22(1)
[76] section 37
[77] Regulation A. 01.045
[78] Regulation C.05.005
[79] section 30

- *Food and Drugs Regulations*
- Importations
- No person shall import a drug for sale into Canada the sale of which would constitute a violation of the Act or the Regulations.
- Where a person seeks to import drugs and the sale of such drugs would not be in violation of the Act and the Regulations if the drug is relabelled or modified, the person may import the drug on condition that-
    - The person notifies the inspector of the proposed importation;
    - The drug will be relabelled and modified.
- No person shall sell a drug that has been imported into Canada unless the drug has been relabelled or modified within 3 months or longer period as may be determined (by the Director *meaning* the Assistant Deputy Minister, Health Products and Food Branch of the Department of Health) after the importation.

9. THE UNITED KINGDOM

9.1 *Act*: Medicines Act, 1968

9.2 *Scope of the Act*: Medicines:

- Includes products[80] (specified by Ministers by order) which are not by themselves medicines but;
- Are used as ingredients in the manufacture of medicines;
- If used without proper safeguards are capable of causing danger to health.

- Specifically excludes;[81]
    - Substances used in dental surgery for filling dental cavities;
    - Bandages / surgical dressings unless medicated;
    - Those excluded by order of the Ministers.

[80] sec 105
[81] sec 130(5)

9.3 *Structure*: Medicines Commission[82]

- Established in terms of the Act.
- Composition;
    - Not less than 8 members-
    - Appointed by the Ministers[83] after consultation with appropriate organizations taking into account the following:
        i. Practice of medicine / veterinary medicine;
        ii. Practice of pharmacy;
        iii. Chemistry / pharmaceutical chemistry.
    - The Ministers appoint one of the members as chairperson.
- The Commission is a body corporate (juristic person).
- Functions
    - Advises the Ministers on matters relating to the execution of the Act;
    - Makes recommendations to the Ministers with regard to the number of committees to be established under the Act and on the composition and functions of such committees;
    - Advises licensing authorities;
    - To perform some functions that would ordinarily be performed by some committees in instances where those functions have not yet been assigned to a committee.
    - Commission furnishes Ministers with an annual report on its activities.

9.4 *Licensing Authority* (two ministers)

- The authority responsible for the grant, renewal, variation, suspension and revocation of licenses and certificates is the two Ministers (health and agriculture).
- One of the Ministers may act alone or jointly with the other.
- The Ministers issue the following licenses:
    - For selling, supplying and exporting medicinal products;

[82] sec 2
[83] Minister of Health & Minister of Agriculture

- Manufacturing, assembling or importing a medicinal product;
- (The necessary exemptions apply - the provisions do not apply to professionals in the ordinary course of their professional activities).

- The licensing provisions do not apply to herbal remedies where the process of producing the remedy consists only of drying and crushing and the remedy is to be supplied:
  - Under a designation that only specifies the plant and the process; and
  - Without any written recommendation (label, leaflet) as to the sue of the remedy.

9.5 *Applications for licenses*

- Applications are made to the Licensing Authority (the two Ministers).
- Factors relevant to the determination of application:
  - Safety; efficacy and quality.
- The Authority cannot refuse an application on the basis of safety, efficacy and quality without first consulting with a committee and in the absence of a committee, the Commission.
- The Authority cannot:
  - Take into account in deciding on the application any grounds relating to price of the product;
  - Insert any condition for issuing a licence relating to price.
- Where a licence is refused. The applicant is entitled to the reasons for such a decision.
- Licence is valid for 5 yrs.

9.6 *Inspectors:* are appointed by enforcement authority (ministers responsible for respective sections of the Act).

10. USA

10.1 *Act*: Federal Food, Drug and Cosmetic Act

10.2 *Scope of the Act*: Food, Medicines (including homeopathic) Cosmetics and Devices.

10.3 *Registration of establishments* of producers of drugs and devices (with necessary exemptions for professionals)

- A person who operates an establishment engaged in the manufacture, preparation, propagation, compounding, or processing of medicines / devices shall register his / her name / place of business / establishment annually (on or before 31 December) with the Secretary.[84]
- Every person upon first engaging in the manufacture, preparation, propagation, compounding and processing of medicines / devices shall immediately register his / her name / place of business / establishment with the Secretary.
- Establishments outside the USA that produce medicines / devices for importation into the USA must annually register electronically with the Secretary:
  - Name and place of business of establishment;
  - Name of the US agent for the establishment;
  - The name of each importer in the US known to the establishment.
- Establishments registered with the Secretary shall be inspected by officers or employees duly designated by the Secretary at least once in every 2 years.

[84] Secretary of Health and Human Services

10.4 *Registration of new medicinal products*[85]

- An application for the registration of new drugs is lodged with the Secretary.
- Amongst information that must be contained in the application is certification by applicant that the intended registration will not infringe on any patent rights.
- As a rule, applications are considered and decisions made within 180 days and any extended period must be agreed to by both the applicant and the Secretary.
- Appeals against the Secretary's decision to refuse registration are lodged with
- The US Court of Appeal for the circuit where the applicant resides or does business.

10.5 *Structure*: Food and Drugs Administration (FDA)

- The FDA is established by the Act.[86]
- It is headed by the Commissioner, who is appointed by the US President with advice and consent of the Senate.
- The Secretary, through the Commissioner:
  - Provides overall direction in the FDA and establishes and implements policies with regard to the management and operation of programmes and activities;
  - Conducts research and education / public information programmes;
  - Establishes technical / review groups as are needed to carry out its functions.
- Its broad mandate is to promote and protect public health by:
  - Promptly and efficiently reviewing clinical research;
  - Ensuring that drugs / devices / foods / cosmetics / electronic products radiation are safe and effective;
- It does its work, and also as determined by the Secretary:

[85] sec 355
[86] sec 393

- In consultation with experts in medicine, science and public health;
- In co-operation with consumers, users, manufacturers, importers, packers, distributors and retailers.

- Disputes with the FDA are resolved with the assistance of scientific advisory panel.

10.6 *Plan for Statutory Compliance / Annual Report*

- The Secretary, after consultation with appropriate experts, health professionals, consumer groups and the regulated industry, publish a plan to ensure that the Secretary complies with the Act. The Secretary shall review the plan every 2 yrs and revise it.
- The Secretary must produce an annual report that provides detailed statistical information on the performance of the Secretary under the Plan.

11. CHINA

11.1 *Act:* The Drug Administration Law of the People's Republic of China, 1984 (amended in 2001)

11.2 *Scope of the Act*: Medicines

11.3 *General Principles*[87]

- As one of the principles, the national government has an obligation to-
  - Develop both modern and traditional Chinese medicines;
  - Protect wild medicinal plants and encourage cultivation of Chinese medicinal materials;
  - Encourage development of new drugs.

11.4 *Administration*

[87] chapter 1.

- The drug administration department of the State Council (SDA or SFDA) is in charge of national drug administration affairs.[88]
- The drug administration department of the people's government of each province, autonomous region or municipal city is responsible for drug administration affairs within its authority.[89]

11.5 *Manufacturers (Drug Manufacturing Enterprises)*

- A licence to establish a drug manufacturing enterprise is issued by the drug administration department of a province, autonomous region or municipal city where the enterprise is located.[90]
- The enterprise shall also register with the administrative department for Industry and Commerce.
- In approving the establishment of an enterprise, the drug administration department shall comply with relevant national development plans and policies for the pharmaceutical industry so as to avoid redundant construction.[91]
- The following are some of the requirements that must be met before the establishment of an enterprise can be approved:[92]
  - Qualified pharmaceutical and engineering personnel;
  - Factory buildings and facilities appropriate for pharmaceutical production;
  - Departments, personnel and equipment necessary for quality management and control of drug manufacturing;
  - Adoption of relevant regulations and rules to ensure drug quality.
- The manufacture of a new drug which is subject to national standards shall be approved by the SDA and approval number issued before it can start manufacturing.
- The above requirement shall not apply to TCM herbs and preparations, which are not subject to approval numbers. With

[88] Art 5
[89] Art 5
[90] Art 7
[91] This suggests that before approval is granted, the department must satisfy itself that there is a <u>need</u> for such an enterprise.
[92] Art 8

regard to herbs and preparations requiring approval numbers, these shall be approved jointly by the SDA and the TCA administration bureau of the State Council.

- Manufacturer's certificate is valid for 5 yrs and is renewable.[93]

11.6 *Wholesalers and Retailers*

- Wholesale enterprises shall obtain approval for business operations and a Licence for Drug Operation Enterprise from the local drug administration department at the level of a province, autonomous region or municipal city.
- The requirements[94] are more or less the same as those for manufacturers and relate to-
  - Qualified pharmacological personnel;
  - Business site, equipment and storage facilities;
  - Quality management department commensurate with its drug operation business;
  - Adoption of relevant regulations and rules to ensure the quality of drugs in its operations.

11.7 *Importation of Drugs*

- Import certificates are issued by the SDA.

11.8 *Inspections*

- The SDA conducts inspections on drugs that are approved for manufacture or importation.

11.9 *Drug Reserve System*[95]

- The national government implements a drug reserve system wherein departments authorised by the State Council may allocate a supply of drugs from enterprises in cases of serious disasters, epidemic diseases or other sudden incidents.

[93] Art 8 of the Regulations
[94] Art 15
[95] Art 43

11.10 *Restrictions / Prohibition on exports*

- The State Council has the right to restrict or prohibit the export of drugs, which are in short domestic supply.[96]

11.11 *Health Examinations for employees*

- Employees of drug manufacturing enterprises, drug operation enterprises or am medical institution who has direct contact with drugs shall undergo a health examination every year. An employee suffering from an infectious disease or other diseases which may contaminate drugs shall not engage in work that has direct contact with drugs.[97]

11.12 *Medicine Pricing*[98]

- Relevant government departments responsible for setting prices and price guideline principles shall comply with the laws in setting and adjusting prices reasonably according to the society's ability to pay, social average cost, market condition in order that prices match quality, arbitrary high prices are controlled and the legitimate interests of consumers are protected.[99]
- Enterprises and medical institutions shall comply with the prices set by government and shall not arbitrarily raise drug prices.
- Enterprises shall honestly submit relevant material regarding its manufacturing and other business costs including actual transaction prices and volumes to relevant drug administration departments. Failure to report or reporting false information is prohibited.
- There are drugs that are subject to free market pricing and enterprises may determine own prices but these must be

[96] Art 44
[97] Art 51
[98] chapter 7
[99] Art 55

determined in accordance with principles of fairness, reasonableness, honesty amongst others.[100]

- Drugs whose prices are fixed by the State are those that are listed in the directory of drugs for national basic medical insurance and drugs not listed but those that are manufactured / distributed under a monopoly.[101]
- In fixing prices, the relevant department shall organise experts in pharmaceutical medical, economic and other fields to conduct assessments.[102]

11.13 *Perverse Incentives*

- Enterprises are prohibited from providing and accepting kick-backs and other benefits not included in accounting records during the process of drug transactions to medical institutions, drug purchasers, doctors and others working in medical institutions.[103]

11.14 *Appeals*

- When the drug administration department violates this Act, the superior level department or the supervision agency shall issue orders to revoke any certificates or approval documents issued in violation of the law.

This legal scan enabled the Ministerial Task Team to consider the various legal models of Regulatory Authorities of the selected countries and to develop the recommendations for the New Regulatory Authority for Health Products in South Africa.

[100] Art 56
[101] Art 48 of the Regulations
[102] Art 51 of the Regulations
[103] Art 59

CHAPTER 7

MODELS

An in-depth study of the current MCC and of other selected regulatory authorities, outlined above in this report, was undertaken. Two major aspects were defined, viz governance and the scope.

Governance.

1. Regulatory Authority as a line function unit within Government.
2. An Agency within Government.

The majority of the mature Regulatory Authorities are within Government. The alternative model of an Agency exists in other Regulatory Authorities. The benefits of an Agency is that it advantages the recruitment and retention of staff as it allows flexibility. It also enables cost recovery from fees which reduces the burden on the fiscus and ensures affordability and sustainability.

The Task Team favoured the concept of an Agency of Government where the RA is placed in the Department of Health and a full time Head/CEO reports directly to the Minister of Health and is the accounting officer.

The intrinsic Governance of the RA is based on the model of all work being done within the RA and a panel of experts consulted for expert opinion, peer review and advice when needed. Good Governance is enabled by this model as all the work is under the control of the RA led by the CEO. This enables adherence to time lines, time frames, efficiency and successful delivery. The major problem with the current MCC and MRA was that major dependence was on committees comprised of external experts who were unable to devote adequate time to meet deadlines. This has been the experience of other Regulatory Authorities which have moved to the model recommended by the Task Team of full time, in-house evaluators.

Scope

Two principle models were identified under the scope of the Regulatory Authorities.

1. A Specific Medicines Regulatory Authority
2. An independent umbrella regulatory authority for all Health Products

An Umbrella Regulatory Authority for all Health Products is the chosen model as it fulfils all the requirements of a modern regulatory authority, will keep abreast to scientific developments, will ensure the coordination of the registration of the various health products, will deal with the residue effect of health products, will ensure the control of contamination of the food chain and / or the environment and will enable the effective control of all the health products in the country. This model will be able to take the country forward in the regulatory environment and ensure that it can keep pace with future developments.

The Specific Medicines Regulatory Authority is not suitable under the current complexity and diversity of health products, their inter-relationships and that they are often combined for optimum utilization. The Global trend, now for Regulatory Authorities is to be a single one with various pillars. Even where this was not initially done, a review has precipitated a move to a single comprehensive regulatory authority.

The current MCC/MRA model has deficiencies and gaps that do not allow it to fulfil the requirements of a new regulatory authority and to undertake its functions. It is a model that has outgrown itself due to the scientific developments and the additional requirements and demands of such a body.

The Structure of the New South African Health Products Regulatory Authority is illustrated in Chapter 8.

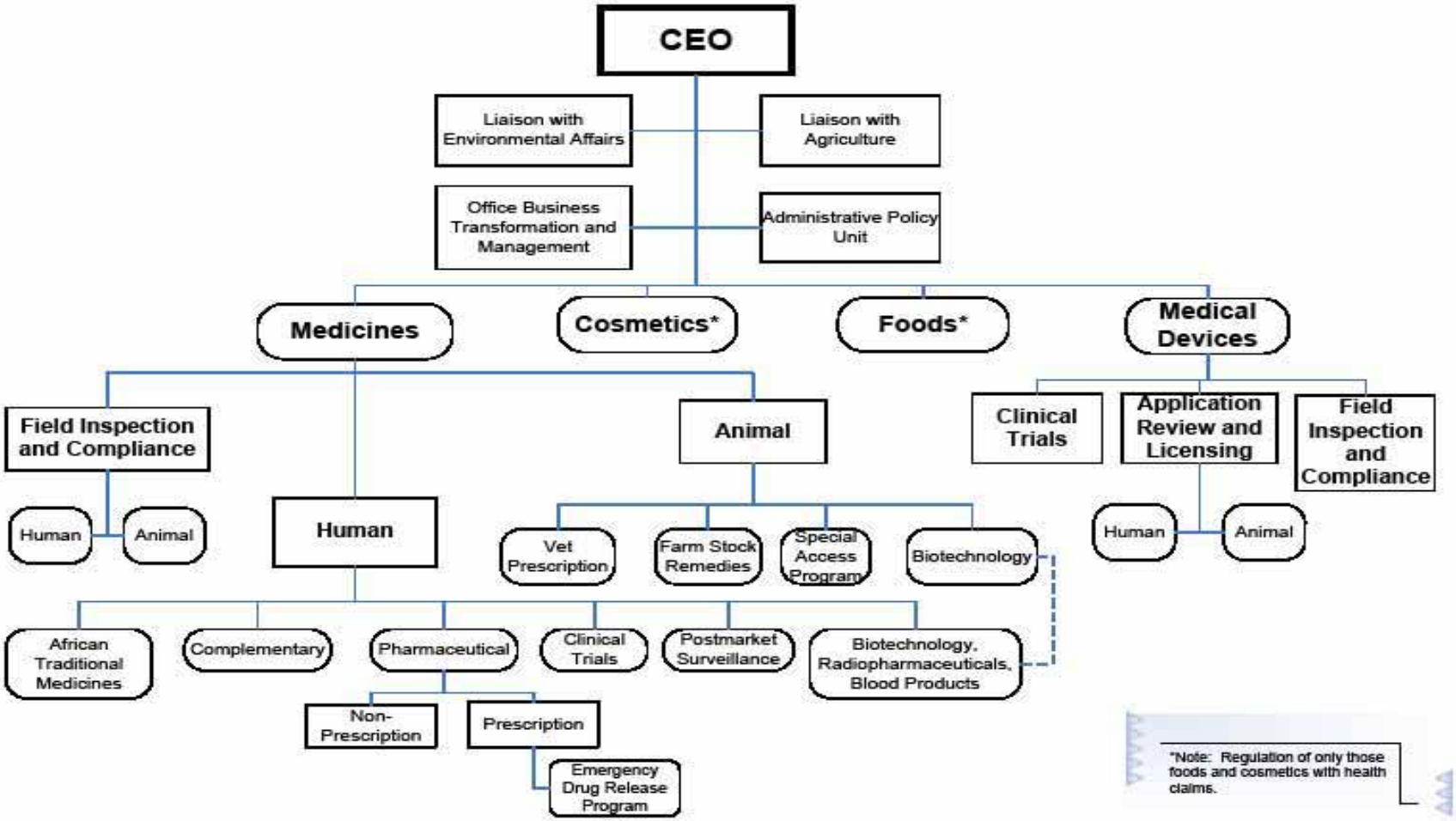
The structure provides the gestalt. It indicates the flow from the full time Head that is the CEO with the sequential boxes.

The structure is that of the independent umbrella regulatory authority for all Health Products in South Africa, which includes those for Humans and Animals. It indicates that there are separate pillars for each of the divisions while it indicates also the relationships between the different pillars.

Under Human Medicines it provides separate sub pillars for African Traditional Medicines, Complementary Medicines and Pharmaceuticals, which is divided into prescription and non-prescription. A separate box for the Emergency Drug Release Programme has been developed to enable the Regulatory Authority to deal with emergency requirements.

Cosmetics (cosmetics with medicinal claims or containing medicines), Food and Medical Devices have separate pillars.

Structure of the South African Health Products Regulatory Authority (SAHRA)



CHAPTER 9

PRINCIPLES

General Principles

The new South African Health Products Regulatory Authority (SAHRA) will be solely responsible for the regulation of all therapeutic products seeking market authorization in South Africa. As such, it will integrate the functions of a number of entities or government organizations presently engaged in the fractionated responsibilities for this function. These therapeutic products will include all human prescription medicines, including pharmaceuticals, products of biotechnology, and radiopharmaceuticals; all non-prescription medicines for use in humans, including non-prescription pharmaceuticals, African Traditional Medicines, herbal, homeopathic, and other products referred to as complementary medicines; medical devices; medicines for farm, companion, and wild animals, both prescription and non-prescription; cosmetics with medicinal content or claims; and, certain foods with medicinal content or claims. It will also be responsible for the authorization, audits, and investigations of all clinical trials, including veterinary animal trials leading to veterinary medicines; surveillance of marketed products; as well as inspections and investigations of manufacturing standards within South Africa. Through international agreements, it will ensure the manufacturing quality of all therapeutic products marketed in South Africa.

It will meet these responsibilities in a rapidly changing scientific and medical environment managing resources in a fiscally responsible manner ensuring effective regulation. It recognizes the importance of balancing the benefit-to-harm profile of a therapeutic product against society's need for early access to products where there is a demonstrated medical necessity, particularly for serious, life-threatening conditions where effective alternatives do not presently exist.

The new SAHRA will support the mission of the Minister of Health, Minister of Agriculture and Minister of Environmental Affairs to safeguard and promote the health of South Africans and will be responsible to the Minister of Health. All decisions for product registration (market authorization, licensing, etc) will be the responsibility of the RA which holds the distinctive competency to review and consider all elements of product quality, safety, efficacy, risk management plans for post-market surveillance, and product life-cycle labelling. Under most circumstances, this will be the level of the CEO of the SAHRA, who will make decisions informed by review staff of the regulatory authority, or externally contracted by the regulatory authority to provide such reviews. Provision should be made for each division to make recommendations to the central body for consideration and for ratification. The Minister may request the RA to consider urgent evaluation for Public Health good.

The SAHRA will conduct itself in a suitable business-like and transparent manner, integrating all aspects of regulation into a single organization in order to allow for the predictable and timely review of all applications submitted to it by entities wishing to market a therapeutic product in South Africa. It will be held accountable to performance standards which are made public and for which a suitable funding base has been established.

The timescales within which it will conduct its business will be in accordance with best Health Product Regulatory Practice. In the case of NCE the timescale will be prescribed as 12 months or less, for generics it will prescribed as 6 months or less, for emergency drug release it will be 24 hours, for clinical trials it will be 30-60 days. There will be no fast track, as the various tracts will be expedited. Section 21 registrations will continue as per the status quo.

The SAHRA will allocate resources in support of the recognition that all therapeutic philosophies contribute to the health of the public of South Africa. Its decisions and processes will be transparent and at the same time

respectful of commercial trade secrets, particularly as set out in international treaties to which South Africa is signatory.

The SAHRA will not make **government policy**, but will be responsive to Policy Makers in providing scientific and medical advice and in setting standards for the licensing and monitoring of licensed products. It will ensure transparency in the development of its own **administrative policy**, particularly when such policies will influence application or review processes.

It will be **respectful of professional staff** within the regulatory authority and recognize the need to access expert advice from competent professionals in universities, other departments of government, and various individuals in the private sector. Further, it recognizes the need for the sharing of knowledge between competent regulatory authorities in other jurisdictions and for flexibility in meeting its mission through access to the reviews of identical therapeutic products by other national regulatory authorities. It will seek co-operative agreements with other regulators where the mission of the SAHRA will be strengthened through such agreements.

It will adopt internationally accepted guidelines wherever appropriate, to allow for the facilitation of applicant understanding of the requirements for bringing a therapeutic product to the South African market for constant review of applications. In this respect, South Africa will consider regional and international harmonization of its guidelines, application requirements, and performance standards as well as the standards of the International Conference on Harmonization. The importance of harmonisation of standards within the region are also important with the understanding the progressive movement towards greater patient protection and higher standards should take place.

The generally acceptable international format CTD for application should b considered. This will assist with a migration of standards to get a balance between current South African Scientific Standards and International standards as well as benefiting from International Best Practices.

The SAHRA respects the value of its functions not only as they contribute to promoting and supporting health of the public in South Africa, but also respects the value of the research and development and manufacturing sectors, which it regulates to the economic, and innovation strength of South Africa. While always promoting and protecting the health of the public as a priority, it will do so in a manner that stimulates rather than impedes economic growth.

Each of these general principles is addressed in greater detail in the paragraphs, which follow.

Scope of SAHRA

The scope of activity of the new SAHRA will include, but not be limited to the following.

Setting of Policy and standards for the registration and **ongoing monitoring** of health products within the context of a National Drug Policy and the National Health Policy framework.

Pre-market scientific review of applications seeking market authorization will occur for all therapeutic products except in cases where an administrative review may be specified (for example, where an identical product which holds market authorization in South Africa is sub-licensed to a second party which holds an establishment (GMP) license in South Africa). The pre-market review will entail **due diligence** in the assessment of the manufacturing and quality aspects of the product; the animal and other pre-clinical data in support of product safety and efficacy; the clinical trial data submitted in support of the labelled indication; data from market surveillance studies in other jurisdictions where the identical product is registered; and information from other

regulatory authorities which will further clarify the data supporting the therapeutic use of the product in South Africa.

The rapidly changing scientific and medical environment will require a degree of corporate agility of the SAHRA which permits the sharing and exchange of information with other competent national regulatory authorities. This may occur through treaty or through less formal mechanisms of mutual or unilateral recognition agreements.

In all instances, the **decision for market authorization** in South Africa will be made by the new SAHRA. Use of pre-market review materials from other regulators will assist or complement the South African review, but not substitute for full consideration of the safe and judicious evaluation of the product in the South African market. Such consideration will include a specific risk management plan for the product in South Africa, reporting requirements for adverse reactions, and notification of all regulatory actions on similar products at any time or place within the global market for the product or product line. Generic products will be given special consideration for abbreviated submissions where product safety and efficacy has been previously established for these products. Provisions for a **risk management plan** will apply to generic products irrespective of whether they are granted authorization by means of a bioequivalence or other study.

Clinical trials for humans and animals will be regulated by SAHRA. The ethical approval will be granted by the Ethics Council of the Department of Health after considering all ethical issues inclusive of that in the public interest. All clinical trials evaluation inclusive of pharmaceuticals should subscribe to a performance target of 30 to 60 days from acceptance of the application. This will apply to Phase I, Phase II, and Phase III studies. This coupled with skills transfer and capacity building will strengthen the conduct of Clinical Trials on candidate medicines that respond to conditions that disproportionately affect developing countries. See comments below on policy and clear guidelines.

It should be noted that this element of the regulatory authority will interface with research ethics boards and with academic and private medical facilities where clinical trials will take place. A revision of the regulations regarding clinical trials may be required in order to specify the authority of the SAHRA in protecting the safety of human subjects in clinical trials, the reporting requirements of clinical trial sponsors, the roles and responsibilities of investigators, institutions, and composition and function of ethics boards, and other considerations which will provide for a safe and competitive environment for clinical trials in South Africa. An example of modern clinical trial regulations is provided in Appendix A. Noteworthy in the example provided is the provision for audit/inspection of clinical trial sites, an activity of the new SAHRA which must be created, meeting internationally accepted review practices. Further, certain veterinary animal trials leading to market authorization of animal medicines need to be regulated.

Clinical trials and veterinary animal trials will also be regulated for certain medical devices, all biotechnology products, certain radiopharmaceuticals, African Traditional Medicines, Complementary Medicine products, and certain foods with medicinal claims. Specification of the requirements for clinical trials in these areas will be created either in regulation or through administrative policies.

A clear policy on clinical research including ethical considerations and acceptability of various types of research will be in place to guide both the research community and evaluators and to ensure that the interest of patients are served. Policy will give guidance on all types of research including general new product development and research into conditions that disproportionally affect developing countries. The ethical approval should be provided in accordance with the ethical policy and guidelines of the Department of Health (or Agriculture in the case of animal trials) as approved by the Ethics Council of the Department of Health (or Agriculture) before approval by SAHRA is granted.

Post-market activities of the SAHRA will include participation in international pharmacovigilance (adverse drug reaction reporting) programs such as those sponsored by the WHO. Authority will be limited to the requirements for reporting by manufacturers, but reporting mechanisms for consumers, health care professionals, and other interested parties will be facilitated by the SAHRA through the creation of a user-friendly South African reporting system.

Periodic Safety Update Reports (PSURs) will be required for certain products where risk management is best managed by such reports. These must be provided by manufacturers in a format that summarizes the safety profile of the product and facilitates the review of the data (i.e., not as simple line listing of adverse events in PDF or other file format).

Provisions will be made in regulation to provide authority of the SAHRA to revoke or suspend market authorization where product safety cannot be supported by updated clinical data by the manufacturer.

In any instance where market authorization is granted by using review materials from another national regulatory authority, the South Africa license holder will be held responsible for reporting, in a timely fashion, all regulatory actions, warnings, or other activities within that foreign jurisdiction on the corresponding South African product.

Differences in requirements for submissions to the SAHRA will be recognized across the safety spectrum of all therapeutic products. In this respect, the requirements for a generic copy of a product which has been in use in South Africa for a sufficient time to support its safe, effective, and judicious use will be less than those for a new molecular entity or product not previously marketed in South Africa. Requirements for the contents of applications made for market authorization in South Africa will be created in regulation and, where appropriate, through administrative policy and these requirements will follow a **risk-based framework** for products. A link to an example of Management of Drug Submission Policy is provided in Appendix B. Such a risk-based framework would recognize a lower requirement for application

materials for products where safety is generally recognized not to be a concern, and would require extensive documentation for new molecular entities where concerns for safety will be the highest. This is depicted below.

Food with Health Claims ----- AFT's ----- Complementary Medicines ----- Non-Prescription Medicines ----- New Molecular Entities
Low Risk ---------- Moderate Risk ----------High Risk

Animal therapeutic products will be regulated according to a similar risk-based framework for data requirements. It is recognized that therapeutic animal products may find their way into humans through the food system; therefore, consideration for products to be used in food production animals will be identified separately from those used in domestic pets or wildlife not to be consumed by humans.

Similarly, a risk-based framework will be followed in the requirements for applications supporting the market authorization of **medical devices** where low risk devices such as non-sterile, non-invasive devices, which do not affect public health will require basic manufacturing information and invasive medical devices such as implantable cardiac pacemakers or devices which may have an important impact on public health such as diagnostic tests for screening or diagnosing serious communicable infections, will require extensive documentation. A system of classification for medical devices which recognizes these principles will be created in regulation, or administrative policy, where appropriate. An example of such a classification is provided in Table 4.

This table is in keeping with the proposed Departmental Medical Device classification in the Draft Regulations as outlined in Chapter 1.

TABLE 4

Medical device classification system			
Device Class	**Risk**	**Examples**	**Licence Requirements**
Class I	Lowest	Surgical instruments, laboratory culture media	A device licence is not required, but the establishment where it is made and/or distributed must be licensed.
Class II	Low	Contact lenses, pregnancy test kits, endoscopes, ultrasound scanners	Manufacturers require a Health Canada licence before selling or advertising Class II, III and IV devices. Annual licence renewals are required.
Class III	Moderate	Orthopedic implants, glucose monitors, dental implants, hemodialysis machines	
Class IV	High	Cardiac pacemakers, angiography catheters, cranial shunts	

The new SAHRA will have authority for **Food Products** only to the extent that such products contain medicinal ingredients or represent a medicinal benefit. Such claims will include claims of both general and organ/functional-specific benefit (such as “improved immune function”, or “strengthens the liver”). Authority will also be created in regulation or administrative policy, where appropriate, for food supplements and for certain food residues where health considerations exist.

Authority will be created in regulation or administrative policy, where appropriate, for the regulation of **Cosmetics** with medicinal content or claims. The SAHRA will create an organizational structure which will reflect the varying regulatory requirements of these various product lines and will be resourced along these as business lines in order to fulfil its mission

The new SAHRA will be funded through a combination of tax-based appropriations and **fees that are charged to sponsors of applications**, annual license fees, and fees for facility and importation licenses. In all instances where fees are charged, they will be levied following discussion with appropriate stakeholders and used to support the activities for which they have been specified. In general, fees will be allocated according to a

government-wide policy, which recognizes the existence of both a public "good", and a private "good" when government interfaces with or regulates a for-profit industry. Certain activities may not be allocated fees, but may be directly cost-recovered. An example of the latter would be repeat inspection of a facility, which was previously deemed to be sub-standard in respect of regulatory requirements. Fees schedules will be re-visited according to a timeframe to be established in regulation or, where appropriate, in administrative policy in order to maintain or enhance the ability of the regulator to respond to the needs of the regulated environment. Fees will be linked to performance in a manner that will sustain the ability of the regulatory authority to meet or exceed published performance standards at least 95% of the time. The applicant will be timeousely advised should there be a problem with finalising the registration within the prescribed timescale.

Special attention will need to be given to the backlog of regulatory submissions, which require immediate attention. The new SAHRA will require resources for the conversion of records and materials that are considered legacy documents carried forward from previous regulatory entities. Corporation with the industry should be sought, if desired, in this respect.

The new SAHRA should monitor compliance within the requirement of the legislation, within the prescribed timescale and ensure conformant of the provisions.

The new SAHRA should ensure that legislation includes a self-regulating code of ethical practices for the marketing all health products including medicines. The joint industry self-regulatory document is included in the appendices. The Department of Health should ensure that this occurs and enforce the abidance of the ethical practices by enforcement if necessary.

The new SAHRA will accrue **human resources** as required to meet its mission. In this regard, it will recognize the value of varied therapeutic philosophies in South Africa and make provisions for the timely regulation of all generally recognized therapeutic modalities, which fall within its authority.

In so doing, it will recognize the expertise, which exists within South Africa universities; and, wherever possible, seek to strengthen university-based expertise within the regulatory review procedures. It is anticipated that the majority of review activities and all regulatory decisions will occur within the human resources of the new SAHRA. However, regardless of where the review occurs, contemporary business practices such as use of the principles of project management will apply. Where appropriate, **service level agreements** will be developed in order to support the responsible allocation of financial resources both within and exterior to the SAHRA. For example, a university may enter into a service level agreement with the regulatory authority in the provision of expert reviews of clinical trial applications or product market applications. An example of a service level agreement within the organization would be in the performance of a human resources unit supporting the recruitment and retention of regulatory authority staff.

Effectively, all functional units of the new SAHRA will be held accountable for **performance** since each individual unit will impact on overall performance of the regulatory authority.

The SAHRA may recognize the regulatory reviews of **other competent national regulators** where appropriate. It will do so with transparency and following established rules under a Memorandum of Understanding, a Mutual Recognition Agreement, or other formal treaty. It further recognizes that it cannot independently enter into formal inter-jurisdictional agreements and will consult and advise other responsible government departments as required for the development of such agreements.

Notwithstanding the recognition of the regulatory reviews in certain other jurisdictions, it is definitive that all decisions for regulatory actions will reside fully within the SAHRA and all review materials external to those created within the regulatory authority will only be used as individual elements of the complete review package developed by the SAHRA to reach its final decision.

Where review materials from other jurisdictions are relied upon in regulatory decisions, special obligations on the part of the sponsors of those products may be specified; including, but not limited to, timely reporting of regulatory actions in the relied-upon jurisdiction that are relevant to the product marketed in South Africa.

The SAHRA will establish procedures regarding a quality systems approach to its business lines, including, but not limited to, Good Review Practices; Training and Maintenance of Competency Programmes; Transparency Initiatives; Effective Communication with Stakeholders; Publication of Performance Standards; Published Performance Reports and Scientific and Technical Standards.

The SAHRA will demonstrate evidence of cooperation with statutory health and veterinary professions councils.

A business-like environment will be created where regulatory practices will occur in a predictable, transparent, and decisive manner. These practices will be supported through modern management practices such as regulatory project management and good review practices. They will further be supported through the creation of an Office of Business Transformation and Management, which will audit and assist the work of the scientific, medical, and inspection units. Clearly, success in this element of SAHRA function will be tied closely to adequate access to scientific competencies and overall adequate financial and human resources. In order to do so, it will require flexibility in human resourcing including remuneration which allows for recruitment and retention of highly competent scientific and clinical professional staff; in external contracting for specified, and frequently sole-sourced deliverables; in acquisition and support of information technology to allow submission of internationally standardized applications and for the electronic tracking of all applications; and, in the negotiation of cost-recovery fees to support these functions.

Despite the establishment of this business-like environment, the SAHRA will be respectful of the needs of professional and non-professional staff. Further, during the transition from the current regulatory environment to the new SAHRA, will respect and recognize the needs of current staff working in MCC and MRA.

In all aspects of its role as the national therapeutic product regulator, it will **recognize its accountability to the South Africa Government through the Minister of Health**. In this respect, it is expected that the SAHRA will develop an **annual strategic plan**, which will be linked to an **annual budget** and reviewed and approved by the Ministry of Health. There will be **quarterly as well as annual reporting to the Minister of Health** on this budget; however, the SAHRA will fulfil the obligations of any government entity according to administrative and fiscal responsibility as set out in the Public Finance Management Act.

The SAHRA will **publish quarterly performance reports** for stakeholders and the general public. Such reporting will be of sufficient detail to provide an understanding of slippage or fulfilment of performance targets and will provide an accurate picture of regulatory activities according to its business lines. A link to an example of a quarterly performance report is presented as Appendix C.

The SAHRA will interface and cooperate with other Departments in areas of therapeutic product regulation, which intersect with other Acts. An example of such cross-departmental intersection may exist between therapeutic products and the **environmental impact assessment** of new medicinal substances as may be required by an Act or Acts administered by the Department of Environmental Affairs and Tourism.

In regulating therapeutic products for the South African market, the SAHRA will not typically engage in direct discussions or deliberations surrounding

pricing of products. It will, however, contribute scientific and medical advice, where requested, from other government entities seeking such information for the purposes of pharmaco-economic analyses such as cost-effectiveness determinations. Decision to register or not to register products by SAHRA will be based on scientific and technical principles to ensure the quality, safety and efficacy of the products.

It is recognized that the SAHRA will be provided with documents disclosing confidential details of **intellectual property** and commercial interests in the course of its due diligence. It will be respectful of such commercial interests and comply fully with South African laws and regulations protecting such commercial properties. In this regard, the SAHRA will also comply with all relevant international treaties to which South Africa is a signatory. However, where such materials have been previously placed into the public domain, the SAHRA will not be constrained in its obligations regarding transparency of its reviews or decisions. All efforts will always be made to discuss in advance of the release of materials considered to be public domain with the owners of such intellectual property.

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The SAHRA will be cognizant of the cooperative role of South Africa within the Region and will actively seek opportunities to **share and exchange reviews** and other regulatory activities with such nations. Such exchanges will take place within the limits defined by the government of South Africa, but the SAHRA will identify opportunities to government through the Minister of Health where agreements permitting such exchanges may be developed. It is further recognized that the competency of the SAHRA will be at a standard typically expected of a leading national therapeutic products regulator at the global level.

The applicant should in all cases certify that Intellectual Property Rights Legislation recognised by the country are not infringed. This must be

submitted in a form of an affidavit. Should there be any infringement, all the responsibility will borne by the applicant

CHAPTER 10

GOVERNANCE

Aspects of Governance should be in accordance with the principles laid out in the Chapter 9 of this report. Special attention needs to be given to the following as they are of particular significance.

- Authority, responsibility and accountability of the CEO who will be bound the PFMA, any other relevant legislation or recommendations
- Panel of Experts
- Advisory Committees
- Authority and/or obligations of the panel of experts and the Advisory Committees
- Conflict of Interest
- Alignment of Functions at cost division but within policy
- Communication with the Public and with applicants for the registration of health products (Include development of an authoritated information and reliable advise system to improve public awareness)
- Relationship with other Regulatory Authorities
- Office of Business Transformation and Management
- Electronic systems versus manual systems (E-tracking system, ECDT)
- Pharmacovigilance
- Surveillance (Advertising, counterfeits, effective use of products, phytovigilance)
- Knowledge Management
- Key Performance Areas
- Prevention and Management of overlaps and gaps
- Monitoring and enforcement
- Relationship with the office of Standard Compliance within the Department of Health

Intrinsic Governance of SAHRA will conduct all regulatory work within the authority. This is the pattern of most regulatory authorities globally. Expert opinion advice and/or peer review will be sourced from a panel of experts when required. This will ensure best practice, meeting of deadlines and fulfilment of responsibilities by SAHRA.

CHAPTER 11

ROLES AND RELATIONSHIPS

The role of the regulatory authority is to ensure that all health products manufactured or released to the market in South Africa are safe, efficacious and of quality and that the Public are not subjected to misleading advertising or misleading information on health products.

The relationships will be to internal and external structures and bodies.

- Internal

  The NRA should relate with the relevant units, structures and personnel within the Department of Health and the other Departments necessary for its work and fulfilment of its responsibilities.

  The relationship with Law Enforcement should be clearly defined.

  The relationship with the Pricing Unit/Component within the Department should be clearly defined in accordance with the principles laid out in Chapter 9.

- External

There will be relationships with a variety of external bodies for it to undertake its work. The list will be developed and adjusted when necessary but will be inclusive of :

Statutory bodies,
Research Institutions,
Tertiary Educational Institutions,
African Continent Bodies – SADC and AU,
Global Bodies inclusive of Regulatory Authorities
Applicant for the registration of health products

CHAPTER 12

NEW REGULATORY AUTHORITY HUMAN RESOURCE AND FINANCIAL REQUIREMENTS

1. Human Resources

- Human Resource requirements of the Regulatory Authority have been estimated and costed, recognising that adjustments will have to be made. The authority will develop sequentially and will grow, variations will be required once approval of the recommendation of the New Regulatory Authority is granted and work is conducted on the final recommendation. Human Resources for a regulatory authority is the largest cost item as specialised, highly trained, experienced technical and professional staff are required. This is the experience of all the regulatory authorities studied.

- Human Resource strategy based on the pillars should be robustly managed:

- Human Resource Development

  The competencies and skills required by the regulatory authority will need ongoing discussion with the Tertiary Education Institutions and the Professional Councils. Curriculum enrichment will be required and should be incorporated wherever necessary to ensure the needed output skills and competencies of the trained health professionals. Deficiencies, to mention a few, were recognised in health economics, regulatory knowledge, competencies and skills, project management, pharmaco-vigilance, bioequivalence and the legal implications of the regulation of health products.

  In-service training and continued professional development are imperative. A comprehensive programme for this should be developed.

- Human Resource Recruitment and Retention

The loss of highly trained and skilled staff should be prevented as it impacts on the effective functioning of the regulatory authority and tarnishes its integrity. This is well recognised by regulatory authorities globally and is one of the important issues that confronted them and was brought to the attention of the MTT. There should be an effective recruitment and retention strategy developed together with an appropriate implementation plan otherwise the regulatory authority will not be successful.

- Human Resource Management

Effective overall management of the human resources should be comprehensive and effective. The Office of Business Administration and Transformation should assist the Human Resource Component in this.

- Performance Agreements and Service Level Agreements

This was identified as requiring special mention as it became apparent during the operations of the MTT that this was a critical factor for the effective management of the human resources and their performance. All staff within the SAHRA must have job descriptions. The CEO and/or staff must have signed performance agreements.

2. PROJECTED FINANCIAL COSTING OF HUMAN RESOURCE REQUIREMENTS

2.1 OPTION 1 IDEAL

CATEGORY	NUMBER	COST RAND MILLION
CEO	1	1.5
Technical Evaluators Allopathic	90	43.94
Clinical Trials	15	9.76
Pharmacovigilance	10	6.23
Scheduling, names etc	5	1.97
GMP & GCP	20	7.68
Lawyer	1	0.56
Law Enforcement	12	4.47
Project Managers	8	4.46
Unit Heads	9	5.01
Management Support	30	3.1
Admin support higher	20	4.8
Admin Support	60	3.4
IT support	2	1.0
External Experts (scientific, rare skills, scientific appeals, opinion leaders for cutting edge technologies etc.)	20 FTE	24
Complementary & Traditional medicines including evaluators, clinical trials, post marketing surveillance	60	20.62
External Experts (Comp& Trad)	20FTE	8
GCP GMP GLP Wholesalers etc. (Comp & Trad)	7	2.39
Medical devices and equipment evaluation, clinical trials etc.	30	11.05
GCP,GMP inspectors, post marketing surveillance (devices)	6	2.81
External Experts (devices)	20	14
Food Control	20	7.41
External Experts Food Control	3FTE	1.8
Other commodities to be regulated	10	7
Financial management support	3	1
TOTAL	**482**	**197.96**

TOTAL HR = R198M

ASSUMPTIONS (Ideal option)

Allopathic Evaluators

The total number required is 90

50 Level 12 @ R394 000 =	R19.7M
20 Level 13 @ R557 000 =	R11.140M
20 Level 14 @ R655 000 =	R13.1M
SUBTOTAL	**R43.94M**

Clinical Trials

The number required is 15

2 Level 13 @ R557 000 =	R1.114M
10 Level 14 @ R655 000 =	R6.55M
3 Level 14 @ R700 000 =	R2.1M (upper Leve14)
SUBTOTAL	**R9.76**

Pharmacovigilance

The number required is 15

3 @ Level 11 @ R326 000 =	R0.98M
5 @ Level 12 @ R380 000 =	R1.9M
4 @ Level 13 @ R557 000 =	R2.23M
3 @ Level 14@ R700 000 =	R2.1M
SUBTOTAL	**R6.23M**

Scheduling and Names

The number required is 5

2 @ Level 11 @ R326 000 =	R0.652M
2 @ Level 12 @ R380 000 =	R0.760M
1 @ Level 13 @ R557 000 =	R0.557M
SUBTOTAL	**R1.97M**

GMP & GCP Inspectors

The number required is 20

5 @ Level 11@ R326 000 =	R1.63M
13@ Level 12@ R350 000 =	R4.94M
2 @ Level 13 @ R557 000 =	R1.114M
SUBTOTAL =	**R7.68M**

Lawyer

1 @ Level 13 @ R557 000	**R 0.56M**

Law Enforcement

The number required is 12

5 @ Level 11 @ R326 000 =	R1.63M
6 @ Level 12 @ R380 000 =	R2.28M
1 @ Level 13 @ R557 000 =	R0.557M
SUBTOTAL =	**R4.47M**

Project Managers

The number required is 8
8@ Level 13@ R557 000 = R4.456M
SUBTOTAL= R4.46M

Unit Heads

The number required is 9
All Level 13 @ R557 000 = **R5.01**
as in current arrangement

External Experts Allopathic

The number required is 20 FTE
Estimated @ R1.2M on average
SUBTOTAL = R24M

Traditional & Complementary Medicines

The number required is 60
This covers evaluations, clinical trials evaluation, post marketing surveillance, phytovigilance for all the disciplines e.g naturopathy, herbs, homeopathy, Ayuverda, Chinese etc.
10 @ Level 10 @ R270 000 = R2.7M
20 @ Level 11 @ R326 000 = R6.52M
30 @ Level 12 @ R380 000 = R11.4M
SUBTOTAL = R20.62M

External experts Traditional & Complementary medicines
The number required is 20 FTE
Estimated @ R400 000
SUBTOTAL = R8.M

GMP& GCP Inspections African Traditional Medicines

The number required is 7
5 @ Level 11 @ R326 000 = R1.63M
2 @ Level 12 @ R380 000 = R0.76M
SUBTOTAL = R2.39M

Medical Devices & Equipment

The number required is 30

6 @ Level 10 @ R270 000 =	R1.62M
10 @ Level 11@ R326 000 =	R3.26M
10 @ Level 12@ R380 000 =	R3.80M
3 @ Level 13 @ R557 000 =	R1.671M
1 @ Level 14 @ R700 000 =	R0.70
SUBTOTAL =	**R11.05M**

GMP & GCP Inspectors Devices

The number required is 6

3 @ Level 12 @ R380 000 =	R1.14M
3 @ Level 13 @ R557 000 =	R1.671M
SUBTOTAL =	**R2.81M**

External Experts Devices & Equipment

The number required is 20 FTE
Estimated at an average of R700 000

SUBTOTAL =	**R14.00M**

Food Control

The number required is 20

10 @ Level 10 @ R326 000 =	R3.26M
8 @ Level 12 @ R380 000 =	R3.04M
1 @ Level 13 @ R557 000 =	R1.114M
SUBTOTAL =	**R7.41M**

External Experts Food Control

The number required is 3 FTE
Estimated at R600 000 each **R1.8M**

Other Products

The number required is 10
Estimated at R700 000 each

SUBTOTAL =	**R7M**

2.2 OPTION 2 (LOWER COST, closer to current structure)

CATEGORY	NUMBER	COST RAND MILLION
CEO	1	1.2
Technical Evaluators Allopathic	60	25.26
Clinical Trials	15	6.77
Pharmacovigilance	10	3.13
Scheduling, names etc	5	2.0
GMP & GCP	20	7.13
Lawyer	1	0.54
Law Enforcement	12	3.3
Project Managers	8	3.85
Unit Heads	9	4.95
Management Support	30	3.1
Admin support higher	20	4.8
Admin Support	60	3.4
IT support	2	0.6
External Experts (scientific, rare skills, scientific appeals, opinion leaders for cutting edge technologies etc.)	20 FTE	18
Complementary & Traditional medicines including evaluators, clinical trials, post marketing surveillance	40	13
External Experts (Comp& Trad)	20FTE	8.37
GCP GMP GLP Wholesalers etc. (African Traditional)	3	1.1
Medical devices and equipment	25	9.5
GCP,GMP inspectors, post marketing surveillance (devices)	4	1.5
External Experts (devices)	10FTE	5.85
Food Control	10	3.71
Other commodities to be regulated	8	2.12
Financial management support	3	1
TOTAL	**285**	**117.44**

TOTAL HR = R117M

Though there are suggested Level 10 positions, it has been very difficult to recruit and retain professional staff at this level. Levels 10 and 11 technical staff leave the regulatory authority as soon as they are trained for the positions in industry. As envisaged, evaluation will be done in-house, and therefore experienced technical and specialised personnel will be required. Other incentives may be desirable.

ASSUMPTIONS (lower cost option)

Allopathic Evaluators

The total number required is 60

1/3 Level 11 i.e 20 @ R330 000 =	R6.66M
1/3 Level 12 i.e 20 @ R400 000 =	R8.0M
1/3 Level 13i.e 20 @ R530 000 =	R10.6M
SUBTOTAL	**R25.26**

Clinical Trials

The number required is 15

2 Level 11 @ R330 000 =	R0.66M
6 Level 12 @ R400 000 =	R2.4M
7 Level 13 @ R530 000 =	R3.71M
SUBTOTAL	**R6.77**

Pharmacovigilance

The number required is 10

3 @ Level 10 @ R200 000 =	R0.6M
4 @ Level 11 @ R300 000 =	R1.2M
2 @ Level 12 @ R400 000 =	R0.8M
1 @ Level 13 @ R530 000 =	R0.53M
SUBTOTAL	**R3.13**

GMP & GCP Inspectors

The number required is 20

10 @ Level 11@ R300 000 =	R3M
9 @ Level 12 @ R400 000 =	R3.6M
1 @ Level 13 @ R530 000 =	R0.53M
SUBTOTAL =	**R7.13**

Lawyer @ Level 12 R 0.4M

Law Enforcement

The number required is 12

5 @ Level 10 @ R200 000 =	R1.0M
5 @ Level 11 @ R300 000 =	R1.5M
2 @ Level 12 @ R400 000 =	R0.8M
SUBTOTAL =	**R3.3M**

Project Managers

The number required is 8

3@ Level 11@ R350 000 =	R 1.05M
3@ Level 12@ R400 000 =	R1.2M
2@ Level 13@ R530 000 =	R1.6M
SUBTOTAL=	**R3.85**

Unit Heads

The number required is 9

All Level 13 @ R550 000 =	**R4.95M**
as in current arrangement	

External Experts Allopathic

The number required is 20 FTE

10 Level 14 @ R640 000 =	R6.4M
5 Level 15@ R800 000 =	R4.0M
5 Level 16 @ R1.5 =	R7.5M
SUBTOTAL =	**R17.9M**

Traditional & Complementary Medicines

The number required is 40

This covers evaluations, clinical trials evaluation, post marketing surveillance, phytovigilance for all the disciplines e.g. naturopathy, herbs, homeopathy, Ayuverda, Chinese etc.

10 @ Level 10 @ R200 000 =	R2M
20 @ Level 11 @ R350 000 =	R7M
10 @ Level 12 @ R400 000 =	R4M
SUBTOTAL =	**R13M**

External experts Traditional & Complementary medicines

The number required is 20 FTE

10 @ Level 11 @ R350 000 =	R3.5M
5 @ Level 12 @ R400 000 =	R2M
3 @ Level 13 @ R530 000 =	R1.59
2 @ Level 14 @ R640 000 =	R1.28
SUBTOTAL =	**R8.37**

GMP& GCP Inspections African Traditional Medicines

The number required is 3

2 @ Level 10 @ R200 000 =	R0.4M
2 @ Level 11 @ R350 000 =	R0.7
SUBTOTAL =	**R1.1M**

Medical Devices & Equipment

The number required is 25

10 @ Level 11@ R350 000 =	R3.5M
15 @ Level 12@ R400 000 =	R6.0M
SUBTOTAL =	**R9.5M**

GMP & GCP Inspectors Devices

The number required is 4

2 @ Level 11 @ R350 000 =	R0.7
2 @ Level 12 @ R400 000 =	R0.8
SUBTOTAL =	**R1.5**

External Experts Devices & Equipment

The number required is 10

5 @ Level 13 @ R530 000 =	R2.65
5 @ Level 14 @ R640 000 =	R3.2
SUBTOTAL =	**R5.85**

Food Control

The number required is 10

6 @ Level 11 @ R330 000 =	R1.98M
3 @ Level 12 @ R400 000 =	R1.2M
1 @ Level 13 @ R530 000 =	R0.53M
SUBTOTAL =	**R3.71**

Other Products

The number required is 8

4 @ level 10 @ R200 000 =	R0.8
4 @ Level 11@ R330 000 =	R1.32
SUBTOTAL =	**R2.12**

The two tables below were utilised to inform the projections.

NB: WORKLOAD PROJECTIONS OBTAINED FROM INDUSTRY

TABLE 5

TYPE OF APPLICATIO N	2008-2012	2013 -2018
Generic	600-700	700
NCE	62	50
Line Extensions	20	65
Amendments	1375	1500
Biologicals	5 (1 Biosimilar)	7 (1Biosimilar)
Biological generic	12	12
Veterinary NCE	4	2
Veterinary generic	3	2
Clinical Trials	330	?
Radioisotopes	1	1

COMPARISON WITH OTHER NATIONAL REGULATORY AUTHORITIES

TABLE 6

Country	Budget Est. Tot Rand (million)	Population	Full/Abridged	Staff Number	Cost/Capita	Cost/Staff member
Zimbabwe	17.59	12.3		51	1.43	0.345
Uganda	1.22	1.7		40	0.72	0.031
Tunisia	8.84	10.3		86	0.86	0.103
UK	872.3	60.8	F		14.35	
Canada	835.84	33.4	F	1500	25.03	0.557
Australia	211.5	20.4	F	500	10.37	0.423
Malaysia	35.46	24.8		170	1.43	0.209
Cuba	6.52	11.4		67	0.57	0.097
Venezuela	9.3	26		272	0.36	0.034
USA	12870	301	F		42.76	
South Africa	197.96	48	F	482	4.12	0.410

CHAPTER 13

LEGAL IMPLICATIONS FOR THE NEW RECOMMENDED SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

Introduction

This serves as an analysis of the existing legal framework within which the current Medicines Control Council (MCC) operates and to contrast such framework with the recommendations on the newly envisaged South African Health Products Regulatory Authority (SAHRA). The analysis seeks ultimately to determine the changes that are required in the existing legislation in order to create a legal framework for the proposed structure (attached) of SAHRA.

The MCC

The MCC is established in terms of section 2 of the Medicines and Related Substances Act, 1965 (Act No. 101 of 1965) (the Act) as amended. It comprises members appointed by the Minister who are not full time, but only meet at least every eight weeks to consider reports and make decisions.

The MCC committees also comprise persons appointed by the MCC who are not full time, and also meet to consider reports and make decisions.

The actual work in respect of which decisions are made by the MCC and its committees is performed by the Registrar's office and some consulting entities from outside the Department of Health (Department). The Registrar's office, in the form of a Cluster of the Department, the Medicines Regulatory Affairs (the MRA), performs the actual work and also provides secretariat's services to the MCC. The other work that the MRA is unable to perform like laboratory services or chooses not to perform is outsourced to entities outside the Department.

Section 2(3) of the Act provides that the MCC is a juristic person. Section 33A(4) provides that the MCC shall open a bank account and deposit in it amongst others money the MCC raises for rendering services.

The following are some of the sections of the Act that specifically provide for matters relating to the MCC:

- 2 (section): establishment
- 3: composition
- 4: term of office and remuneration
- 5: chairperson and vice-chairperson
- 6: disqualifications
- 7: meetings
- 8: quorum
- 9: committees
- 12: appointment of Registrar
- 33A: funds of the MCC

There are other sections that refer to the many decisions that the MCC must make in relation to the functions it performs in terms of the Act, eg on registration of medicines; exemptions from registration; etc.

It is envisaged, according to the recommendations that SAHRA shall:

- Have a full time head: CEO
- Report directly to the Minister
- Be within the Department as an Agency.

The recommendations in relation to the above three aspects have implications on existing legislation and will therefore be dealt with individually and the implications highlighted.

Full Time Head

Currently the chairperson of the MCC is not full time whereas the Registrar is full time as the Registrar is the head of the MRA. This means that section 5 of the Act that provides for the Chairperson and Vice-Chairperson must be repealed. The recommendation also suggests that the entire MCC as it exists will cease to exist as it is based on a board system where members are called to attend meetings and take certain decisions that are left to the MRA to implement. Provision will need to be made in the legislation for the responsibilities and accountability of the CEO.

Report Directly to the Minister

Currently the MCC advises the Minister or furnishes the Minister with reports on matters referred to the MCC by the Minister. The MCC does not report directly to the Minister and does not produce reports independently of the MRA. It therefore means that section 2 of the Act that provides for the MCC advising the Minister must be amended or repealed so that it is made clear that SAHRA shall report directly to the Minister.

Be Within the Department as an Agency

The MCC is currently independent but outside the Department whereas the MRA is within the Department and not independent. The recommendation that SAHRA be within the Department as an Agency means that section 2 of the Act must be replaced by a new section that will establish SAHRA within the Department but also as an Agency. It will also mean that all the other sections that specifically provides for matters relating to the MCC must be repealed. Provision should be made in the regulations for an executive committee to ensure effective management of the authority led by the CEO. Provision must be made in the legislation for the management of regulation and registration of health products by the various divisions within the SAHRA.

It appears that there are no such models existing currently in the Department. The other components that are within the Department and make some form of regulatory decisions include the Radiation Control Unit; Food Control Unit and the Compensation Commissioner (for compensatable diseases).

The Structure

The recommended structure suggests that SAHRA shall be headed by the CEO. The CEO will report to the Minister directly as suggested in the basic principles. The CEO is the accounting officer subject to the prescripts of the PFMA.

The provision for Office of Business Transformation and Management as well as the Administrative Policy Unit in the structure of SAHRA ensures that the component will have its own business management and administrative policies.

The recommended structure further suggests that in addition to medicines and medical devices, which are currently regulated by the MCC, SAHRA shall also regulate medical devices, foods and cosmetics that contain medicines or have medical claims, products that are currently not regulated by the MCC. This will require amendments to the Act to broaden the scope of the Act. This may also necessitate a repeal of the Foodstuffs, Cosmetics and Disinfectants Act, 1972 (Act No. 54 of 1972) as this Act currently regulates foods and cosmetics.

On medicines, currently the MCC does not regulate African Traditional Medicines; Complementary medicines and Blood products. The Act will have to be amended to broaden the scope in relation to these health products as well as medical devices. However, if one moves from the premise that these products fall under the definition of medicine, then it may not be necessary to amend the Act but to provide for them in the regulations by dealing with these substances as other categories of medicines.

Accountability in general

SAHRA is accountable to the Minister of Health with regards to policy implementation. Concurrence with the Minister of Agriculture and the Minister of Environmental Affairs will be affected where required.

The CEO will be the accounting officer and subject to the requirements of the PFMA

Act 101 of 1965 would have to be amended.

Specific Questions Raised

The following questions have been specifically raised and we will deal with them in the order in which they appear:

1. What existing legislation will require amendment
2. What new legislation, if any, will need to be drafted
3. What existing regulations, if any, need to be drafted
4. What new regulations, if any, will need to be drafted
5. Are there any constitutional matters that need to be dealt with

Existing legislation to be amended

As stated above, it is clear that Act 101 of 1965 will require amendments. The extent of the amendments will depend on the actual policy positions adopted. For instance, if the MCC in its current form ceases to exist, then sections 2, 3, 4, 5, 6, 7, 8, 9, 12 and 33A will have to be repealed and replaced with the necessary ones in relation to SAHRA. Also to be repealed will be all the other sections of the Act that refer to the MCC directly or indirectly.

Further, if SAHRA is going to be an Agency, the Act will have to amend to accommodate this.

Further, if it is SAHRA that will be tasked with the actual registration of medicines, a task currently performed by the MCC, this will also require amendments to sections 13, 14, 15 and 16 of the Act that deal with the registration of medicines.

The scope of the Act will also have to be amended to include both cosmetics and foods, these are currently not regulated under the Act. The Department may need to reflect carefully on this policy choice because the Foodstuffs Act currently regulates foods and cosmetics.

The National Health Act will need to be amendment to enable the SAHRA to regulate medical devices or alternatively SAHRA to use the current National Health Act to do so.

New legislation to be drafted.
It appears from the recommendations made that no new Act will be required. Amendments to existing legislation will suffice.

Existing regulations to be amended
Amendment to the regulations will follow upon amendments to the Act or Acts. With the amendments envisaged on the Act or Acts the general regulations made in terms of the Act or Acts will also have to be amended to be in accordance with the amendment Act or Acts. In general, the amendments will follow upon the new role of SAHRA as opposed to that of the MCC. The changes will not be substantial as the bulk of the regulations provide for the finer details of how to comply with the Act. Generally, compliance issues will not change.

New regulations to be drafted
It is not envisaged that there will be substantial regulations that will require to be drafted. Of course should the Department decide to broaden the scope of the Act to provide for the regulation of foods and cosmetics, regulations dealing with these matters will be required. These regulations already exist, it would mean re-making them in terms of Act 101 of 1965.

New regulations relating to African traditional medicines, biotechnology and complementary medicines may also have to be drafted in line with the scope of the Act that will be broadened to deal with these matters. The code of practice for the marketing of medicines/health products needs to be published as a regulation.

Regulation to section 18a need to be drafted to prevent perversities in the system.

Further, if SAHRA will operate outside the public service legal framework, rules may be required to provide for the finer details on a number of matters in terms of how business will be conducted.

Other Departments legislation

It appears that there is no need to amend any legislation administered by other departments. The current situation in relation to veterinary medicines can continue within the envisaged framework for SAHRA. Currently the MCC registers veterinary medicines, hence the requirement in regulation 35 that amongst MCC members there must be a one veterinarian designated by the Minister of Agriculture and one person with specialised knowledge in veterinary clinical pharmacology.

However, it must be noted that the definition of veterinary medicine excludes stock remedies and farm feeds which are registered in terms of the Fertilizers, Farm Feeds, Agricultural Remedies and Stock Remedies Act, 1947 (Act No. 36 of 1947). This Act is administered by the Department of Agriculture and can continue to be administered as such.

Therefore, it is recommended that SAHRA must continue with the registration of veterinary medicines as currently registered by the MCC and that stock remedies and farm feeds continue to be administered by the Department of

Agriculture. This means that SAHRA will need to have some expertise on veterinary medicines.

Constitutional matters

There are no constitutional matters arising. The fact that the SAHRA will report to the Minister reaffirms the constitutional principle that the executive authority of the Republic vests in the President and that the President exercises that authority together with members of Cabinet, the Minister of Health being central in this regard.

CHAPTER 14

APPEAL PROCESS

THE FOLLOWING APPEAL PROCESS APPLIES IN AN INSTANCE WHERE A PERSON IS AGGRIEVED BY THE DECISION OF A PARTICULAR DIVISION OF THE AUTHORITY.

1. The aggrieved person notifies the CEO of the intention to appeal and sets out full facts on the grounds for appeal.

    a. The CEO will meet with the appellant to identify and state clearly the specific points of disagreement.

    b. A decision will be taken as to whether the dispute is regarding a scientific issue or an administrative / policy issue.

2. The CEO presides over a formal administrative review of the contentious issues formulated in 1a, with a view to have the matter resolved amicably between the parties. Both parties will present their respective arguments either in writing or by appearing in person before the CEO. Legal representatives are not allowed, as the objective is to have the matter settled amicably. No cost orders can be made at this point.

    a. An administrative / policy dispute will be resolved by the CEO. If, in the opinion of the appellant, the policy or administrative decision is in conflict with the Act or regulations, the appellant may approach the High Court for review proceedings.

    b. Should the CEO find for the appellant, the decision is final and the matter settled.

c. A person aggrieved by the decision of the CEO may approach the High Court for a judicial review (on administrative / policy matters) of the decision of the CEO.

3. A scientific dispute which is not settled in favour of the appellant may move forward, at the written request of the appellant within 30 days of the CEO's decision, to a formal appeal. Upon this request, the CEO must convene a Committee of Preliminary Appeal (CPA) of 5 persons in addition to a Chair who will be a person with knowledge of law or dispute resolution. The other persons shall be experts in the subject matter of the appeal and appointed proportionally by both the appellant and the CEO. Conflict of interest rules will apply in appointments to the CPA. Legal representatives are not allowed at this stage.

   a. The CPA will be provided with sufficient materials from the product application to be able to consider those points identified in 1a.

   b. The CPA will respond only to those points identified in 1a and will make recommendations to the CEO as to the appropriate resolution of the contented issues.

   c. The CEO will accept the recommendations of the CPA and reach a final decision with respect to the product application.

   d. The recommendations from the CPA and the final decision of the CEO will be made available to the appellant within 30 days of the date on which the CPA meets.

4. A party aggrieved by the decision of the CPA may approach the High Court for a judicial review. The High Court can set aside the decision of the CPA and order that the matter be reheard but cannot substitute its decision for that of the CPA. Cost orders can be made at this point but

only in exceptional circumstances where, in the opinion of the High Court, a party has deliberately wasted the other's time and resources.

Functions of the structure (Include Regulation of Clinical Trials, design and maintain inclusive of pharmacoequivalance, inspection programmes and bioequivalence)

CHAPTER 15

PROPOSED NEW FEE STRUCTURE FOR A NEW SAHRA FOR SOUTH AFRICA

Introduction

In order for the new SAHRA to deliver and commit to legislated outputs or deliverables, it will be necessary for the current fee structure that the Pharmaceutical Industry pays for dossier review, to be increased dramatically.

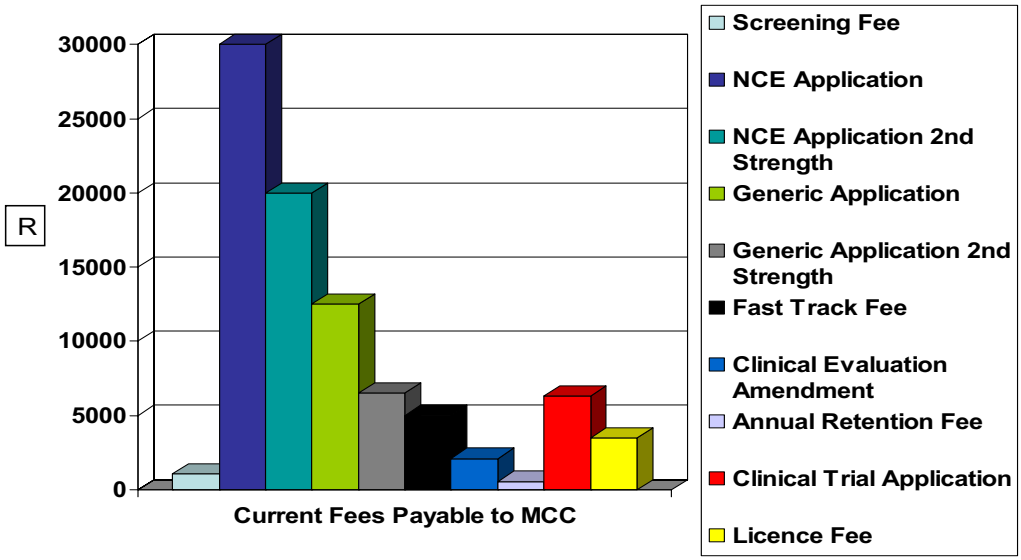
The following regulatory principles need to be adopted by the new SAHRA if the dramatic increase in fees is to be accepted by the Pharmaceutical Industry.

- Transparent Regulatory Process.
- Regulated timelines via a “Clock Stop/Clock Start” mechanism.
- Dedicated Project Managers at the new SAHRA.
- Pre-Defined Meetings with new SAHRA to discuss issues that arise during the Regulatory Process.
- Cooperation with other mature Regulatory Authorities. The regulatory authority will undertake full evaluations of the health products but will consider the evidence and/or documentation utilised by other mature and credible regulatory authorities.
- Dossier Tracking Mechanism.
- Consider a Formalised Pharma Industry Forum to discuss new Policy.
- Common CTD Format of Dossiers.
- IP scan and certification of no infringement by the applicant to the regulatory authority as a regulatory requirement as part of submission
- SAHRA will abide by the prescribed timescales of the various types of applications
- Regard for regular republic reporting on perfomance

Review of Current Major Fees charged by the MCC, Singapore Health Authority and other countries with a similar GDP to South Africa

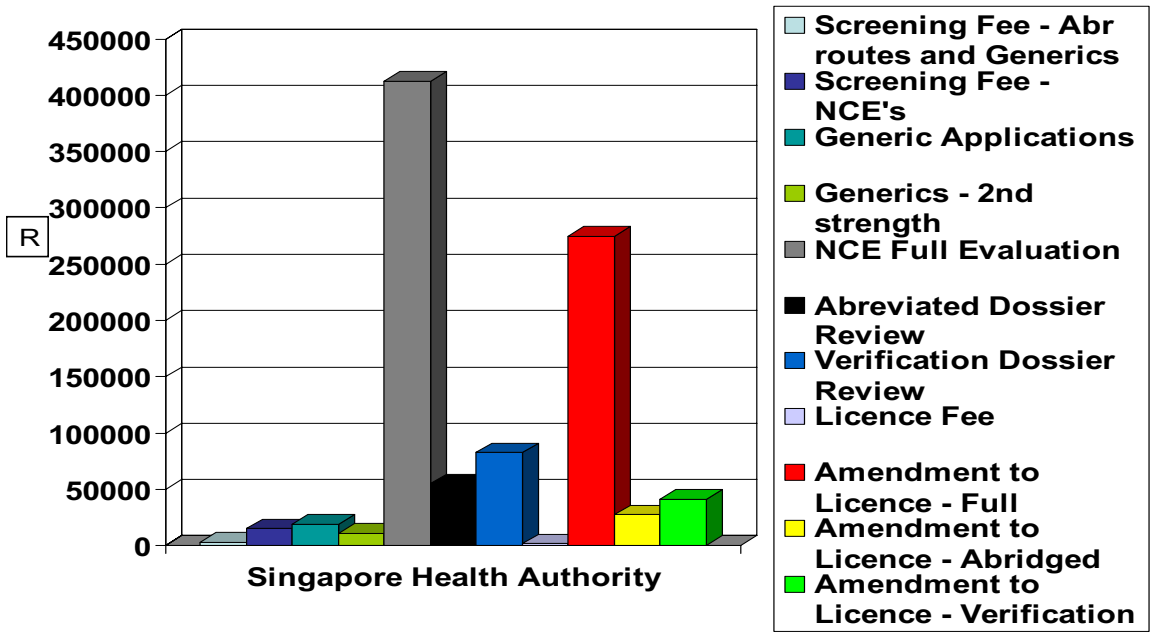
The graph below illustrates the Fees currently charged by the MCC – major categories only.

Current Fees Payable to MCC (Major Categories Only)



Screening Fee	NCE Application	NCE Application 2nd Strength	Generic Application	Generic Application 2nd Strength	Fast Track Fee	Clinical Evaluation Amendment	Annual Retention Fee	Clinical Trial Application	License Fee
R1 050	R30 000	R20 000	R12 500	R6 500	R5 000	R2 100	R550	R6 300	R3 500

A review of the fees charged by the **Singapore Health Authority** show the following at exchange rates Jan 08: -



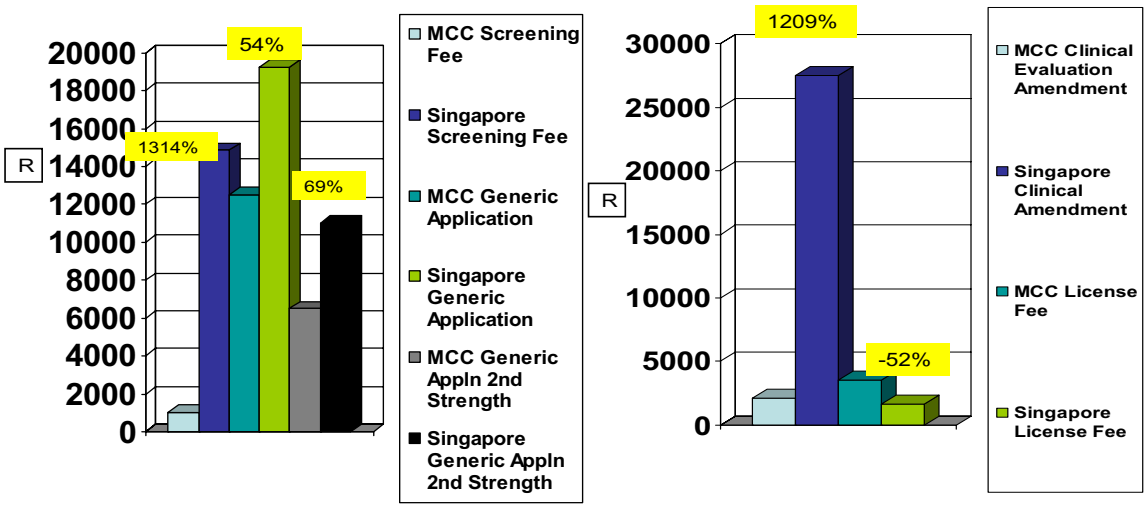
Screening Fee – NCE and Generics Abbreviated routes	**Screening Fee** – NCE's - Full Evaluation	Generic Applications	Generics – 2nd Strength	NCE Full Evaluation
R2 700	R14 850	R19 250	R11 000	R412 500

Abr. Dossier Review NCE - Product approved by one Regulatory Agency	Verification Dossier Review NCE - Product approved by two benchmark regulatory agencies	Company License Fee	Amendment to product license – Full evaluation	Amendment to License – Abridged - Product approved by one Regulatory Agency	Amendment to License – Verification - Product approved by two benchmark regulatory agencies
R55 000	R82 500	R1 650	R275 000	R27 500	R41 250

If a comparison is done between the fees charged by the MCC and that of the Singapore Health Authority (HSA), on a comparable basis; like for like services, the following is observed: -

- Screening Fees, Clinical evaluations and NCE application fees are over 1000% more than that currently charged by the MCC
- Generic applications and second strength Generic applications are 55 to 70 % more than that currently charged by MCC

Comparable Categories MCC/Singapore



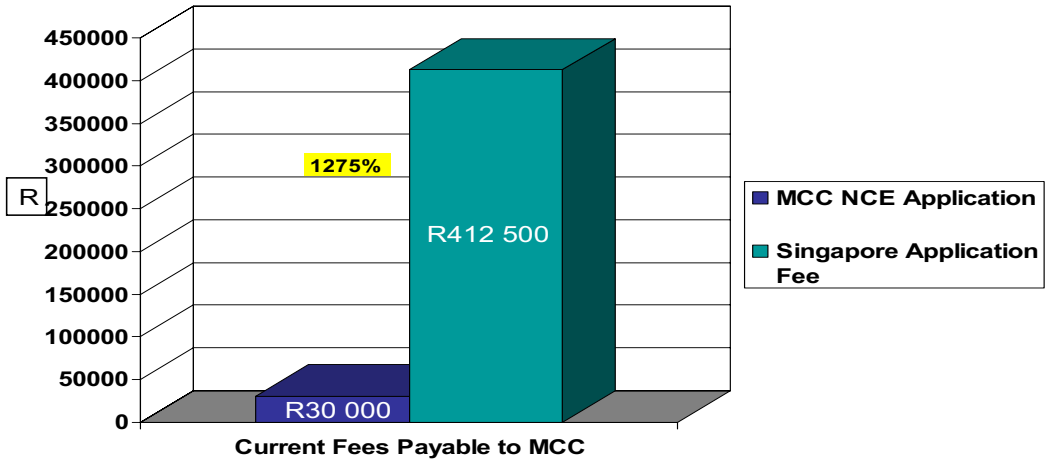
Current Fees Payable to MCC

Screening Fee		Generic Application		Generic Application – 2nd Strength	
MCC	Singapore	MCC	Singapore	MCC	Singapore
R1 050	R14 850	R12 500	R19 250	R6 500	R11 000

Clinical Amendment		License Fee	
MCC	Singapore	MCC	Singapore
R2 100	R27 500	R3 500	R1 650

NB: It must be noted that Singapore does abbreviated evaluations and not full evaluation which is the practice of the majority of Regulatory Authorities.

Comparable Categories MCC/Singapore



Other Country References

A review of countries* that have a **similar GDP** per Capita to South Africa show the following ranges with regards to Application fees for Review

- New Chemical Entity – Malaysia R5000 to Russia R165 200 per application
- Generic - Malaysia R5000 to Russia R165 200 per application

* Chile, Lebanon, Malaysa, Costa Rica, Panama, Turkey, Russia

TABLE 7

Current Comparative Application Fees in similar GDP Countries

Country	NCE	Generic
Chile	R12 600	R12 600
Lebanon	R9 800	R9 800
South Africa	R30 000	R12 500
Malaysia	R5 000	R5 000
Costa Rica	R6 300	n/a
Panama	R8 400	R8 400
Turkey	R128 800	R128 800
Russia	R165 200	R165 200

Thus we can see no differentiation of fees between New Chemical Entities and Generic Applications in the above countries. **In this proposal we will have a differential between Generics & NCE's** in line with the Governments policy to promote generic usage of medicines.

The following countries charge more than South Africa currently for NCEs –

- Turkey – R128 800 per application (330% more than South Africa)
- Russia – R165 200 per application (450% more than South Africa)

The recommendation is that maximum fee structure R165 200 per NCE Application as charged in Russia be adopted, since their GDP is very similar to South Africa's. This represents a four and a half fold increase.

FEE RECOMMENDATIONS IN COMPARISON TO COUNTRIES WITH SIMILAR GDP'S

TABLE 8

Evaluation Route	Description	Proposed Fee per application
Full Evaluation	Product yet to be approved by any Regulatory Agency	R165 200 as per Russia
Abridged Evaluation	Product approved by one Regulatory Agency	R55 000 Singapore model (HSA)
Verification Evaluation	Product approved by two benchmark regulatory agencies	R82 500 Singapore model (HSA)
Generic Evaluation	A generic product	R22 500 Singapore model (HSA)
OTC/Selfcare		R22 500 as per generics
Screening Fee	Screening for both NCE's and Generics	R10 000 as per Singapore model
Company License Fee		R3 500 as per current MCC fees

The current ratio of NCE: Generics submitted to the MCC are 1:40. The number of applications received is in the order of 800 dossiers per year

Clinical Trial Fees

During 2007 the MCC approved 293 clinical trials to be performed in South Africa.

A review of the application fees to perform clinical trials charged in various countries is tabulated below

COMPARISON OF CLINICAL TRIAL FEES WITH SELECTED COUNTRIES

TABLE 9

South Africa	United Kingdom	Australia	Canada	Singapore
R6 300	R39 417 to R47 295 Dependant on Complexity and Length of Trial	R8 642 to R106 641 Short 30 day Trial to Multicentre Long Trial	No Fee	No Fee

The rationale for having No Fee is used in order to stimulate the local Clinical Trial Industry in a particular country.

For the purposes of this paper we have used the current MCC Fee of R6 300 per application and applied an inflationary increase over the last 4 years of an average of 5% since the last fee adjustment in 2003.

The proposal therefore is to increase the Clinical Trial Application Fee to R7 600 per application, which is a 17% increase in on current fees.

Inspection Fees

On average the MCC Inspectorate has been performing 90 GMP Inspections per year. The ratio of Local versus international Inspection sites is 4:1. Therefore on average 85 local inspections are performed and 5 International inspections are performed each year.

The Current Fees charged by the MCC are as follows:

Local Inspection: R160/hr	International Inspection: R400/hr

A review of the Inspection fees charged in various countries is tabulated below:

EMEA (Europe)	Australia	Singapore
R174 000 per site	R 164 640 per site	R132 000 per site
	Rate is R6860 per hour. Assumed 3 Day inspection of 8 hours	

Some countries such as South Africa and Australia charge on an hourly rate, whilst other countries such as Singapore and Europe charge on a per site basis. For the purposes of this paper, and for ease of comparison we have considered a per site inspection fee.

Further Considerations

Funding for the new SAHRA could be split 50/50 between private (Pharma Industry) and Government funding. In the Singapore model the split is 65% Pharma Industry and 35% Government Funding.

It's further suggested that in the interests of capacity building and in the interests of seeing increased efficiencies that the targeted timelines, as introduced in Singapore model, as well as the increased fees, be introduced and reviewed over each five-year period.

Funding Comparator of Old vs. New Fees

Current Fees received from Industry paid to the MCC annually at actual 2007 work volume:-

- New Chemical Entities Applications – 20 x R30 000 = R 600 000
- Generic Applications - 800 x R12 500 = R 10 000 000
- Clinical Trial Applications - 290 x R6 300 = R 1 827 000
- GMP Inspections (assumed all local) - 90 x 160 x 3x 8 = R 345 600

Total R 12 772 600

In the new proposed scenario the income will be (Assuming abridged dossier review for NCE's which will not be the practice of the new SAHRA)

- New Chemical Entities Applications – 20 x R55 000 = R 1 100 000
- Generic Applications - 800 x R22 500 = R 18 000 000
- Clinical Trial Applications - 290 x R7 600 = R 2 204 000
- GMP Inspections (per site) - 90 x R 132 000 = R 11 880 000

Total R 33 184 000

This represents a two and a half fold increase in income from the pharmaceutical industry.

Based on a funding assumption for the new Regulatory Authority of 50% Pharmaceutical Industry and 50% Government funding; the total funding could be as high as R66.4 million which will be inadequate for the 50% cost recovery.

The new fee structure should generate 50% of the required budget of the NRA. A draft new fee schedule to be implemented with modification and consolidation, should the recommendations of the report be accepted, is possible and is given below.

These figures are indicative and will need to be firmed up and/or adjusted so that cost recovery is 50% of the expenditure of SAHRA

NCE's	20 X R180,000	R3.6M
Additional Indications	50 X R100,000	R5.0M
Generic's	800 X R30,000	R24.0M
Clinical Trials	330 X R25,000	R7.5M
GMP Inspections	90 X R150,000	R13.5M
Annual License	11,400 X R3000	R34,2M
Complementary Medicines	2,000 X R15 000	R30M
Medical Devices	? X R??	R??
Total		**R117.8M**

Add to this a Post-Marketing Surveillance Strategy	R20M
Actual Projected Fee Revenues	R137.8M
+ outstanding above amounts	
At 50% Cost Recovery to Tax-based Allocation:	
Add Tax-base	R137.8M
Projected Budget for SAHRA	
(Plus revenues from Medical Devices and ATM)	R275.6M

Option 1 indicated on HR budget R197M and add an additional 20% for capex and opex cost gives a figure of R237.6M. A 50% cost recovery is realistic. The details will be calculated should the principle be approved in the recommendations.

CHAPTER 16

SPECIAL ISSUES

- Safe products body

  A need for a Safe Products Body that will ensure safety of all those products that do not fullfil the criteria of being regulated by this RA e.g. cosmetics without medicinal content or medical claims, electrical appliances, batteries.

  Currently there appears to be no existing safe product body in the country that regulates and/or registers products e.g. cosmetics that do not fulfil the criteria for registration by the new regulatory authority, batteries, cellphones or other appliances etc. to ensure their safety

- Containment and Control of the Healthcare costs

  The need for the Control of the cost of Health Care by an intergrated and comprehensive system e.g. a National Health Insurance so that gains in the containment of health costs in one area e.g. pharmaceuticals is not lost by an over run of the costs in another area e.g. Private Hospital tarrifs and costs.

  The cost of health care in the country is a challenge. The hospital costs have become unaffordable for a significant part of the community. Benefits are shrinking while contributions to Medical Schemes is increasing which has led to out of pocket contributions. There is a need for the regulation of health costs.

- Social Responsibility

  The health product industry, being an important and significant industry needs to contribute to social responsibility. The Health Charter should take care of this aspect.

- Policy for the Pharmaceutical Industry in South Africa

  There is a need for an umbrella policy for the Pharmaceutical Industry that ensures its significant contribution for the economy in the country.

- Marketing Code of Ethics for the Health Product Industry

  A Marketing Code of Ethics has been finalised by the pharmaceutical industry and is attached as annexure H. This is important, as it will deal with perverse incentives, unethical practices in marketing, ensure quality and thereby control costs of health products. It needs to be published as a regulation in section 18c of Act 101, and /or as ammended.

  Regulations are needed in particular to section 18a of the Act to stop preservatives.

- Intellectual Property Rights and the protection of confidential information on innovative products.

  The New Regulatory Authority will adhere to the Legislation of the Country in respect of Intellectual Property Rights. It will be the responsibility of the industry applying for registration of its products to certify that it does not infringe Intellectual Property Rights of the Country. Their declaration will be binding and should it prove to be incorrect legal recourse and responsibility will be borne by the applicant. Where the regulatory authority receives an application that contains confidential supporting information of an innovative product, the authority has the obligation to keep that information confidential, not to use that information to grant another license. The information referred to above maybe disclosed with the consent of the applicant if

in the opinion of the regulatory authority it is necessary to protect the health and/or safety of the public or which is in the public interest.

CHAPTER 17

RECOMMENDATIONS

- Strategic

1. A New Regulatory Authority for Health Products should replace the current MCC and the current MRA. This single entity will be responsible for the regulation and registration of all health products in the country so as to ensure safe, quality and efficacious health products.

2. The SAHRA will be an independent umbrella entity under which components/ divisions will be responsible for the regulation and registration of the various health products. The suggested structure in *Chapter 8* ensures that this will occur. This is keeping with global trends.

3. Concurrence of the Ministers of Health, Agriculture and Environmental Affairs and Tourism is necessary for those aspects of SAHRA that straddle these Departments.

4. The new entity should be an agency within the Department of Health with the CEO reporting directly to the Minister of Health. The benefits of an agency is that it will be advantaged in the recruitment of scarce skills and highly technical staff, as their remuneration packages can be flexible. This is important for the stability of the entity and the performance of its functions. A line function entity reporting directly to the Minister will not be able to recruit and retain scarce skills and highly technical staff. This is a global challenge which compromises functions of the regulatory authority and which maybe overcome by the entity being an agency in the Department of Health.

5. The Head of the New Regulatory Authority should be fulltime, be the accounting officer, be responsible for the regulatory authority and be subject to the PFMA.

6. The Principles in Chapter 9 and the Structure provided in Chapter 8, of the Report, be adopted.

7. The financing of the SAHRA should be part “cost recovery”. This should be 50% of the costs of the authority. This will ensure that it financially feasible and sustainable.

8. Option 1 in Chapter 12 is the recommended option, as it will provide adequate resources for the New Regulatory Authority. Option 2 in the same Chapter is not recommended, as it is not capable of ensuring a sustained resource base for the Regulatory Authority. The revenue generated from the New Recommended Fee Schedule will provide for the 50% cost recovery. An estimated additional R20M needs to be added to the costs structure given to cover capex and the additional opex. The projected revenue generation is provided in Chapter 15, which indicates that it is possible and sustainable.

9. The Regulatory Authority should have its own Inspectorate but it should work closely with the Office of Standard Compliance of the Department of Health.

10. Memoranda of Understanding should be developed with selected regulatory authorities of other countries in specific areas so as to enhance efficiency and maximise resources utilisation. This will assist with scarce skills shortages. The MOU’s will be signed by the Minister.

11. The Regulatory Authority should undertake full evaluation of all applications of Health Products submitted for registration and licensing but should consider best practices across the family of health products and the evaluation of other credible regulatory authorities where

necessary. This will ensure efficiency and meet prescribed timeframes. Risk based assessments maybe utilised where decided in accordance with the policy of SAHRA.

12. The evaluation and consideration of Clinical Trials should consider the not only the safety and efficacy of the trial product but also the possible adverse effects, ethical considerations and community ramifications.

13. All Health Products inclusive of Blood Products, Food and Cosmetics with medicinal claims or containing medicines will be regulated by SAHRA.

14. SAHRA should be able to retain all revenue generated so as to be able to contribute to the 50% cost recovery of the expenditure.

15. As SAHRA will be an agency a flexible remuneration structure should be developed so as enable it to recruit and retain the critical staff required by the authority.

16. The CEO must sign the performance Agreement with the Minister of Health and should submit strategic plans to the Minister of Health for approval.

17. The CEO should submit quarterly and annual report to the Minister of Health.

18. The strategic plans and annual reports should be tabled before the assembly after approval by the Minister in accordance with the PFMA.

19. All clinical trials for humans and animals conducted for all health products will be evaluated and regulated by SAHRA in accordance with the prescribed policies for the clinical trials. Ethical approval inclusive of the consideration of public interest should be considered in accordance of the Ethical Policy and Guidelines as approved by the

Ethics Council of Department of Health or of Agriculture in the case of animal clinical trials prior to SAHRA granting approval.

- Operative

1. An Office of Business Transformation and Administration should be developed, as it will assist the CEO to ensure good governance.

2. The clearance of the current backlog should be a priority for the NRA and undertaken in a specific time. Resources should be provided to achieve this.

3. MOU's, Service Level Agreements and Performance Agreements should be implemented in order to ensure efficiency, and function within the prescribed timeframes provided in the report.

4. An electronic document management system should be implemented that will enable tracking, improve efficiency, enhance communication, ensure confidentiality and privacy, and improve archiving and sourcing of documents.

5. Human Resource Management should include in-service training. Employment Conditions of service should be established in accordance with prescripts but be flexible in order encourage recruitment of the requisite staff and the retention of scarce skills.

6. Conflict of interest policy should be strengthened and the declaration signed by all staff inclusive of the contract staff.

7. Pricing will only be considered as part of the regulatory process should an NHI be established. The SAHRA will cooperate with other

components in the Department of Health responsible for pricing of health products.

8. Suitable premises and adequate physical resources should be made available for the NRA.

CHAPTER 18

IMPLEMENTATION PLANS

The implementation plan should be structured once the recommendations have been approved.

This will be in a manner that will address immediate challenges of the backlog and governance while the new structure is being implemented in suitable premises and with the necessary resources.

The implementation plan should ensure that the new regulatory authority is in place as soon as possible. Strict timeframes of the implementation should be provided and adhered to.

CHAPTER 19

ACKNOWLEDGEMENTS

We need to thank the Minister of Health, Dr Manto Tshabalala-Msimang for entrusting the task to the members of the Ministerial Task Team.

The work of the Task Team Members requires special acknowledgement as the product of this report is a result of teamwork, considerable effort and dedication.

The Health Product industry must be commended for their inputs and contributions and particularly for the positive and constructive manner, which enabled the task to be undertaken successfully.

Mention must be made of the following for the assistance, cooperation and contributions provided by :
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(SARHA)
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Health Product Association (HPA)
South African Medical Device Industry Association (SAMED)
Pharmacy Council of South Africa (PCSA)
Medicines Control Council (MCC)
Medicines Regulatory Authority (MRA)

The Task Team wishes to record a special thanks to all those that were consulted and contributed to the success of the report. One would like

to mention the people individually but it is difficult to do this because of logistical challenges.

The secretariat must be thanked and commended for the work undertaken

CHAPTER 20

CONCLUSION

The Ministerial Task Team has fulfilled its mandate. It recommends the creation of the NRA for Health Products in South Africa as an Agency that will replace the current MCC and MRA. It should be 50 percent self funded from the revenue collected from fees and 50 percent funded by the fiscus. This will ensure adequate funding, affordability and sustainability. The adoption of Good Governance and Management Principles will be essential for its success. Once approved the process of implementation should commence as soon as possible and completed within a short prescribed period.

CHAPTER 21

ANNEXURES / APPENDICES

Appendix A: Part C, Division 5 of the Canadian Food and Drugs Regulations

DIVISION 5
DRUGS FOR CLINICAL TRIALS INVOLVING HUMAN SUBJECTS

Interpretation

C.05.001. The definitions in this section apply in this Division.
"adverse drug reaction" means any noxious and unintended response to a drug that is caused by the administration of any dose of the drug. (*réaction indésirable à une drogue*)

"adverse event" means any adverse occurrence in the health of a clinical trial subject who is administered a drug, that may or may not be caused by the administration of the drug, and includes an adverse drug reaction. (*incident thérapeutique*)

"clinical trial" means an investigation in respect of a drug for use in humans that involves human subjects and that is intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of the drug, identify any adverse events in respect of the drug, study the absorption, distribution, metabolism and excretion of the drug, or ascertain the safety or efficacy of the drug. (*essai clinique*)

"drug" means a drug for human use that is to be tested in a clinical trial. (*drogue*)

"good clinical practices" means generally accepted clinical practices that are designed to ensure the protection of the rights, safety and well-being of clinical trial subjects and other persons, and the good clinical practices referred to in section C.05.010.(*bonnes pratiques cliniques*)

"import" means to import a drug into Canada for the purpose of sale in a clinical trial. (*importer*)

"investigator's brochure" means, in respect of a drug, a document containing the preclinical and clinical data on the drug that are described in paragraph C.05.005(*e*). (*brochure du chercheur*)

"protocol" means a document that describes the objectives, design, methodology, statistical considerations and organization of a clinical trial. (*protocole*)

"qualified investigator" means the person responsible to the sponsor for the conduct of the clinical trial at a clinical trial site, who is entitled to provide health care under the laws of the province where that clinical trial site is located, and who is

(a) in the case of a clinical trial respecting a drug to be used for dental purposes only, a physician or dentist and a member in good standing of a professional medical or dental association; and
(b) in any other case, a physician and a member in good standing of a professional medical association. (*chercheur qualifié*)

"research ethics board" means a body that is not affiliated with the sponsor, and

(*a*) the principal mandate of which is to approve the initiation of, and conduct periodic reviews of, biomedical research involving human subjects in order to ensure the protection of their rights, safety and well-being; and

(*b*) that has at least five members, that has a majority of members who are Canadian citizens or permanent residents
under the *Immigration and Refugee Protection Act*, that is composed of both men and women and that includes at least

(i) two members whose primary experience and expertise are in a scientific discipline, who have broad experience in the methods and areas of research to be approved and one of whom is from a medical discipline or, if the clinical trial is in respect of a drug to be used for dental purposes only, is from a medical or dental discipline,

(ii) one member knowledgeable in ethics,

(iii) one member knowledgeable in Canadian laws relevant to the biomedical research to be approved,

(iv) one member whose primary experience and expertise are in a non-scientific discipline, and

(v) one member who is from the community or is a representative of an organization interested in the areas of research to be approved and who is not affiliated with the sponsor or the site where the clinical trial is to be conducted. (*comité d'éthique de la recherche*)

"serious adverse drug reaction" means an adverse drug reaction that requires in-patient hospitalization or prolongation of existing hospitalization, that causes congenital malformation, that results in persistent or significant disability or incapacity, that is life threatening or that results in death. (*réaction indésirable grave à une drogue*)

"serious unexpected adverse drug reaction" means a serious adverse drug reaction that is not identified in nature, severity or frequency in the risk information set out in the investigator's brochure or on the label of the drug. (*réaction indésirable grave et imprévue à une drogue*)

"sponsor" means an individual, corporate body, institution or organization that conducts a clinical trial. (*promoteur*) SOR/2001-203,s. 4; 2001, c. 27, s. 273.

Application

C.05.002. (1) Subject to subsection (2), this Division applies to the sale or importation of drugs to be used for the purposes of clinical trials involving human subjects.

(2) Except for paragraph C.05.003(*a*), subsections C.05.006(2) and (3), paragraphs C.05.010(*a*) to (*i*), section C.05.011,subsections C.05.012(1) and (2), paragraphs C.05.012(3)(*a*) to (*d*) and (*f*) to (*h*), subsection C.05.012(4) and sections C.05.013, C.05.016 and C.05.017, this Division does not apply to the sale or importation of a drug for the purposes of a clinical trial authorized under subsection C.05.006(2). SOR/2001-203, s. 4.

Prohibition

C.05.003. Despite sections C.01.014, C.08.002 and C.08.003, no person shall sell or import a drug for the purposes of a clinical trial unless
(*a*) the person is authorized under this Division;

(*b*) the person complies with this Division and sections C.01.015, C.01.036, C.01.037 to C.01.040, C.01.040.2, C.01.064 to C.01.067, C.01.070, C.01.131, C.01.133 to C.01.136, and C.01.435; and

(*c*) if the drug is to be imported, the person has a representative in Canada who is responsible for the sale of the drug.SOR/2001-203, s. 4.

General

C.05.004. Despite these Regulations, a sponsor may submit an application under this Division to sell or import a drug for the purposes of a clinical trial that contains a substance the sale of which is prohibited by these Regulations, if the sponsor establishes, on the basis of scientific information, that the inclusion of the substance in the drug may result in a therapeutic benefit for a human being. SOR/2001-203, s. 4.

Application for Authorization

C.05.005. An application by a sponsor for authorization to sell or import a drug for the purposes of a clinical trial under this Division shall be submitted to the Minister, signed and dated by the sponsor's senior medical or scientific officer in Canada and senior executive officer and shall contain the following information and documents:

(*a*) a copy of the protocol for the clinical trial;

(*b*) a copy of the statement, as it will be set out in each informed consent form, that states the risks and anticipated benefits arising to the health of clinical trial subjects as a result of their participation in the clinical trial;

(*c*) a clinical trial attestation, signed and dated by the sponsor's senior medical or scientific officer in Canada and senior executive officer, containing

(i) the title of the protocol and the clinical trial number,

(ii) the brand name, the chemical name or the code for the drug,

(iii) the therapeutic and pharmacological classifications of the drug,

(iv) the medicinal ingredients of the drug,

(v) the non-medicinal ingredients of the drug,

(vi) the dosage form of the drug,

(vii) the name, address and telephone number and, if applicable, the facsimile number and electronic mail address of the sponsor,

(viii) if the drug is to be imported, the name, address and telephone number and, if applicable, the facsimile number and electronic mail address of the sponsor's representative in Canada who is responsible for the sale of the drug,

(ix) for each clinical trial site, the name, address and telephone number and, if applicable, the facsimile number and electronic mail address of the qualified investigator, if known at the time of submitting the application,

(x) for each clinical trial site, the name, address and telephone number and, if applicable, the facsimile number and electronic mail address of the research ethics board that approved the protocol referred to in paragraph (*a*) and approved an informed consent form containing the statement referred to in paragraph (*b*), if known at the time of submitting the application, and

(xi) a statement

(A) that the clinical trial will be conducted in accordance with good clinical practices a nd these Regulations, and
(B) that all information contained in, or referenced by, the application is complete and accurate and is not false or misleading;

(*d*) the name, address and telephone number and, if applicable, the facsimile number and electronic mail address of any research ethics board that has previously refused to approve the protocol referred to in paragraph (*a*), its reasons for doing so and the date on which the refusal was given, if known at the time of submitting the application;

(*e*) an investigator's brochure that contains the following information, namely,

(i) the physical, chemical and pharmaceutical properties of the drug,

(ii) the pharmacological aspects of the drug, including its metabolites in all animal species tested,

(iii) the pharmacokinetics of the drug and the drug metabolism, including the biological transformation of the drug in all animal species tested,

(iv) any toxicological effects in any animal species tested under a single dose study, a repeated dose study or a special study in respect of the drug,

(v) any results of carcinogenicity studies in any animal species tested in respect of the drug,

(vi) any results of clinical pharmacokinetic studies of the drug,

(vii) any information regarding drug safety, pharmacodynamics, efficacy and dose responses of the drug that were obtained from previous clinical trials in humans, and

(viii) if the drug is a radiopharmaceutical as defined in section C.03.201, information regarding directions for preparing the radiopharmaceutical, the radiation dosimetry in respect of the prepared radiopharmaceutical and a statement of the
storage requirements for the prepared radiopharmaceutical;

(*f*) if the drug contains a human-sourced excipient, including any used in the placebo,

(i) information that indicates the human-sourced excipient has been assigned a drug identification number under subsection C.01.014.2(1) or, in the case of a new drug, issued a notice of compliance under subsection C.08.004(1), as the case may be, or

(ii) in any other case, sufficient information to support the identity, purity, potency, stability and safety of the humansourced excipient;

(*g*) if the drug has not been assigned a drug identification number under subsection C.01.014.2(1) or, in the case of a new drug, a notice of compliance has not been issued under subsection C.08.004(1), the chemistry and manufacturing information in respect of the drug, including its site of manufacture; and

(*h*) the proposed date for the commencement of the clinical trial at each clinical trial site, if known at the time of submitting the application. SOR/2001-203, s. 4.

Authorization

C.05.006. (1) Subject to subsection (3), a sponsor may sell or import a drug, other than a drug described in subsection (2),for the purposes of a clinical trial if

(*a*) the sponsor has submitted to the Minister an application in accordance with section C.05.005;

(*b*) the Minister does not, within 30 days after the date of receipt of the application, send to the sponsor a notice in respect of the drug indicating that the sponsor may not sell or import the drug for any of the following reasons:

(i) that the information and documents in respect of the application

(A) were not provided in accordance with these Regulations, or

(B) are insufficient to enable the Minister to assess the safety and risks of the drug or the clinical trial, or

(ii) that based on an assessment of the application, an assessment of any information submitted under section C.05.009 or a review of any other information, the Minister has reasonable grounds to believe that

(A) the use of the drug for the purposes of the clinical trial endangers the health of a clinical trial subject or other person,

(B) the clinical trial is contrary to the best interests of a clinical trial subject, or

(C) the objectives of the clinical trial will not be achieved;

(*c*) for each clinical trial site, the sponsor has obtained the approval of the research ethics board in respect of the protocol referred to in paragraph C.05.005(*a*) and in respect of an informed consent form that contains the statement referred to in paragraph C.05.005(*b*); and

(*d*) before the sale or importation of the drug at a clinical trial site, the sponsor submits to the Minister the information referred to in subparagraphs C.05.005(*c*)(ix) and (x) and paragraphs C.05.005(*d*) and (*h*), if it was not submitted in respect of that clinical trial site at the time of submitting the application.

(2) Subject to subsection (3), a sponsor may sell or import a drug for the purposes of a clinical trial in respect of

(*a*) a new drug that has been issued a notice of compliance under subsection C.08.004(1), if the clinical trial is in respect of a purpose or condition of use for which the notice of compliance was issued; or

(*b*) a drug, other than a new drug, that has been assigned a drug identification number under subsection C.01.014.2(1), if the clinical trial is in respect of a use or purpose for which the drug identification number was assigned.

(3) A sponsor may not sell or import a drug for the purposes of a clinical trial

(*a*) during the period of any suspension made under section C.05.016 or C.05.017; or

(*b*) after a cancellation made under section C.05.016 or C.05.017. SOR/2001-203, s. 4.

Notification

C.05.007. If the sale or importation of a drug is authorized under this Division, the sponsor may make one or more of the following changes if the sponsor notifies the Minister in writing within 15 days after the date of the change:

(*a*) a change to the chemistry and manufacturing information that does not affect the quality or safety of the drug, other than a change for which an amendment is required by section C.05.008; and

(*b*) a change to the protocol that does not alter the risk to the health of a clinical trial subject, other than a change for which an amendment is required by section C.05.008. SOR/2001-203, s. 4.

Amendment

C.05.008. (1) Subject to subsections (4) and (5), when the sale or importation of a drug is authorized under this Division and the sponsor proposes to make an amendment referred to in subsection (2), the sponsor may sell or import the drug for the purposes of the clinical trial in accordance with the amended authorization, if the following conditions are met:

(*a*) the sponsor has submitted to the Minister an application for amendment in accordance with subsection (3);

(*b*) the Minister does not, within 30 days after the date of receipt of the application for amendment, send to the sponsor a notice in respect of the drug indicating that the sponsor may not sell or import the drug in accordance with the amendment for any of the following reasons, namely,

(i) that the information and documents in respect of the application for amendment

(A) were not provided in accordance with these Regulations, or

(B) are insufficient to enable the Minister to assess the safety and risks of the drug or the clinical trial, or

(ii) that based on an assessment of the application for amendment, an assessment of any information submitted under section C.05.009 or a review of any other information, the Minister has reasonable grounds to believe that

(A) the use of the drug for the purposes of the clinical trial endangers the health of a clinical trial subject or other person,

(B) the clinical trial is contrary to the best interests of a clinical trial subject, or

(C) the objectives of the clinical trial will not be achieved;

(*c*) before the sale or importation of the drug, the sponsor submits to the Minister

(i) for each clinical trial site, the name, address and telephone number and, if applicable, the facsimile number and electronic mail address of the research ethics board that approved any amended protocol submitted under paragraph (3)(*a*) or approved any amended statement submitted under paragraph (3)(*c*), and

(ii) the name, address and telephone number and, if applicable, the facsimile number and electronic mail address of any research ethics board that has previously refused to approve any amendment to the protocol, its reasons for doing so and the date on which the refusal was given;

(*d*) before the sale or importation of the drug, the sponsor maintains records concerning

(i) the information referred to in paragraph C.05.005(*h*), and

(ii) the information referred to in subparagraph C.05.005(*c*)(ix), if any of that information has changed since it was submitted;

(*e*) before the sale or importation of the drug in accordance with the amended authorization, the sponsor ceases to sell or import the drug in accordance with the existing authorization; and

(*f*) the sponsor conducts the clinical trial in accordance with the amended authorization.

(2) For the purposes of subsection (1), amendments are

(*a*) amendments to the protocol that affect the selection, monitoring or dismissal of a clinical trial subject;

(*b*) amendments to the protocol that affect the evaluation of the clinical efficacy of the drug;

(*c*) amendments to the protocol that alter the risk to the health of a clinical trial subject;

(*d*) amendments to the protocol that affect the safety evaluation of the drug;

(*e*) amendments to the protocol that extend the duration of the clinical trial; and

(*f*) amendments to the chemistry and manufacturing information that may affect the safety or quality of the drug.

(3) The application for amendment referred to in subsection (1) shall contain a reference to the application submitted undersection C.05.005 and shall contain the following documents and information:

(*a*) if the application is in respect of an amendment referred to in any of paragraphs (2)(*a*) to (*e*), a copy of the amended protocol that indicates the amendment, a copy of the protocol submitted under paragraph C.05.005(*a*), and the rationale for the amendment;

(*b*) if the application is in respect of an amendment referred to in paragraph (2)(*e*), a copy of the amended investigator's brochure or an addendum to the investigator's brochure that indicates the new information, including supporting toxicological studies and clinical trial safety data;

(*c*) if the application is in respect of an amendment referred to in any of paragraphs (2)(*a*) to (*f*) and, as a result of that amendment, it is necessary to amend the statement referred to in paragraph C.05.005(*b*), a copy of the amended statement that indicates the new information; and

(*d*) if the application is in respect of an amendment referred to in paragraph (2)(*f*), a copy of the amended chemistry and manufacturing information that indicates the amendment, and the rationale for that amendment.

(4) If the sponsor is required to immediately make one or more of the amendments referred to in subsection (2) because the clinical trial or the use of the drug for the purposes of the clinical trial endangers the health of a clinical trial subject or other person, the sponsor may immediately make the amendment and shall provide the Minister with the information referred to in subsection (3) within 15 days after the date of the amendment.

(5) A sponsor may not sell or import a drug for the purposes of a clinical trial

(*a*) during the period of any suspension made under section C.05.016 or C.05.017; or

(*b*) after a cancellation made under section C.05.016 or C.05.017. SOR/2001-203, s. 4.

Additional Information and Samples

C.05.009. If the information and documents submitted in respect of an application under section C.05.005 or an application for amendment under section C.05.008 are insufficient to

enable the Minister to determine whether any of the reasons referred to in paragraph C.05.006(1)(*b*) or C.05.008(1)(*b*) exist, the Minister may require the sponsor to submit, within two days after receipt of the request, samples of the drug or additional information relevant to the drug or the clinical trial that are necessary to make the determination. SOR/2001-203, s. 4.

Sponsor's Obligations

Good Clinical Practices

C.05.010. Every sponsor shall ensure that a clinical trial is conducted in accordance with good clinical practices and, without limiting the generality of the foregoing, shall ensure that

(*a*) the clinical trial is scientifically sound and clearly described in a protocol;

(*b*) the clinical trial is conducted, and the drug is used, in accordance with the protocol and this Division;

(*c*) systems and procedures that assure the quality of every aspect of the clinical trial are implemented;

(*d*) for each clinical trial site, the approval of a research ethics board is obtained before the clinical trial begins at the site;

(*e*) at each clinical trial site, there is no more than one qualified investigator;

(*f*) at each clinical trial site, medical care and medical decisions, in respect of the clinical trial, are under the supervision of the qualified investigator;

(*g*) each individual involved in the conduct of the clinical trial is qualified by education, training and experience to perform his or her respective tasks;

(*h*) written informed consent, given in accordance with the applicable laws governing consent, is obtained from every person before that person participates in the clinical trial but only after that person has been informed of

> (i) the risks and anticipated benefits to his or her health arising from participation in the clinical trial, and
>
> (ii) all other aspects of the clinical trial that are necessary for that person to make the decision to participate in the clinical trial;

(*i*) the requirements respecting information and records set out in section C.05.012 are met; and

(*j*) the drug is manufactured, handled and stored in accordance with the applicable good manufacturing practices referred to in Divisions 2 to 4 except sections C.02.019, C.02.025 and C.02.026. SOR/2001-203, s. 4.

Labelling

C.05.011. Despite any other provision of these Regulations respecting labelling, the sponsor shall ensure that the drug bears a label that sets out the following information in both official languages:

(*a*) a statement indicating that the drug is an investigational drug to be used only by a qualified investigator;

(*b*) the name, number or identifying mark of the drug;

(*c*) the expiration date of the drug;

(*d*) the recommended storage conditions for the drug;

(*e*) the lot number of the drug;
(*f*) the name and address of the sponsor;

(*g*) the protocol code or identification; and

(*h*) if the drug is a radiopharmaceutical as defined in section C.03.201, the information required by subparagraph C.03.202(1)(*b*)(vi). SOR/2001-203, s. 4.

Records

C.05.012. (1) The sponsor shall record, handle and store all information in respect of a clinical trial in a way that allows its complete and accurate reporting as well as its interpretation and verification.

(2) The sponsor shall maintain complete and accurate records to establish that the clinical trial is conducted in accordance with good clinical practices and these Regulations.

(3) The sponsor shall maintain complete and accurate records in respect of the use of a drug in a clinical trial, including

(*a*) a copy of all versions of the investigator's brochure for the drug;

(*b*) records respecting each change made to the investigator's brochure, including the rationale for each change and documentation that supports each change;

(*c*) records respecting all adverse events in respect of the drug that have occurred inside or outside Canada, including information that specifies the indication for use and the dosage form of the drug at the time of the adverse event;

(*d*) records respecting the enrolment of clinical trial subjects, including information sufficient to enable all clinical trial subjects to be identified and contacted in the event that the sale of the drug may endanger the health of the clinical trial subjects or other persons;

(*e*) records respecting the shipment, receipt, disposition, return and destruction of the drug;

(*f*) for each clinical trial site, an undertaking from the qualified investigator that is signed and dated by the qualified investigator prior to the commencement of his or her responsibilities in respect of the clinical trial, that states that

> (i) the qualified investigator will conduct the clinical trial in accordance with good clinical practices, and
>
> (ii) the qualified investigator will immediately, on discontinuance of the clinical trial by the sponsor, in its entirety or at a clinical trial site, inform both the clinical trial subjects and the research ethics board of the discontinuance, provide them with the reasons for the discontinuance and advise them in writing of any potential risks to the health of clinical trial subjects or other persons;

(*g*) for each clinical trial site, a copy of the protocol, informed consent form and any amendment to the protocol or informed consent form that have been approved by the research ethics board for that clinical trial site; and

(*h*) for each clinical trial site, an attestation, signed and dated by the research ethics board for that clinical trial site, stating that it has reviewed and approved the protocol and informed consent form and that the board carries out its functions in a manner consistent with good clinical practices.

(4) The sponsor shall maintain all records referred to in this Division for a period of 25 years. SOR/2001-203, s. 4.

Submission of Information and Samples

C.05.013. (1) The Minister shall require a sponsor to submit, within two days after receipt of the request, information concerning the drug or the clinical trial, or samples of the drug, if the Minister has reasonable grounds to believe that

(*a*) the use of the drug for the purposes of the clinical trial endangers the health of a clinical trial subject or other person;

(*b*) the clinical trial is contrary to the best interests of a clinical trial subject;

(*c*) the objectives of the clinical trial will not be achieved;

(*d*) a qualified investigator is not respecting the undertaking referred to in paragraph C.05.012(3)(*f*); or

(*e*) information submitted in respect of the drug or the clinical trial is false or misleading.

(2) The Minister may require the sponsor to submit, within seven days after receipt of the request, any information or records kept under section C.05.012, or samples of the drug, in order to assess the safety of the drug or the health of clinical trial subjects or other persons. SOR/2001-203, s. 4.

Serious Unexpected Adverse Drug Reaction Reporting

C.05.014. (1) During the course of a clinical trial, the sponsor shall inform the Minister of any serious unexpected adverse drug reaction in respect of the drug that has occurred inside or outside Canada as follows:

(*a*) if it is neither fatal nor life threatening, within 15 days after becoming aware of the information; and

(*b*) if it is fatal or life threatening, within seven days after becoming aware of the information.

(2) The sponsor shall, within eight days after having informed the Minister under paragraph (1)(*b*), submit to the Minister a complete report in respect of that information that includes an assessment of the importance and implication of any findings made.

(3) Sections C.01.016 and C.01.017 do not apply to drugs used for the purposes of a clinical trial. SOR/2001-203, s. 4.

Discontinuance of a Clinical Trial

C.05.015. (1) If a clinical trial is discontinued by the sponsor in its entirety or at a clinical trial site, the sponsor shall

(*a*) inform the Minister no later than 15 days after the date of the discontinuance;

(*b*) provide the Minister with the reason for the discontinuance and its impact on the proposed or ongoing clinical trials in respect of the drug conducted in Canada by the sponsor;

(*c*) as soon as possible, inform all qualified investigators of the discontinuance and of the reasons for the discontinuance, and advise them in writing of any potential risks to the health of clinical trial subjects or other persons; and

(*d*) in respect of each discontinued clinical trial site, stop the sale or importation of the drug as of the date of the discontinuance and take all reasonable measures to ensure the recovery of all unused quantities of the drug that have been sold.

(2) If the sponsor has discontinued the clinical trial in its entirety or at a clinical trial site, the sponsor may resume selling or importing the drug for the purposes of a clinical trial in its entirety or at a clinical trial site if, in respect of each clinical trial site where the sale or importation is to be resumed, the sponsor submits to the Minister the information referred to in subparagraphs C.05.005(*c*)(ix) and (x) and paragraphs C.05.005(*d*) and (*h*). SOR/2001-203, s. 4.

Suspension and Cancellation

C.05.016. (1) Subject to subsection (2), the Minister shall suspend the authorization to sell or import a drug for the purposes of a clinical trial, in its entirety or at a clinical trial site, if the Minister has reasonable grounds to believe that

(*a*) the sponsor has contravened these Regulations or any provisions of the Act relating to the drug;

(*b*) any information submitted in respect of the drug or clinical trial is false or misleading;

(*c*) the sponsor has failed to comply with good clinical practices; or

(*d*) the sponsor has failed to provide

> (i) information or samples of the drug as required under section C.05.009 or C.05.013, or
>
> (ii) information or a report under section C.05.014.

(2) Subject to section C.05.017, the Minister shall not suspend an authorization referred to in subsection (1) unless

(*a*) the Minister has sent to the sponsor a written notice of the intention to suspend the authorization that indicates whether the authorization is to be suspended in its entirety or at a clinical trial site and the reason for the intended suspension;

(*b*) the sponsor has not, within 30 days after receipt of the notice referred to in paragraph (*a*), provided the Minister with information or documents that demonstrate that the authorization should not be suspended on the grounds that

> (i) the situation giving rise to the intended suspension did not exist, or
>
> (ii) the situation giving rise to the intended suspension has been corrected; and

(*c*) the Minister has provided the sponsor with the opportunity to be heard in paragraph (*b*).

(3) The Minister shall suspend the authorization by sending to the sponsor a written notice of suspension of the authorization that indicates the effective date of the suspension, whether the authorization is suspended in its entirety or at a clinical trial site and the reason for the suspension.

(4) If the Minister has suspended an authorization, the Minister shall

(*a*) reinstate the authorization in its entirety or at a clinical trial site, as the case may be, if within 30 days after the effective date of the suspension the sponsor provides the Minister with information or documents that demonstrate that the situation giving rise to the suspension has been corrected; or

(*b*) cancel the authorization in its entirety or at a clinical trial site, as the case may be, if within 30 days after the effective date of the suspension the sponsor has not provided the Minister with the information or documents referred to in paragraph (*a*). SOR/2001-203, s. 4.

C.05.017. (1) The Minister shall suspend an authorization to sell or import a drug for the purposes of a clinical trial, in its entirety or at a clinical trial site, before giving the sponsor an opportunity to be heard if the Minister has reasonable grounds to believe that it is necessary to do so to prevent injury to the health of a clinical trial subject or other person.

(2) The Minister shall suspend the authorization by sending to the sponsor a written notice of suspension of the authorization that indicates the effective date of the suspension, whether the authorization is suspended in its entirety or at a clinical trial site and the reason for the suspension.

(3) If the Minister has suspended an authorization, the Minister shall

(*a*) reinstate the authorization in its entirety or at a clinical trial site, as the case may be, if within 60 days after the effective date of the suspension the sponsor provides the Minister with information or documents that demonstrate that the situation giving rise to the suspension did not exist or that it has been corrected; or

(*b*) cancel the authorization in its entirety or at a clinical trial site, as the case may be, if within 60 days after the effective date of the suspension the sponsor has not provided the Minister with the information or documents referred to in paragraph (*a*). SOR/2001-203, s. 4.

Appendix B: Management of Drug Submission Policy, from Canada

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/mgmt-gest/mands_gespd_e.html

This file can also be accessed by double-clicking on the following:

Management of Drug Submission Policy

Appendix C: Example of Quarterly Performance Report, from Canada

http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/bpa_bepp_01q3_e.pdf

This file can also be accessed by double-clicking on the following:

Quarterly Report

Appendix D

MEDICINES CONTROL COUNCIL

FEES PAYABLE TO THE REGISTRAR

The Minister of Health has, in consultation with the Medicines Control Council, in terms of Section 35(1) of the Medicines and Related Substances Act, 1965 (Act No. 101 of 1965), made the regulations in the Schedules relating to Fees payable to the Registrar.

Government Gazette No 24808 Notice R 539 released for implementation	**25 April 2003**
Government Gazette No 25837 Notice R 1807 released for implementation	**19 December 2003**

REGISTRAR OF MEDICINES
MS M.P. MATSOSO

SCHEDULE

Definition

1. In this Schedule “the Regulations” means the Regulations Relating to Fees payable to the Registrar, published under Government Notice No. R 352 of 21 February 1975 and Government Notice No. R 539 of 25 April 2003, as amended and “the Act” means the Medicines and Related Substances Act, 1965 (Act No. 101 of 1965)

Fees

2. The following fees shall be payable to the Registrar

Category A medicines

(1) Human medicines, including Biologicals, compounded in its entirety in the RSA or not, for which an application for registration has been submitted as contemplated in Section 15 of the Act,

(a) in respect of the submission of an application for registration of-

(i) New Chemical Entities or highly technological products, which have been processed by the abbreviated registration process (first strength, first dosage form): R30 000 per application;

(i): R15 000 per application;

(ii) Strengths and dosage forms other than those referred to in sub-paragraph

(iii) New Chemical Entities, including highly technological products, (first strength,
first dosage form): R30 000 per application;

(iv) Strengths and dosage forms other than those referred to in sub-paragraph

(iii): R20 000 per application;

(v) Biological products (pharmaceutical, analytical and bioavailability evaluated): R30 000 per application;

(vi) Generic products (pharmaceutical, analytical and bioavailability evaluated) and all other dental and radio pharmaceutical products (first strength, first dosage form): R12 500 per application;

(vii) Strengths and dosage forms other than those referred to in sub-paragraph (vi): R6 500;

(viii) screening fee on receipt of an application: R1 050;

(ix) evaluation of additional submitted clinical data: R1 900;

(x) an application in terms of Section 15C of the Act: R12 500.

(xi) any medicine, the registration of which has been approved by the Council in terms of section 15(3) of the Act:

(aa) evaluation of request for rescheduling of products: R1 900;
(bb) Evaluation of request to amend package insert in respect of which clinical data relating to safety and efficacy must be evaluated: R2 100.

(xii) of any medicine in accordance with an expedited registration procedure in terms of section 15(2)(b) of the Act: R 5 000

(b) In respect of registration of any medicine, the registration of which has been approved by the Council in terms of section 15(3) of the Act (in the case of medicines in minute-dose form; the fee encompasses different dilutions and different volumes, when submitted simultaneously for the same indication or intended use) and in respect of which an application fee has been paid: R600 for each registration.

(c) Annually, in respect of the retention of the registration of a medicine, the registration of which has been approved by the Council in terms of Section 15(3): R550: Provided that this provision shall come into effect one year after the date on which the registration of the said medicine was approved by the Council in terms of Section 15(3); Provided further that the said fees payable during a particular calendar

year shall be payable on or before the last working day of June that year, failing which the registration may be cancelled in terms of Section 16(4).

Category C medicines

(2) Veterinary medicines, including Biologicals, whether compounded in the RSA or not and for which Council has determined by resolution that they are registrable:

(a) In respect of the submission of an application for registration of-

(i) New Chemical Entities, including highly technological products, (first strength, first dosage form): R3 800 per application;

(ii) Generic products (pharmaceutical, analytical and bioavailability evaluated): R3 800 per application;

(iii) screening fee on receipt of the application: R1 050;

(iv) evaluation of additional submitted clinical data: R1 900

(v) any medicine, the registration of which has been approved by the Council in terms of section 15(3):

(aa) evaluation of request for rescheduling of products: R1 900;
(bb) evaluation of request to amend package insert in respect of which clinical data relating to safety and efficacy must be evaluated: R2 100."

(b) In respect of the registration of any medicine, the registration of which has been approved by the Council in terms of section 15(3) (in the case of medicines in minute-dose forms; the fee encompasses different dilutions and different volumes, when submitted simultaneously for the same indication or intended use) and in respect of which an application fee has been paid: R600 for each registration.

(c) Annually, in respect of the retention of the registration of a medicine, the registration of which has been approved by the Council in terms of Section 15(3): R350: Provided that this provision shall come into effect one year after the date on which the registration of the said medicine was approved by the Council in terms of Section 15(3): Provided further that the said fees payable during a particular calendar year shall be payable on or before the last working day of June that year, failing which the registration may be cancelled in terms of Section 16(4).

(3) In respect of the submission of an application for the authorization of the use of an unregistered medicine:

(a) clinical trials (Companies): R6 300;
(b) clinical trials (Institutions): R3 100;
(c) any other clinical trial: R1 075;
(d) any other application except for the purpose of performing a clinical trial: R200.

(4) In respect of clinical trials amendments:

(a) fees in respect of an application for technical amendments: R1 050 per amendment;
(b) fees in respect of an application for administrative amendment: R320 per amendment.

(5) In respect of licences:

(a) an application for a license in terms of section 22C(1)(b) of the Act:

(i) Manufacture: R3 500;
(ii) Distribution: R2 400;
(iii) Wholesale: R2 400
(iv) Import: R2 400
(v) Export: R2 400

(b) an application for the renewal of a license in terms of section 22D of the Act, the licensing of which has been approved by the Council in terms of section 22C(1)(b) of the Act:

(i) Manufacture: R3 500;
(ii) Distribution: R2 400;
(iii) Wholesale: R2 400;
(iv) Import: R2 400
(v) Export: R2 400

(c) Annually, in respect of the retention of a licence issued in terms of section 22C(1)(b) of the Act: R600, and this fee is payable on or before the last working day of June that year, failing which registration may be cancelled;

(d) licensing for any manufacture, distribution, wholesale, import or export, the license of which has been approved by the Council in terms of Section 22(1)(b) of the Act: R600.

(6) In respect of performance of inspections to assess the quality of medicines:

a. Local manufacturing sites: R160 per hour;
b. International manufacturing sites: R400 per hour.
c. Wholesale sites: R800 per site
d. Distributor sites: R800 per site

(7) In respect of the issuing of a permit or a certificate:

(a) Certificate: R525; (Certificate of a Pharmaceutical Product (WHO), Good Manufacturing Practice (GMP) Certificate, Certificate of Free Sale)
(b) Import permit: R500;
(c) Export permit: R300;
(d) Any other permit: R525;
(e) Permits issued by the Director-General in terms of Section 22A of the Act: R100.

Amendment of entries in register

(8) In respect of all applications for amendments in terms of Section 15A, the name of the medicine approved by the Council under section 15(5), which shall be the proprietary name, the approved name of each active ingredient of the medicine and the quantity thereof contained in a dosage unit or per suitable mass or volume or unit of the medicine, the conditions of registration, and the name of the applicant: R220 per application.

Transfer of certificates of registration

(9) In respect of an application in terms of Section 15B: registered name, approved name of every active ingredient and quantities thereof per dosage unit or per suitable mass or volume or unit of the medicine, dosage form, conditions under which the medicine is registered; and name of applicant: R400 per application.

Substitution of regulation 35 of the regulations

3. The following regulation substituted regulation 35 of the Regulations:

ME TSHABALALA-MSIMANG
MINISTER OF HEALTH

Appendix E

CURRENT WORKLOAD

Ministerial Task Team

The number of applications for registration of medicines and clinical trials has increased substantively over the last five years as illustrated in figure 1 below. The Number of applications for generic medicines has increased from 508 in 2003 to 801 in 2006. 765 applications for generics had been received by the end of November 2007. Registration timelines are long. Of applications received in 2003, 28% have not yet been registered. Of the applications received in 2004, 2005, 2006 and 2007, 31%, 53%, 80% and 98% respectively had not yet been registered by end 2007.

Table 1

Registration Information as at 08-01-2008

Applications	[1]Received (final)	[3]*Not registered end 2007*	*Percentage not registered*	[2]Registered	NCEs (molecules)	
					Received	Registered
2003						
Human	580	*163*		418	16	20
Veterinary	15	*4*		16		
Total	**595**	***167***	**28 %**	**434**		
Generics	508			318		
2004						
Human	590	*215*		281	25	17
Veterinary	12	*6*		8	2	
Total	**702**	***221***	**31 %**	**289**		
Generics	563			213		
2005						
Human	590	*309*		746	18	20
Veterinary	10	*8*		20		
Total	**600**	***317***	**53 %**	**766**		
Generics	490			633		
2006						
Human	923	*737*		546	18	19
Veterinary	16	*16*		6	3	
Total	**939**	***753***	**80 %**	**552**		
Generics	801			468		
2007 (01/01/2007 – 30/11/2007)						
Human	883	*866*		386	22	9
Veterinary	12	*12*		1		
Total	**895**	***878***	**98 %**	**387**		
Generics	765			342		
Total				**[5]2 428**		
	[4]3 731	**[4]2 336**	**63 %**	**[4]1 395**		

[1]Applications received: Number of **final** applications received, i.e. those that passed screening

[2]Applications registered: The number indicated as registered in a particular year does not indicate the number received AND registered in the *same* year, but indicates the total number registered in that year and includes applications from previous years

[3]Applications not registered: The numbers indicate the number of applications of those submitted in the particular year not yet registered to date.

[4]Of the 3 731 applications received for the period 2003 to 2007, 1 395 were registered and 2 336 have not yet been registered.

[5] 2 428 applications were registered in the period 2003 to 2007, i.e. 1 395 of the applications submitted in that period and 1 033 from the period before 2003.

With clinical trials,, the number of applications has been steadily increasing as reflected in Table 2 below

Table 2

Clinical Trials

YEAR	2004	2005	2006	2007 (up to October)
NUMBER	258	269	274	211

Human Resources

In house capacity must be improved to increase the number of suitably qualified internal reviewers. Additional skills required include in-house clinicians, bio scientists and pharmacists. Financial management and internal IT expertise are also required.

Retention of skilled staff has been a challenge. Remuneration levels must also be reviewed. The same applies to remuneration of external experts.

Appendix F: *Preliminary Considerations for an HR Plan*

Country	US$perCapita	Population (M)	Est Total ($M)	Est Total Rand (Million's)	# Staff	Avg$perStaff (1000's)	AvgRperStaff (1000's)
Zimbabwe	0.20	12.3	2.46	17.59	51	48.24	344.88
Uganda	0.10	1.7	0.17	1.22	40	4.25	30.39
Tunisia	0.12	10.3	1.24	8.84	86	14.37	102.76
Venezuela	0.05	26	1.30	9.30	272	4.78	34.17
Estonia	0.30	1.32	0.40	2.83	34	11.65	83.28
Malaysia	0.20	24.8	4.96	35.46	170	29.18	208.61
Cyprus	0.60	0.788	0.47	3.38	12	39.40	281.71
Cuba	0.08	11.4	0.91	6.52	67	13.61	97.33
Australia	1.45	20.4	29.58	211.50	500	59.16	422.99
Canada	3.50	33.4	116.90	835.84	1,500	77.93	557.22
U.K.	2.01	60.8	122.00	872.30			
USA	5.98	301	1800.00	12,870.00			
Options							
South Africa							
Option 1	0.59	47		198.00	482		410.79
	0.58	48		198.00	482		410.79
Option 2	0.35	47		117.00	285		410.53
	0.34	48		117.00	285		410.53

Abbreviations:

US$perCapita = Total regulatory budget expenditure for drug regulatory authority per capita in US dollars.
Population = estimate based upon US CIA Factsheet found at https://www.cia.gov/library/publications/the-world-factbook/
Est Total ($M) = calculated total US$ in millions from per capita times total population.
Est Total Rand = conversion from US$ based upon 7.15R per 1US$
 # Staff = Total staff identified in regulatory authority. Note ! This may or may not be limited to review staff.
Avg$perStaff = calculated remuneration in 1000's US$ per staff FTE from Total US$ divided by #Staff
AvrRperStaff = conversion from $US currency to remuneration per FTE in 1000's Rand.

Appendix G

MODELS FOR THE REGULATORY REVIEW OF MEDICINES IN SOUTH AFRICA

1. Introduction

Effective drug regulation is required to ensure the safety, efficacy and quality of medicines as well as the accuracy and appropriateness of drug information available to the public.

A regulatory authority should have the following objectives:

- Protecting public health – through regulation and acceptable benefit-risk profiles of medicines and devices

- Promoting public health – by helping patients who use these products to understand their benefits and risks

- Improving public health – by encouraging and facilitating developments in products that will benefit the patients

Any regulatory authority should have a number of strategic objectives namely to:

- Maintain a rigorous authorisation and inspection system

- Maintain and develop a proactive surveillance and enforcement programme

- Communicate authoritative and reliable information

- Support innovation and product development ensuring that research conducted is ethical and patients protected

- Shape and influence the future regulatory framework by working with other regulatory authorities around the world

- Minimise the cost of regulation so far as is compatible with its public health role

- Run a successful operation on business principles with a skilled and equipped workforce dedicated to the agency's aims

This section covers three areas:

- A review of the current regulatory system in South Africa

- Suggested improvements to the current system (Model 1)

- A new model to achieve the above aims and strategic objectives for a regulatory authority in South Africa (Model 2)

2. Review of the Regulatory System in South Africa

The agency responsible for the regulation of medicines in South Africa includes the Medicines Regulatory Authority (MRA) and the Medicines Control Council (MCC). This is currently within the administrative structure of the Department of Health, was established in 1965 and regulates medicinal products for human use, medical devices and veterinary medicines.

The scope of its activities include marketing authorisations, post-marketing surveillance, clinical trial authorisations, regulation of advertising, sample analysis, GMP inspection, issuing of licences and permits related to medicines.

The combined staff in the MRA and MCC is around 250 (full-time and part-time), with around 130 reviewers. The organisation is 100% funded by government•

2.1 Model (for medicines authorisations) Currently Used in South Africa

The regulatory agency in South Africa is capable of carrying out a full assessment of quality, pre-clinical (safety) and clinical (efficacy) data for new medicines.

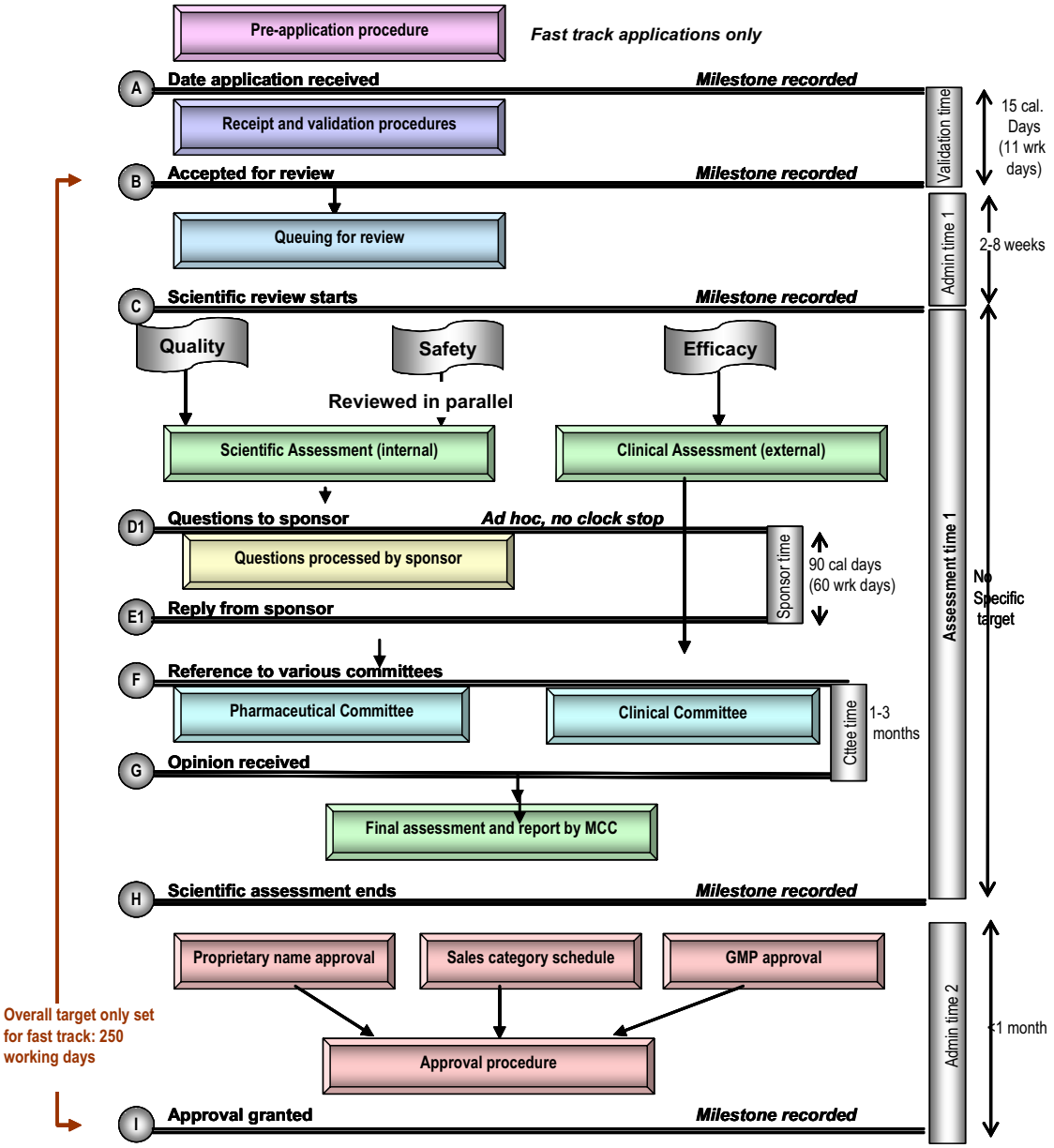
Information on registrations elsewhere (if any) are taken into consideration but are not a pre-requisite to filing or authorisation

2.2 Data Requirements

Submission Format	SA MCC Specific form
Certificate of a Pharmaceutical Product (CPP)	Not essential but a copy of the authorisation letter should be provided if the product has been registered in a reference country (e.g., Fast Track products) and copies of labelling are also required for products authorised in reference countries.
Quality data	Full data (Module 3 of CTD) is required and a detailed assessment carried out and evaluation report prepared.
Non-clinical data	Full data (Module 4 CTD) is required and a detailed assessment carried out and evaluation report prepared.
Clinical data	Full data (Module 5 CTD) is required and a detailed assessment carried out and evaluation report prepared.

Process Map for South Africa

SOUTH AFRICA



2.4 Factors Taken into Account When Assessing Benefit and Risk

Clinical opinion always takes account of:

- Ethnic factors
- National disease patterns

  but differences in medical culture/practice are not generally taken into consideration

The agency sometimes tries to obtain data from:

- Other agencies' internal assessment reports
- Reports, such as EPARs, available on the Internet (but does not carry out a general Internet search)

The agency always refers to pharmacovigilance reports and checks GMP status and product compliance

2.5 Review Model

Notes on the Process Map

A map of the review process in South Africa is given previously. The following should, however, be noted:

- The process map is a simplified representation of the main steps in the review of a **new active substance (NAS)** application.
- The map represents the review and authorisation of a product that is approved on the **first cycle** (i.e., does not include a second cycle for products approved subject to the submission of additional data)
- The map does not include the steps that follow the **refusal** of an application (hearings, appeals etc)
- This representation does not however seem to have been published by the MCC and therefore may not be fully understood.

Additional Factors Impacting the Review Process

The current agency, operating within the Health Ministry, was first established in 1965 and has since that time undergone many changes.

Review Team

Of the 250 staff and consulting experts (full and part time) currently making up the Medicines Regulatory Authority (MRA) and Medicines Control Council (MCC) **130** are assigned to the review and assessment of medicinal products. The professional background of these is as follows:

Physicians	43
Pharmacists	91
Other Scientists	65

These reviewers are generally academics employed by the South African Universities, and review applications on a part time basis for the Authority.

Fast track applications

There is a fast track procedure for applications for certain priority products requiring rapid review. Access to this expedited route requires either that the product is listed on the SA Essential Drug List or has been motivated by the "Applicant" and approved by the Minister as being essential for National Health. The scientific data requirements do not differ between fast track and other products and the level of scientific assessment is similar. Once submitted, however, the products are always given priority in the queuing system and an overall target of **250 working days** set in the legislation for their approval.

Key points in the review procedure

Before submission	**Pre-submission requirements:** Fast track applications need to be notified in advance to establish eligibility for an accelerated review
Validation	**Items checked at the validation stage:** • Legal Status of the applicant/local agent • GMP status of the manufacturer • Whether the company has paid the correct fee • That a product sample has been submitted • That the application is in an acceptable format with the correct sections of scientific data The agency also confirms the qualification and authorisation of the Responsible Person **Certificate of a Pharmaceutical Product (CPP)** A CPP is not a pre-requisite but any CPP is checked as part of the validation process **Incomplete applications** if the information is not complete or dossiers not up to standard,, the application is classified as 'Refuse to file' and a new application must be made. Currently this process can take up to 4-5 months and is perceived to be a critical but avoidable step that is delaying formal review. .
Queuing	**From this step onwards there is no communication with application until such time as review by all expert committees is completed.** **Queue time** Applications have to wait 2-8 weeks after validation before being picked up for review, although priority products are always taken out of turn. ***Backlog*** The agency is concerned about the backlog and is addressing this through in-house capacity building, enlarging the establishment and recruiting additional External Assessors
Scientific assessment	**Scientific review sequence** • Data on quality, safety and efficacy are assessed in parallel **Primary scientific assessment** • The clinical data is sent to outside experts • Otherwise, the primary scientific assessment is carried out by agency staff and reviewed by a committee when deemed necessary. The agency has a panel of 130 part-time academic experts whose main responsibilities to the MCC are to provide detailed assessment reports and recommendations, provide a clinical opinion on the product and advise the agency staff on specific technical issues

Questions to Applicant	**Timing of questions to "Applicants"** Questions are sent to the Applicant to address as they arise, following expert committee review. There is no provision limiting review period by experts per dossier and there is no procedure to stop the review clock or calculate overall applicant response times. **Applicant response** Applicants have a time limit of 90 calendar days to reply to pharmaceutical questions and 180 calendar days for clinical questions. ***Interaction with the Applicant*** The Applicant may hold meetings with the agency staff to discuss questions and queries that arise during the assessment but the meetings must involve more than one member of staff. There is however no possibility of interfacing with committee members and the experts themselves.
Expert Committee(s)	**Scientific Committees** There are various scientific committees to whom the applications are referred including the Clinical Committee and the Quality/Analytical and GMP Committee ***Committee timing*** There is no target time limit for the Committee procedure but its work normally takes 1-3 months ***Use of the Committee advice*** The Agency is not obliged to follow the advice from the Scientific Committee
Recommendation	**Recommendation on the application** After the Committee opinions are received the MCC undertakes a final evaluation of the application and makes a recommendation on registration. The Applicant is informed of a positive scientific opinion before the authorisation is granted. The full process from submission for validation to this stage is estimated to be around 27-33 months, generics taking less time than NCEs.
Authorisation	**Responsibility for the decision** The decision on whether or not to grant an authorisation is made by the Medicines Control Council (MCC) **Criteria for the decisions on applications** The criteria for granting or refusing a marketing authorisation relate only to the scientific assessment of scientific data on quality, safety and efficacy. Before the authorisation can be granted, however, the following are required: • Approval of the proprietary name • Allocation of a scheduling status (Legal sales category) to the active pharmaceutical ingredient (API) • Evaluation of the GMP status of the Applicant, manufacturer, assembler and quality control laboratory as well as the responsibility for Batch Release **Authorisation Procedure** The authorisation is granted in less than a month from receiving a positive scientific opinion.

Timelines in the review procedure

	Target	Comment
Validation	15 calendar days	Industry reports targets not being met.
Scientific assessment		No target set
Applicant response time	Pharmaceutical questions -90 calendar days Clinical questions - 180 calendar days	
Expert Committee(s)	1-3 months	
Authorisation procedure	< 1 month	
Overall Approval time		Target only applies to fast track applications: 250 working days

Actual approval times (average)

	Time from receipt of application to issue of approval		
Type	**2004**	**2005**	**2006 – Aug**
New Active Substances[1]	24-36 months	24-36 months	27 months
Major line extensions	18-24 months	18-24 months	24 months

Fees charged for review applications

	US$
New active substance	5000
Established ingredient – proprietary product	2083
Generic (non-proprietary) product	2083
Major line extension (clinical data)	3300
Major line extension (generic)	2083
Variations	36
Licensing fee	600
Retention fee	92
Screening fee	175
Fast track	840
Registration fee	100

Metrics on NAS applications and Major Line Extensions

Number of applications received in each year

	2004	2005	2006 – Aug
New Active Substance	62	40	42
Major line extension	645	527	611

Number of applications determined in each year

	2004	2005	2006 – Aug
New Active Substances approved	38	50	32
Major line extensions approved	252	719	445

2.6 Regulation of Clinical Trials

Procedure for initiating clinical trials in South Africa

Prior Authorisation of Clinical Trials

This is required for all trials on New Active Substances in South Africa

- The Applicant must apply for a Clinical Trial Authorisation before carrying out trials in the country
- The Agency must grant the authorisation before trials can commence
- Application data is submitted and assessed before the authorisation is granted
- Assessment by independent ethics committee

Data requirements for Clinical trial applications

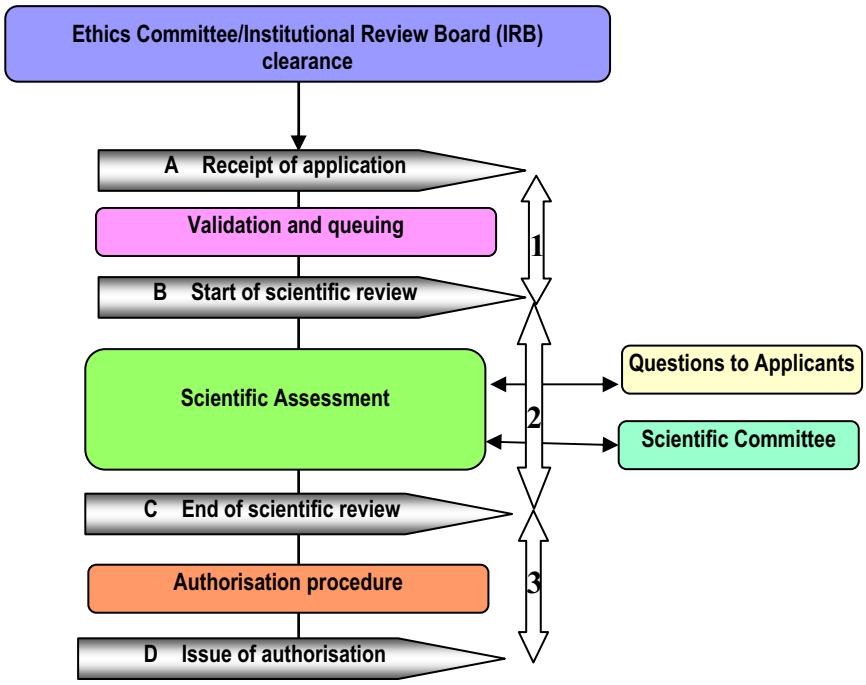
• Clinical trial protocol • Investigator's Brochure • Ethics approval from independent committee	• Full Quality data • Full Non-clinical data • Full Clinical data • Investigators Statement of intent and CV • Financial disclosure

Guidelines are issued by the agency on the content of applications for clinical trial authorisation.

Good Clinical Practice

The Agency accepts trials carried out in accordance with ICH GCP (Guideline E6), WHO GCP or the national Department of Health Guidelines (2006)

Process Model for Clinical Trial Applications



Key points on the CT Authorisation Process

	Ethics Committee approval An application to an Ethics Committee (EC) for approval must be made in advance of applying for a CT Authorisation but there appears to be some flexibility in whether the EC clearance must be available at that stage or only before the authorisation from the MCC is granted.
	Validation • A formal validation of the application is carried out after receipt of clinical trial applications
	Scientific assessment • There are different procedures for different sections of the application Clinical and bioavailabity studies submitted are evaluated for compliance with GCP by the Agency's GCP inspector Bioequivalence is assessed by the Agency's technical staff External experts evaluate the clinical data and present reports to the **Clinical Trials Committee** (CTC) • **Target time:** A target time of 3 weeks is set for the scientific assessment
	Reference to a Scientific Committee • Applications are referred to the **CTC** or the **Pharmaceutical and Analytical Committee for Bioequivalence** • The Committee is consulted as part of the Agency's scientific assessment
	Questions to the Applicant • Questions to the Applicant are sent at any time during the assessment of the application • The Applicant has a time limit of 7 working days in which to reply • The time taken for Applicants to answer questions is recorded separately from the overall review time

Milestones recorded

The following dates are recorded during the review process:

- A: Receipt of application
- B: Start of the scientific review
- C: End of the scientific review
- D: Date of issue of the CT Authorisation

The target time for approval of a CT application is 14 weeks

In practice the time for issuing CT authorisations is about 14-20 weeks, this is out of line with the rest of the world where CT authorisations are between one and two months.

Metrics on processing Clinical Trial applications

CT applications received

	Number of applications received in each year		
Type	**2004**	**2005**	**2006 - Sept**
New Active Substance	78	85	69
Major line extension	159	183	159

CT applications determined

	Number of applications determined in each year		
Type	**2004**	**2005**	**2006**
Trials on NASs approved	73	72	52
Trials on NASs refused	1	2	0
Trials on major line extensions approved	139	154	114
Trials on major line extensions refused	3	5	4

2.7 Building Quality into the Regulatory Processes

General measures used to achieve quality

The agency has implemented, and/or intends to implement, the following quality measures in the review and authorisation of medicinal products:

- **An internal quality policy** defined as '*Overall intentions and direction of the organisation related to quality, as formally expressed by top management'*
  - This is not currently in place but there are plans to introduce such a policy within the next two years but there has not been any open engagement on this with the industry to date.
- **Good Review Practices** defined as '*A code about the process and the documentation of review procedures that aims to standardise and improve*

the overall documentation and ensure timeliness, predictability, consistency and high quality of reviews and review reports'

- GRP is not formally documented at present but there are plans to establish this within the next two years but there has not been any open engagement on this with the industry to date.

- **Standard Operating Procedures (SOPs)** defined as '*Written documents that describe in detail the official procedures to be followed for a specific operation'.* These are used for:
  - Guidance to scientific assessors
  - Advisory committee procedures
  - Issue of manufactures licences
  - International Narcotics control board (INCB) permits for import and export of medicines containing narcotics and psychotropic substances
  - Assessment of variations
- **Assessment templates** setting out the content and format of written reports on scientific reviews
- **Peer Review** defined as 'an additional evaluation of the original assessment that is carried out by an independent person or Committee'
  - Both external and internal peer reviews are carried out when a NAS is assessed

Quality management

The agency has identified the following as the three most important measures for the introduction of quality measures:

- To be more efficient
- To minimise errors
- To ensure consistency

Monitoring to improve quality

The following activities are undertaken to bring about continuous improvement in the assessment and authorisation process:

- Reviewing assessors' feedback and taking necessary action
- Reviewing stakeholders' feedback (e.g. through complaints, meetings or workshops) and taking necessary action
- Carrying out internal quality audits (e.g. self-assessments) and using findings to improve the system (*Inspectorate only)*
- Having external quality audits by an accredited certification body to improve the system (*Inspectorate only, ISO procedures*)

Management responsibility

The Authority does not have a dedicated department for assessing and/or assuring quality in the assessment and registration process for new medicines. There are, however, plans to set up such a department

Quality in the Review and Assessment Process

The following measures have been implemented or are planned to help improve the quality of applications and the scientific review:

- **Guidelines for industry** are available:
  - Through the authority's website
  - Through official publications
  - On request
  - Through industry associations
- **Pre-application scientific advice** is not available to applicants
  - The applicant is, however, given contacts to discuss the application with technical staff during the review
- **Interaction with the applicant:**
  - ***During development:*** Possibility for informal contact exist described by agencies as extensive but channels are not easily accessed by Applicants.
  - ***During assessment:*** Some formal contact with evaluators and no means for Applicants to track dossier interim progress.

- **Interaction with the industry:**
  - Outside of the MTT, there is currently no effective formal platform for dialogue on policy and regulatory reform with the industry.
- **Scientific Committees:**

  Pharmaceutical/analytical and GMP Committee (16 members)

  Clinical Trials Committee (22 Members)

  Clinical Committee (18 members)

  Names and Scheduling Committee (7 Members)
  - The committees meet every 8 weeks
  - All new active substances (NAS) and major line extensions (MLE) applications are reviewed
  - The committees review the assessment reports from the reviewers
- **Shared/Joint reviews** have not been undertaken by the agency but it is anticipated that such reviews might take place in future

Training and continuing education as an element of quality

The Agency has formal training programmes in place for assessors:

- **Training methods:** Training is mainly carried out through:
  - Induction training
  - External courses
  - On-the-job training
  - In-house courses
  - Participation in international workshops/ conferences
  - External speakers invited to the authority
  - Placements and secondments in other regulatory authorities

- **Collaboration with other agencies:** The agency works in partnership with **PIC/S Training for GMP Inspectors, WHO** and the **Australian TGA** to improve training.

- **Completion of training:** There are no formal examinations but completion of training is, to some extent, important for professional advancement within the agency

Transparency of the review process

'Transparency' is defined as '*The ability and willingness of the agency to assign time and resources to providing information on its activities to both the informed public (which includes health professionals) and industry*'.

- **Priority:** The Agency assigns high priority to transparency. Currently the recording of information is limited to paper tracking and no formal reporting occurs during the registration process.
- **Drivers:** The agency has these three incentives for assigning resources to activities that enhance the openness of the regulatory system:
  - Political will
  - Need to increase confidence in the system
  - Need to provide assurances on safety safeguards

Transparency to the public

The agency claim that Information is provided routinely to the general public on the performance of the agency which includes:

- **Information on applications:** The following is provided on marketing authorisation applications:
  - Approval of products
  - Advisory Committee meeting dates
  - Information on approved product labelling

- **Access to information:** The information is made available:
  - Official Journal/periodical publication
  - From an official Internet website

- On request, from the MRA offices, in hard copy

- **In the event of rejection** detailed reasons are given for the decision in some cases only.

Application tracking

An electronic tracking system is not yet in place but an Electronic Data Management System (EDMS) is scheduled to be introduced in 2007. This is considered one of the most critical elements in running an efficient and productive regulatory agency.

In order to comply with the principles of administrative justice, it is recommended that the SAMRA and all its structures and committees, adhere to the practice of providing written reasons, for decisions or requests made, which clearly relates to a particular published policy document and/or a provision in the empowering Act or regulations. This will facilitate speedy resolution of queries, and ensure an appropriate response from applicants. Although these rules are part of the law of administrative justice, its explicit incorporation in the policies and procedures of the Regulatory Authority will greatly enhance legal certainty and efficiency on both the side of the Regulator and the applicants

Suggested Modifications to the Regulatory Review Process in South Africa

Medicine Regulatory Authorities worldwide have a common goal to protect public health in their respective countries by ensuring the availability of medicines that meet not only national but international standards of quality, efficacy and safety as well as ensuring that relevant information is provided on such products.

It is recommended that certain fundamental principles be embraced by the SAMRA and that further, two options exist to improve the regulatory review process in South Africa.

The adoption of certain fundamental principles would benefit the SA regulatory system, whatever model is finally adopted. These principle should apply to any option adopted and are listed below.

1. Fundamental Principles:

1.1 Structure and Organisation

It is suggested that there should be one overarching Medicines Regulatory Authority (MRA) that reports to the Minister of Health at a senior level, mandated to deal with matters of policy and process. This new MRA will be within the Ministry of Health of the South African government. There must be no conflict of interest with the executive Department of Health functions. Such independence, together with transparency and good corporate governance, will promote confidence in the operational and decision- making processes of the new South African Medicines Regulatory Agency (SAMRA).

The overarching Regulatory Authority should be ultimately accountable for all policy relating to medicines regulatory issues, particularly (but not restricted to);

- Standards of quality, safety and efficacy of medicines
- Policy on the marketing code of practice
- Engagement of experts and conflict of interest

Directly under the SAMRA there should be independently accountable technical Divisions for each area of regulation, such as:

- Human allopathic medicines
- Complementary medicines e.g. homeopathic, western herbal, Chinese herbal medicines etc.
- Veterinary medicines (including stock remedies)
- African traditional medicines
- Medical Devices

This new South African Medicines Regulatory Authority (SAMRA) will continue to be responsible for all medicine regulatory issues, including the development of applicable technical guidelines, the appointment of appropriately qualified staff and the registration of products with the same principles applying to other areas, namely medical devices, veterinary medicines, etc. All aspects relating to clinical trials and the registration of human allopathic medicines will continue to be managed within this medicines division, including laboratory and pharmaceutical testing issues, law enforcement, pharmacovigilance, marketing code and inspections.

1.1.1 Conflict of interest

A conflict of interest must be avoided at all times. Should the new SAMRA require the expertise of an external evaluator, a process/procedure must ensure that there is no conflict of interest. These principles must also apply to SAMRA's Expert Committees. This should be written into the Act, including procedures to be taken should such conflict arise.

Potential conflicts of interest arise if financial and or other personal interests or obligations may have a potential influence on decision-making and normal conduct of business.

1.1.2 Project Management

The new SAMRA should establish a project management system similar to that seen in other regulatory authorities such as MHRA (UK) and Canada. Once SAMRA has been notified by an applicant of the intention to submit an application for registration/approval, SAMRA should appoint a dedicated person who will act as a project manager for the product in question. The outcome is that this project manager would be the liaison person for all communication between the authority and the applicant, arranging pre-submission meetings and any other meetings as and when required.

Dedicated staff to handle general telephone, e-mail, letter, facsimile etc queries from the pharmaceutical industry would lead to a much more efficient and productive organisation

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1.1.3 Fee Structure

Fees levied by the SAMRA should not be so high that they discourage applications for essential drugs or act as a barrier to drug availability and affordability. For this reason it is suggested a differential pricing structure is required for allopathic, traditional/herbal/complementary medicines and new chemical entities or first time applications.

The WHO recommends that a Regulatory Authority operates from funds allocated from both government funding and revenue from drug registrations/fees on a fee for service basis. The Regulatory Authority must have a mechanism for actively seeking funds and be able to secure regular funding from the government with an appropriate mechanism for authorisation of expenditure and financial accountability.

1.1.4 Performance Assessment

There must be an appropriate mechanism whereby the Regulatory Authority is required to measure and report on its performance with respect to key performance indicators identified and agreed is the same manner as the EMEA and the FDA. This process together with an Annual report must be transparent to all stakeholders and to parliament.

1.1.5 Transparency, Timelines and Tracking System

Timelines must be regulated and enforced in a consistent manner in order to improve registration timelines. Commitment to time lines and the ability for Applicants to track the progress of their submissions would enhance transparency and give evidence of the efficiency of the system. To avoid the

burden of responding to Applicant queries regarding the progress of applications for registration/approval or amendments to medicine dossiers a website-based tracking system should be established and the system should link in with the prescribed timelines. Similar tracking mechanisms are made available by such regulatory authorities such as Singapore's Health Science Authority, Australia's TGA etc. It is envisaged that the Applicant could log onto the SAMRA's website and establish precisely where the application is in the evaluation queue, and when an Expert Committee or SAMRA decision may be expected. Suitable Applicant-specific passwords and codes could be activated to ensure confidentiality of information.

1.2 Harmonisation

Scientific technologies are evolving at a rapid pace and regulatory authorities are challenged and are required to make decisions over a diverse range of medicines. Effective regulatory authority decision-making can be effectively enhanced and achieved through close cooperation between regulatory agencies, without taking away the autonomy of the regulatory authority. Successful technical and regulatory cooperation between countries leads to harmonisation of drug regulatory standards. Harmonisation leads to more economical use of human, animal and material resources and to the development of regionally or internationally agreed standards. This type of cooperation has effectively been put into place by other authorities by means of Memoranda of Understanding, Mutual Recognition Agreements and other similar agreements.

The requirements and standards for medicine registration documentation and clinical research standards should be aligned with the ICH guidelines. This is fundamentally already taking place in South Africa and is described in the MRA's guidelines but the principles need to be fully and formally adopted and systematically implemented.

The CTD and the e-CTD (ICH) application submission formats, as used by the ICH countries, should be used as the format for medicine registration applications.

Manufacturing standards must be aligned with the Pharmaceutical Inspection Convention scheme (PIC/s) Good Manufacturing Practice (GMP) standards. This is currently taking place and SA has recently been accepted into the PIC's Scheme.

In the long-term it will be relevant to consider harmonisation of SADC countries into a co-operative regulatory environment.

1.3 Monitoring Clinical Research

An effective clinical trial environment will encourage investment and research in SA. Problems in the current process are recognised by both industry and the Regulatory Authority with a very long review time 14-20 weeks. The result is that multi-national companies are starting to find it preferable to place studies overseas. An efficient process will reverse this trend that is undesirable both for investment in this country and for companies operating here.

Communication between the Applicant and the Medicines Regulatory Authority should be built on mutual trust and respect. It is proposed that SAMRA appoint a dedicated group of staff to handle clinical trial authorisations.

The approval and conduct of clinical trials is generally aligned with international guidelines. Processes are in place although the timelines and efficiency need to be improved. On the other hand, monitoring of research site activities by the Authority is not done. Monitoring of research practices and protocol compliance during the actual research phase, should be introduced by the Authority.

2. Option 1: Risk-Based Assessment of Applications for the Registration of Medicines

This model proposes the adoption of the principles described above but is different from current practice in that it relies on co-operation of SAMRA with appropriate Regulatory Bodies globally. The extent to which assessment will be done by SAMRA will be dictated by the extent to which the product has been evaluated by other authorities. This is a trend that is increasingly seen and being followed particularly by developing and under resourced country authorities. The advantages of this model are that:

- Reviews will be based on Approved Reference Authority – thereby limiting dependence upon part-time assessors
- Dossiers will be comparable to leading Health Authorities in terms of standards and format
- Risk of flawed decisions will be reduced because decisions take into account status of recognised Health authorities

The most obvious drawback of this method would be that an update of Act 101 of 1965 is required to give new SAMRA authority to act as an independent parastatal and to introduce new principles in the evaluation process

2.1 Risk-based assessment

A stepwise, risk-based approach to medicine registration, is recommended by the WHO, and is effectively utilised by many regulatory authorities. This approach takes account of the decisions of 'Approved Reference Authorities' in other countries. The risk-based approach to medicine registration is aimed at:

- Allowing the new authority to effectively and economically utilize its resources, focusing on compliance and audit aspects of regulation

rather than on routinely conducting a full review evaluating medicine registration data that has already been assessed and approved by other competent regulatory authorities;

- Ensuring that new and / or generic medicines are quickly made available to the public, in accordance to the principles of the SA National Drug Policy;
- Maintaining the sovereignty of the new SA regulatory authority over the registration of medicines in SA.

It is recommended to use the term 'Approved Reference Regulatory Authority' (ARRA) when referring to authorities deemed by SA to be appropriate for the purpose of referencing evaluation reports and decisions for the purposes of registering a medicine. The term ARRA must be distinguished from the WHO term 'Competent Authority', which has a different meaning. This is an applicant *regulatory authority* declaring (i.e. a self assessment declaration) that it possesses suitable systems and competencies to ensure certain registration and regulatory criteria are in place, but the standard would not be the same as will be needed for an "ARRA".

The 'ARRA' proposed here differs from the WHO competent authority in that its status as an 'ARRA' depends on the authority being identified and '*approved* ' (as opposed to self-assessed) by SAMRA. A pre-requisite for the approval of an ARRA is a suitable infrastructure and operating system to competently evaluate and assess registration information. The list of ARRA's should be under continual review by SAMRA and the decisions made by any ARRA should not be binding on the new SAMRA.
It is suggested that for the purpose of registration of medicines, SAMRA aligns itself with the following authorities that it considers to be of sufficiently high standard, *USA (FDA); UK (MHRA); Sweden (MPA); Australia (TGA); Canada (Health Canada); European Union (EMEA) and Japan (MWH).*

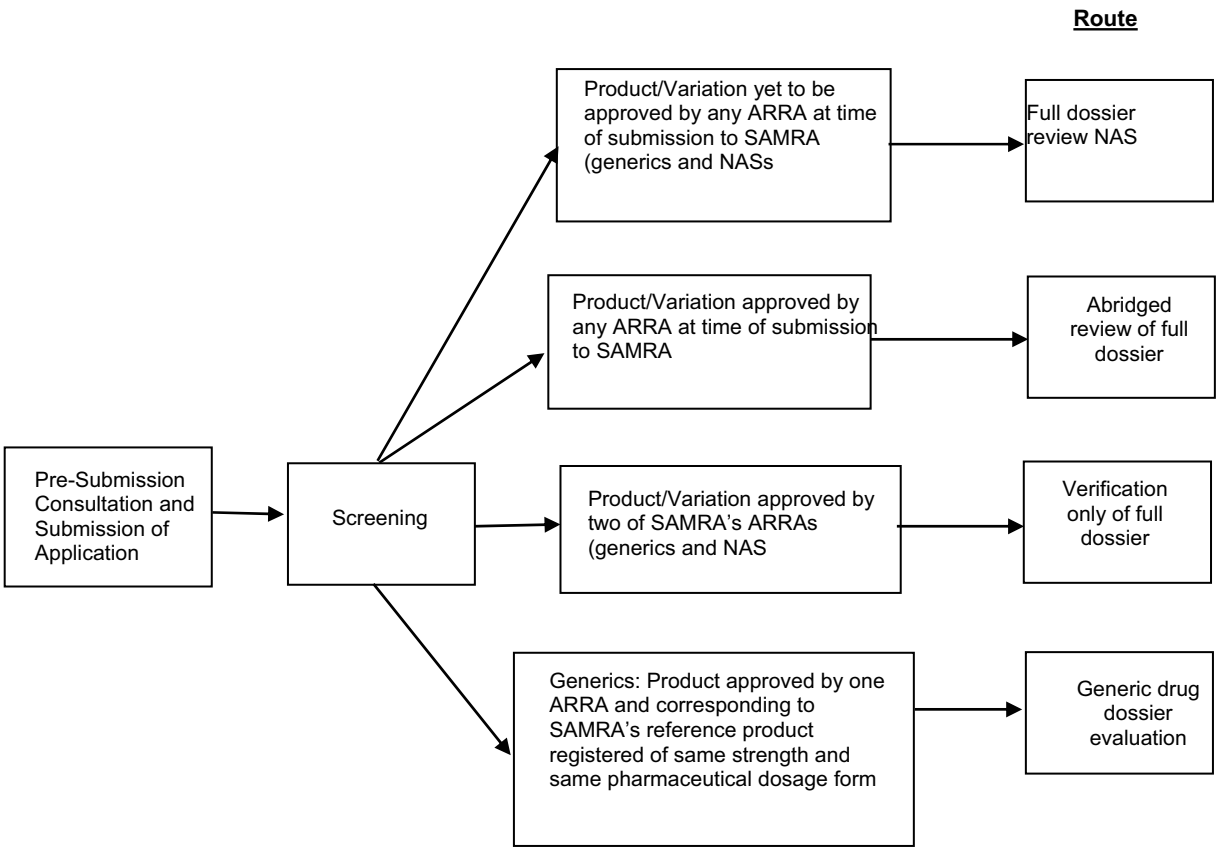
In the same context the identification and approval of an "ARRA" must be based upon the following criteria:

- A competent infrastructure to conduct proper and full pharmaceutical and clinical evaluations against the internationally acceptable registration standards as determined by the ICH (International Convention on Harmonisation);
- Membership to the PICs (Pharmaceutical Inspection Convention Scheme)
- The ability and willingness to effectively communicate with the new SAMRA on such matters as pharmacovigilance, evaluators' reports, inspection reports, etc.

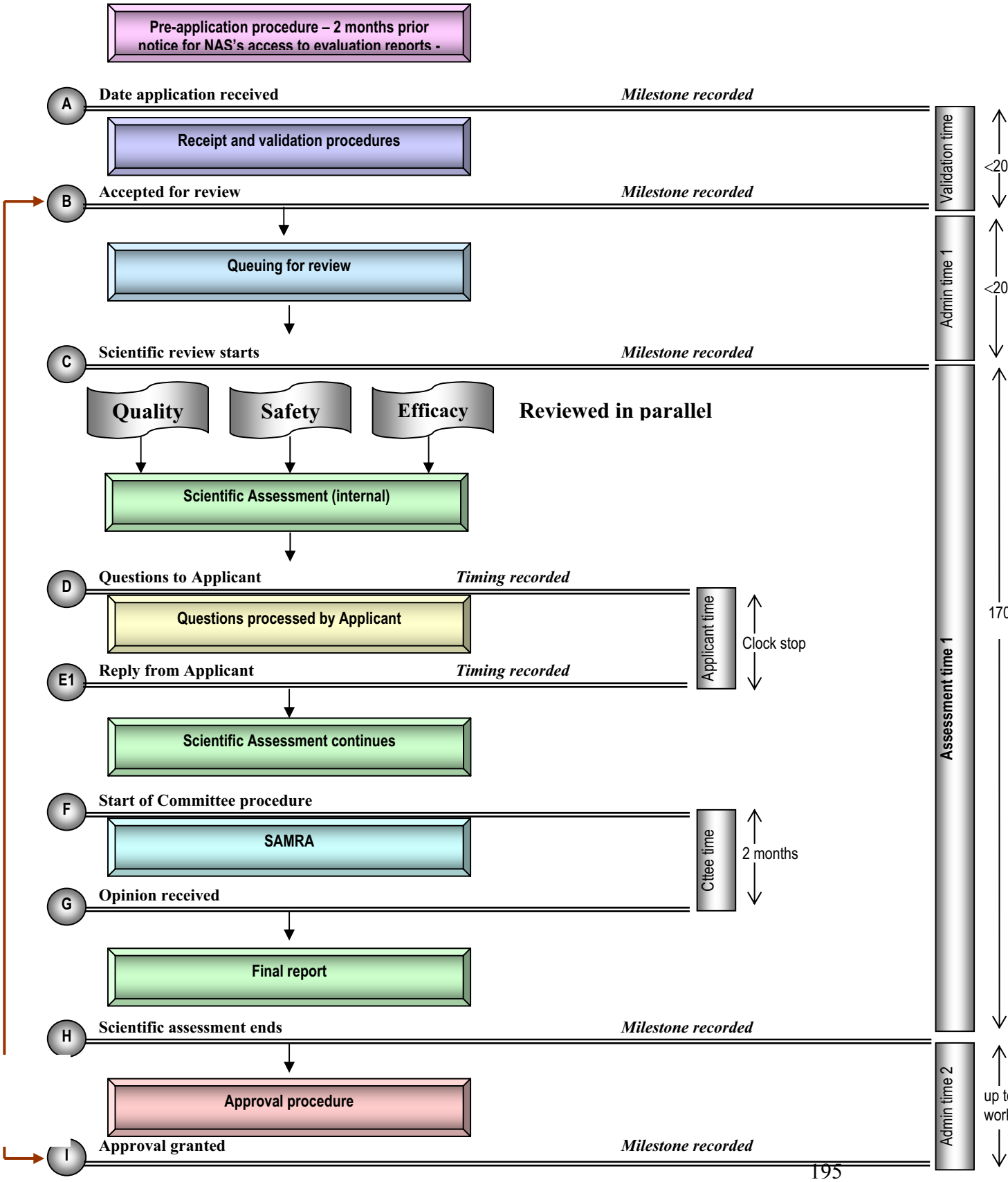
It is proposed that the registration of a medicine by an 'ARRA' is not be binding on the SAMRA, but rather that reports and approvals from such authorities be used to guide the new SA regulatory authority's assessors so that resources are effectively utilised.

This means Memorandums of Understanding, Confidentiality Agreements, Co-operation Agreements and other Harmonisation agreements are put in place to enable the SAMRA to share information with 'ARRAs'. Such agreements will facilitate this sharing of information and facilitate a resource effective review of medicine registration applications.

It is proposed, based on the assumption that there will be recognised ARRAs, that there are four types of assessment for the evaluation of new drug applications and major variations.


Route
Product/Variation yet to be approved by any ARRA at time of submission to SAMRA (generics and NASs
Full dossier review NAS
Product/Variation approved by any ARRA at time of submission to SAMRA
Abridged review of full dossier
Pre-Submission Consultation and Submission of Application
Screening
Product/Variation approved by two of SAMRA's ARRAs (generics and NAS
Verification only of full dossier
Generics: Product approved by one ARRA and corresponding to SAMRA's reference product registered of same strength and same pharmaceutical dosage form
Generic drug dossier evaluation

Proposed process map for SAMRA for new active substance and major variations where a full dossier review is required (Adapted from Australian and Singapore models). The same process follows for all evaluations, only the review time and the supporting documentation differs.



2.2 Evaluation Routes and data required for new Drug Applications and Major Variation Applications

2.2.1 *Full Review:* For medicines that have NOT been registered by another ARRA it is suggested that the new SAMRA would require 2 months advance notice before submission for planning purposes. All new application dossiers include complete quality, clinical and pre-clinical data that would require a full and complete evaluation by SAMRA.

Timelines: 210 working days for evaluation and 60 working days for regulatory decision making. Total registration time: 270 working days.

It is suggested that the process maps adopted for this procedure be similar to that structure in the Figure above which is based on the Australian Model.

2.2.2 *Abbreviated Review:* For medicines and/or variations approved by 1 ARRA. These application dossiers include the complete data package of quality, clinical and pre-clinical data that was registered by the ARRA as well as *proof of approval* from the ARRA. It is suggested that the new SAMRA would require 2 months advance notice before submission for planning purposes in order for the SAMRA to access the evaluation reports from the ARRA.

Timelines: The process would follow a similar flow to that described above but have shortened time lines. Process would need to incorporate time lines for the accessing of evaluation reports from the various ARRAs. 120 working days for evaluation and 60 working days for regulatory decision-making. Total registration time: 180 working days.

Abbreviated and / or Abridged evaluations do not mean that the application information is abbreviated – rather these refer to an abbreviated review

process in which the full data is not evaluated and the evaluation reports from Approved Reference authorities (ARRAs) are used as a guide to the Regulatory Authority's assessment. This procedure forms the basis of the EU Mutual Recognition Procedure and is the process adopted by Singapore.

2.2.3 *Verification Review*: This review should be used where a product is approved by at least 2 of the 'ARRAs'. The dossier submitted to the SAMRA must be essentially similar to that registered by the 'ARRA'. Any differences must be clearly identified by the Applicant. These application dossiers include the complete data package of quality, clinical and pre-clinical data that was registered by the ARRA as well as proof of approval from the ARRA. It is suggested that the new SAMRA would require 2 months advance notice before submission for planning purposes in order for the SAMRA to access the evaluation reports from the ARRA.

Total evaluation and regulatory decision making timeline:
45 working days. The process would follow a similar flow but have shortened time lines. Process would need to incorporate time lines (2 months) for the accessing of evaluation reports from the various ARRAs.

SAMRA should consider not accepting a verification dossier if

- The product is a biologic
- The product proposed re: indications, dose regimen, specific patient groups have been rejected by ARRA
- The product needs more stringent assessment as a result of local disease patterns and/or medical practices
- The product has been designated an orphan product by at least one ARRA

2.2.5 *Proof of 'ARRA' approval would amount to:*

- Proof of registration (the Applicant must confirm that the product applied for is based upon an essential similar dossier to that registered by the Approved Reference regulatory authority)

- Approved current Summary of Product Characteristics (SmPC) / Package Insert

- Complete approved quality documentation, non-clinical overviews summaries and clinical overview (e.g. Evaluator's reports on quality, safety and efficacy).
- The registration evaluation 'assessment report' prepared by the ARRA to be accessed by the SAMRA in terms of the MoU with the ARRAs

Comparatively, the following authorities require the following evidence:

TGA (Australia):	Approval letter; Clinical evaluation report; delegates Overview;
Health Canada:	Notice of Compliance, approved product information, Approved product monograph (PI), evaluation report.
EMEA (EU):	Approval letter; PI; European Public Assessment Report
MHRA(UK):	Approval letter, PI, evaluation report.
US FDA:	Approval letter; PI, Medical review / assessment report. (Review of efficacy and safety).

2.3. Specific processes for variations and amendments to registered dossiers should be provided for in the 'new' framework including the option of "for notification only" submissions

Variations to clinical and quality sections of a dossier should be sub-divided into minor and major variations:

- Minor variations are amendments that do not require prior approval before implementation by the Applicant and

- Major variations being amendments for which prior approval is required before implementation by the Applicant.

2.4 Managing Pre-registration risks

In making the assessment as to which model should be used for the assessment of quality, safety and efficacy, the following pre-registration risks need to be taken into account:

- A copy of the full registration data if it was registered by an ARRA – irrespective of format, including the SmPC (package insert) as approved by the ARRA;
- A declaration from the local Applicant that the dossier registered by the ARRA is essentially similar to the dossier submitted and includes all information submitted to support any variation which has been applied for and accepted at the time of submission of the application.
- The ARRA must make available to the new SAMRA their assessment reports as well as any conditions to registration (marketing authorisation), if any, imposed by the ARRA.
- A declaration by the local Applicant that the medicinal product will be kept identical in the post-approval phase e.g. in the post-authorisation phase applicant will notify SAMRA on all urgent safety issues simultaneously and he will submit and implemental variations, once approved by the new SAMRA, without unnecessary delay
- A declaration that the submitted proposed package insert (SmPC) in local language is the translation of SmPC as last approved by the ARRA.

2.5 Managing Post-registration risks

Any collaboration agreements with ARRAs must ensure the exchange of information relating to:

- Post approval developments
- Urgent safety issues and
- Variations

The onus remains, at all times, with the local Applicant to ensure the above is achieved by not withholding any other information relating to variations, repeat use, rapid alerts, urgent safety restrictions.

2.6 Timelines

The timelines are linked to the type of registration application and the associated registration processes

- **Full Evaluation:** Total of 270 working days: 210 working days for evaluation and 60 working days for regulatory decision-making.

- **Abridged Evaluation:** Total of 180 working days: 120 working days for evaluation and 60 working days for regulatory decision-making.

- **Verification Evaluation:** Total evaluation and decision making time: 45 working days

- **Generics not registered by other ARRAs:** 180 days

The processes of the SAMRA should be designed around achieving the timelines set out in legislation. Meetings of committees of the SAMRA should also be held at a frequency that ensures that all agenda items can be addressed to meet timelines.

The clock stops whenever SAMRA requires clarification and is restarted when a complete and satisfactory response is received. An application is to be considered withdrawn if the stop-clock time exceeds the timeframe agreed by the Applicant and SAMRA. Withdrawn applications must be refilled.

2.7 Resources

- In line with the option and principles outlined above, the new SAMRA should be able to raise and use its own fees to meet its expenditure. This can be achieved by the new SAMRA operating on a "no profit no loss basis", and therefore it will be able to retain and use fees that it generates from the Pharmaceutical Industry during the review process. The application fees for the new SAMRA will need to be revised in order to reach the objective that the SAMRA must fund its existence on the fees generated by its activities.

- The Regulatory Authority must be able to recruit its own professionals, experts and support staff. This process must fall outside the Public Service recruitment process. Salaries must be competitive in order to retain talent within the SAMRA.

- In order to promote accountability to the process of legislated timelines, it is proposed that the SAMRA applies the principle that should it not perform its legislated timelines, the applicant may seek relief by getting a Supplementary Protection Certificate (SPC). An SPC gives the applicant extended patent relief due to the SAMRA not being able to meet its obligations in terms of review times.

Option 2: Model retains the full review process

The model proposed as option 1 is a more contemporary approach when international practices are reviewed. However, should policy dictate that the SAMRA should retain and indeed develop the capacity needed to continue as a self sufficient authority then the following option should be adopted. The following would be an outcome of taking this route:

- Increase resource needed for project management
- Introduction of transparency and tracking system
- Accountability via mechanism of reporting on performance to parliament

Disadvantages of this system would be:

- It does not address additional resources needed to drive change to a more efficient Regulatory system –e.g. appointment of internal reviewers to decrease dependency on external reviewers

Modifications should be made to the existing structure in order to fully support the full evaluation of dossiers by SAMRA and ensure an effective system. Additional resources and capacity would be a key requirement here. Modifications should include the adoption of fundamental principles to be followed (as described above) and the process map followed would be the same as that described under option 1, “Proposed process map for SAMRA for new drug applications and major variations, full dossier. In these circumstances the challenge would be to complete assessments in regulated and reasonable time lines.

Model for African Traditional Medicines

To be completed

Model for Complementary Medicines

To be completed

Model for Veterinary Medicines

To be completed

Model for Devices

To be completed

Appendix H

SA CODE OF PRACTICE FOR THE MARKETING OF MEDICINES

29th January 2008

Code Document finalised and agreed by Marketing Code Steering Committee 29th January 2008.

TABLE OF CONTENTS

SA CODE OF PRACTICE FOR THE MARKETING OF MEDICINES

1. PREAMBLE

WHEREAS

1.1 Section 18C of the Medicines Act 101 of 1965 ('the Act") empowers the Minister, after consultation with the pharmaceutical industry and other stake holders, to make regulations relating to the marketing of medicines, including an enforceable Code of Practice.

1.2 the companies in the pharmaceutical industry have agreed to subscribe to a code of practice for the marketing of medicines in South Africa based on the principle of self regulation as set out in this Code;

1.3 the enforcement of the Code will be entrusted to a MARKETING CODE AUTHORITY as herein provided.

2. INTRODUCTION TO-, APPLICATION AND INTERPRETATION OF THE CODE

2.1 Introduction

The ethical promotion of medicines is vital in helping to ensure that healthcare professionals and the public have access to the information they need, that patients have access to the medicines they need and that medicines are prescribed and used in a manner that provides the maximum healthcare benefit to patients.

All marketers of medicines should maintain high ethical standards when conducting promotional activities and must comply with applicable legal, regulatory and professional requirements.

Compliance with the Code will ensure that ethical promotional practices are established for all marketers, prescribers, dispensers, advisers and users of medicines. The overarching philosophy is a principle of compliance with the spirit of the Code.

The "Code of Practice for the Marketing of Medicines in South Africa" is referred to throughout as "the Code".

The National Department of Health, the pharmaceutical industry and other stakeholders are committed to the provision of affordable and quality healthcare for all South Africans. High quality, effective and accessible medicines are a cornerstone of healthcare. Accurate information about medicines is integral to providing quality healthcare services.

This Code is issued in terms of section 18C of the Medicines and Related Substances Act No 101 of 1965, and is adopted by pharmaceutical trade associations to signify the industry's commitment to ensure that the marketing of medicines to healthcare professionals and the public is carried out in a responsible, ethical and professional manner, based on practical and scientifically validated information.

The pharmaceutical industry is committed to educational and promotional efforts that benefit patients and promotional programs and collaborations that enhance the rational use of medicine and fair competition in the marketing of medicine. The industry seeks to preserve the independence of the decisions taken by healthcare professionals. The pharmaceutical industry has an obligation and

responsibility to provide accurate information and education about its products to healthcare professionals in order to establish a clear understanding of the appropriate use of medicines. Industry relationships with healthcare professionals must support, and be consistent with the professional responsibilities healthcare professionals have towards their patients.
This Code takes cognisance of other professional and industry codes applicable to the pharmaceutical sector and professions it interacts with.

2.2 Application of the Code

2.2.1 The Code is applicable to the following organisations and situations:

2.2.1.1 All registered medicines licence holder, their agents, contractors, third party distributors / marketers. Companies that circumvent the code by engaging or using other companies or agents or dispensing system software vendors or ordering systems will be infringing the Code.

2.2.1.2 All advertising and promotional activities and communication directed at influencing any member of the medical, dental, pharmacy, nursing or allied health professions who in the course of his or her professional activities may prescribe, purchase, supply, administer a medicine or recommend the use of a medicine.

2.2.1.3 It also covers advertising material, which is directed to members of the public to inform the general public about the medicines available for self medication.

2.2.1.4 All advertising and promotion and all activities directly or indirectly related to marketing which may reflect on the marketing practices of the pharmaceutical industry, including but not limited to sponsorships, patient information-sharing, meetings and entertainment.

2.2.1.5 Interactions between the pharmaceutical industry and healthcare professionals (Part A) and the pharmaceutical industry and the general public (Part B).

2.2.2 The Code does not apply to the following situations:

2.2.2.1 Factual, accurate, informative announcements and reference material concerning registered medicines and relating, for example, to adverse reactions and warnings.

2.2.2.2 The following documents are not covered by the Code:

2.2.2.2.1 Trade catalogues to suppliers including price lists.

2.2.2.2.2 Product labels, packaging materials and in-pack leaflets. These are subject to the labelling and package insert requirements in terms of the Regulations to the Medicines Act and the Guidelines pertaining thereto.

2.2.2.3 The marketing or promotion of veterinary medicines, complementary medicines and medical devices.

2.2.2.4 Issues relating to pricing, bonusing and perverse incentives governed elsewhere in legislation and in codes issued in terms of the Medicines Act, National Health Act, Act No 61 of 2003, etc.

2.2.2.5 The Code is not applicable to wholesalers, distributors and logistics companies except to the extent that they may influence the demand for medicines.

2.3 Interpretation of the Code

2.3.1 The provisions in this Code should be interpreted in light of both the letter and spirit of the Code. Guidance notes, issued from time to time by the MCA will provide companies with an indication as to how the Code should be applied and adhered to, in practical terms. The rulings of the bodies established as part of the Marketing Code Authority, forms precedent on what constitutes acceptable practices in the marketing of medicines.

2.3.2 The Code should not be construed in conflict with any existing law applicable to the marketing of Medicine, including but not limited to the Medicines Act, the Patents Act No 57 of 1978, the Copyright Act No 98 of 1978, the Trade Marks Act No 194 of 1993 and the National Health Act.

2.3.3 Any interpretation of the provisions of this Code as well as interaction with healthcare professionals not specifically addressed in this Code should be made in light of the following principle:

"Companies shall adhere to ethical business practices and socially responsible industry conduct and shall not use any unlawful or any unethical inducement in order to sell, recommend or arrange for the sale or prescription of their products."

2.3.4 In any review of advertising material or promotional activities covered by this Code, consideration will be given not only to the impression created by a careful study of an advertisement or activity, but also to the impression likely to be gained from a brief or partial exposure.

2.4 Status of the guidelines to the Code

2.4.1 Guidance on the interpretation of the Code appears as supplementary information to the text in a separate document, Guidance Notes on the South African Marketing

Code. The examples given are intended to illustrate and clarify the meaning of the Code. They are not exhaustive and do not cover all possible situations to be covered by the provisions of the Code.

2.4.2 These guidelines will be updated regularly by the MCA, as part of its mandate to ensure education, application and enforcement of the Code. These guidelines will also be used to regularly update applicable monetary values and examples of conduct that constitutes violations of the Code.

2.5 Scope of application

2.5.1 PART A - The marketing and promotion of medicines to healthcare professionals

PART A of the Code applies to the promotion of all medicines to members of the healthcare professions, and to appropriate administrative staff by the pharmaceutical industry or by other health professions such as those involved in managed healthcare or medical schemes, regardless of the scheduling status of the medicine.

It includes the marketing and promotion of self-medication products to healthcare professionals when such promotion is aimed at generating prescriptions or recommendations to patients.

Advertising of medicines in Schedules S0 and S1 to the general public is permitted but advertising of medicines in Schedules S2 to S6 to the general public is not allowed under the Medicines Act and Regulations. Therefore the provisions of PART A apply to all medicines marketed to healthcare professionals, irrespective of the scheduling.

2.5.2 PART B - The marketing and promotion of medicines directly to the consumer

The advertising of medicines in Schedules S0 and S1, to the general public is permitted by law. The main purpose of the Code is to help ensure that advertising of self-medication medicines complies with applicable codes and laws. The Code is applied in spirit as well as in principle.

The scope of PART B relates to all self-medication (S0 and S1) medicines registered or sold in terms of the Medicines Act.

PART B of the Code applies to advertising materials and promotional activities for medicines, as defined by the Medicines Act, which are aimed at general public and persons who may legitimately purchase medicines on behalf of other consumers (e.g. parents, who purchase medicines on behalf of their children). The provisions of PART B of the Code do not apply to advertising aimed at healthcare professionals.

The provisions in PART B have to be seen in the light of the exemption for S0 medicines from the provisions of section 18A to the Medicines Act.

2.6 PART C - ENFORCEMENT OF THE CODE

2.6.1 The Code is based on the principle of self regulation of the industry through a procedure for handling complaints which is in line with international standards and practice, but made binding through the legislative recognition of the self-regulatory and subsequent processes which may include the medicines regulatory authority.

2.6.2 The process of enforcement and the relevant bodies responsible for such enforcement are set out in Part C of this Code.

2.6.3 The MCA has the power to refer issues not within the scope and ambit of this Code to the appropriate authorities, councils or bodies with the authority to deal with such issues.

2.7 Glossary

In this Code, words and phrases that are defined in the Medicines Act shall bear the same meanings as they do in the Act and all regulations issued in terms of this Act.

The following additional definitions are provided to guide the interpretation of this Code:

2.7.1 **Advertising and promotional materials or activities**, include, but are not limited to Advertorials; Branded materials relating to product sponsorship; Aerial promotions such as on hot air balloons and / or blimps; Booklets; Cinema commercials; Consumer leaflets; Consumer broadsheets; Direct mail materials; Website and other Internet materials, including press releases intended for internet publication; On-pack statements; Outdoor advertising; Point of sale materials; Posters; Print advertisements (for use in newspapers, magazines, etc.); Promotional aids including those used for direct selling activities; Promotional scripts for use by telephone help lines; Promotional text messages; Consumer promoters; Telephone help lines; Television and radio/audio commercials; Sports, art and other sponsorships; Airport, washroom, shopping centre advertising; Touch screen advertising; Aisle, ceiling, floor advertising and other signs; Counter top advertising; Window displays; Gondola end advertising; Bunting; Advertising on electronic ordering systems; Bus, taxi and other vehicle advertising; and Light box advertising.

2.7.2 **Company:** may refer to a company, closed corporation, organisation, vendor or individual who may sell or promote medicines.

2.7.3 **Company Code Compliance Officer:** means anyone duly authorised by the company, or appointed by the company in writing, to sign documents or give instructions on behalf of the company.

2.7.4 **Electronic journals:** Electronic versions of journals that can be viewed online via any personal computer or other electronic device.

2.7.5 **Health Care Professional (HCP):** includes members of the medical, dental, pharmacy or nursing professions and any other persons registered with a professional council or body who in the course of their professional activities may prescribe, recommend, purchase, evaluate, supply or administer a medicine as registered under the Medicines Act and, for the purposes of this Code, includes all persons operating under the HCP.

2.7.6 **Honorarium:** is a payment or an award granted in recognition of a special service by a professional person. Honorariums can be paid at fair market value for speeches, articles, appearances or other services rendered.

2.7.7 **Medicines Act (i.e. Medicines and Related Substances Act No 101 of 1965 as amended)**: refers to the body of legislation governing the registration and marketing of medicine, as amended from time to time.

2.7.8 **Promotional item:** is merchandise given away free of charge in an effort to create awareness of a company or product.

3. OBJECTIVES OF THE MCA

The objectives of the MCA ("MCA") shall be –

3.1 to ensure and maintain the ethical promotion and advertising of medicines by all parties and entities, including companies and their employees and agents as described in clause 2.2 and who are or may be subject to the Act (hereinafter referred to as the "Companies" and the company);

3.2 to ensure that those bound by the Code maintain high ethical standards when conducting promotional activities and comply with applicable legal, regulatory and professional requirements.

3.3 to adjudicate on disputes in terms of the Code.

PART A --- MARKETING AND PROMOTION OF MEDICINES TO HEALTHCARE PROFESSIONALS

4. REGISTRATION STATUS OF MEDICINES

A medicine must not be promoted:-

4.1 prior to the product being registered by the medicines regulatory authority or

4.2 unless an application has been submitted in terms of Section 14(3) of the Medicines Act ("old medicine"), which permits its sale, supply and use in South Africa.

The promotion of a medicine must be in accordance with the terms of its registration, and must not be inconsistent with the particulars listed in its package insert.

5. ADVERTISING AND PROMOTION MATERIAL

5.1 The approved package insert may be used as a reference in all promotional material and advertising.

5.2 The minimum requirements must:

5.2.1 Conform with the applicable regulations in terms of the Medicines Act.

5.2.2 Form part of the promotional material and not be separate.

5.2.3 Be included in all promotional material (except for promotional items- see Clause 18.3).

5.2.4 Be provided in a clear and legible manner.

5.2.5 Be consistent with the most recently approved package insert for the medicine.

5.3 In all forms of advertising i.e. written, audio, audio-visual, internet, the statement “For full prescribing information refer to the package insert approved by the medicines regulatory authority” should appear or be stated. This does not apply to promotional items as referred to in Clause 18.3.

5.4 In the case of an advertisement included as part of independently produced information on the internet, the statement should be in the form of a direct link between the first page of the advertisement and the minimum information.

5.5 In the case of printed promotional material consisting of more than two pages, the minimum information can appear either on the first or last page.

5.6 Promotional material other than advertisements appearing in professional publications must include the date or a code number identifying the version on which the promotional material was drawn up or last revised.

5.7 Audio-visual or audio material such as films, video recordings, sound bytes, interactive data systems and such like:

5.7.1 The minimum information may be provided either by way of a document that is made available to all persons to whom the material is shown or sent, or by inclusion on the audio-visual recording or in the interactive data system itself.

5.7.2 When the minimum information is included in an interactive data system, instructions for accessing it must be clearly displayed.

5.7.3 If the material that consists of sound only, the minimum information may be provided by the way of a document that is made available to all persons to whom the material is played or sent.

6. JOURNAL ADVERTISING

6.1 An advertisement which contains two or more pages must not be false or misleading when each page is read in isolation.

6.2 An advertisement taking the form of a loose insert in a journal may not be of a size larger than the page size of the journal itself.

6.3 Advertisements in journals must not resemble editorial matter unless clearly identified as advertorial or as a sponsored feature.

6.4 In case of a journal advertisement where the prescribing information appears overleaf, a reference to where it can be found must appear in a type size which is legible at either the beginning or the end of the advertisement.

7. INFORMATION, CLAIMS AND COMPARISONS

7.1 Accuracy, balance, fairness of claims.

Information, claims and comparisons whether in advertisements, promotional items, product detailing and all information relating to medicines, whether verbal or in writing, must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence, and must reflect that evidence clearly. Such information or the manner, in which it is portrayed, must not mislead either directly or by implication by distortion or undue emphasis. Material must be sufficiently complete to enable the recipients to form their own opinion of the therapeutic value of the medicine.

Any information, claim or comparison must be capable of substantiation. No substantiation is required for claims in the package insert which has been approved by the medicines regulatory authority.

7.2 Exaggerated or misleading claims

Promotion material must encourage the rational use of medicine by presenting it objectively and without exaggerating its properties. Exaggerated or all-embracing claims must not be made and superlatives must not be used except for those limited circumstances where they relate to a clear fact about a medicine. Claims should not imply that a medicine or an active ingredient has some special merit, quality or property unless this can be substantiated.

7.3 Comparisons

A comparison in the marketing and promotion of medicines is only permitted in promotional material if:

7.3.1 It is not misleading or disparaging.

7.3.2 Medicines or services for the same needs or intended for the same purpose are compared.

7.3.3 One or more material, relevant, substantiable and representative features are compared.

7.3.4 No confusion is created between the medicine advertised and that of a competitor or between the advertisers' trademarks, proprietary names, other distinguishing marks and those of a competitor.

7.3.5 The trademarks, proprietary names, other distinguishing marks, medicines, services, activities or circumstances of a competitor are not discredited or denigrated.

7.3.6 Trademarks/ tradenames or company names of another company may only be mentioned with written permission from the other company.

7.3.7 No unfair advantage is taken of the reputation of a brand, trademark, proprietary name or other distinguishing marks of another company.

7.3.8 Medicines or services are not presented as imitations or replicas of goods or services bearing another company trademark or tradename.

7.4 **Substantiation**

Substantiation for any information, claim or comparison must be provided without delay at the request of members of the health professions or appropriate administration staff. It need not be provided in relation to the validity of a medicines regulatory authority approved indication(s) in the package insert.

7.5 **References**

When promotional material refers to published studies, clear and complete references must be given.

7.6 **Unpublished supporting data**

When promotional material refers to (unpublished) data on file, the relevant part of this data must be provided without delay at the request of members of the health professions or appropriate administrative staff.

If confidential information, such as information relating to trade secrets, sensitive commercial information or information of a competitive nature is involved, the material may be given to an independent arbitrator acceptable to both parties or a person appointed by the MCA from its Adjudication Panel for assessment, in the case of a dispute. The arbitrator or person appointed by the MCA will make an assessment as to whether the unpublished data in fact support the statement(s) made in the promotional material.

7.7 **Artwork**

All artwork, including illustrations, graphs, tables, logos and trade dress must conform to the letter and spirit of the Code. Graphs and tables must be presented in such a way as to give a clear, fair, balanced view of the matters with which they deal, and must not be included unless they are relevant to the claims or comparisons being made.

7.8 **Use of the word ‘safe’**

The word ‘safe’ or words containing reference to safety must not be stated in such a way as to imply that a product has no side effects, toxic hazards or risks of addiction. The word ‘safe’ must not be used without scientific substantiation.

7.9 **Use of the word ‘new’**

The word ‘new’ must not be used to describe any product or presentation, which has been generally available or any therapeutic indication, which has been available for more than twelve months in South Africa.

7.10 **Other claims**

It must not be stated that a product has no side-effects, toxic hazards or risk of addiction or dependency.

8. DISPARAGING REFERENCES

8.1 The medicines, products and activities of other pharmaceutical companies must not be disparaged.

8.2 The health professions and the clinical and scientific opinions of their members must not be disparaged.

9. HIGH STANDARDS, FORMAT, SUITABILITY AND ENDORSEMENT BY HCP'S

9.1 All materials and activities must recognise the special nature of medicines, and the professional standing of the audience to which they are directed and must not be likely to cause offence. High standards must be maintained at all times.

9.2 The name or photograph or film of a member of a health profession must not be used in any way that is contrary to the applicable professional codes for that profession and all endorsements, where permitted by professional codes, have to be done within the scope of such codes.

9.3 Promotional material must not imitate the devices, copy, slogans or general layout adopted by other companies in a way that is likely to mislead or confuse.

9.4 Promotional material must not include any reference to the medicines regulatory authority unless this is specifically required by the medicines regulatory authority, through the applicable legislative and other provisions. This provision does not preclude references to important medicines regulatory authority Guidelines and Policies, such as those on the reporting of adverse events, which serves as important regulatory frameworks for the utilisation of a medicine.

9.5 Reproductions of official documents must not be used for promotional purposes unless permission has been given in writing by the appropriate body.

9.6 The telephone, SMS, e-mail, telex or facsimile machines must not be used for promotional purposes, except where, when first contact is made, the option to opt out and the decision is subsequently respected. The option to opt out should also be provided on all subsequent communications, even if the addressee has not opted out after the first contact.

9.7 All material relating to medicines and their uses, which is sponsored by a pharmaceutical company, must clearly indicate the details of the company that sponsored it. The only exception to this clause is market research material that need not reveal the name of the company involved but must state that a pharmaceutical company sponsors it.

9.8 Postcards, other exposed mailings, envelopes or wrappers must not carry matter which may be regarded as advertising to the general public contrary to relevant legislation. .

10. DISGUISED PROMOTION

10.1 Promotional material and activities must not be disguised.

10.2 Market research activities, post-marketing surveillance studies, post authorisation studies, clinical trials and the like must not be disguised promotion, nor contain or lead to disparaging comments about competitors or their products. Such trials/ studies must be conducted with a primarily scientific or educational purpose. Material relating to pharmaceutical products and their uses, whether promotional in nature or not, which is sponsored by a company should clearly indicate by whom it has been sponsored.

10.3 Clinical trials should not be undertaken for the purpose of promotion.

10.4 Observation/ Non-interventional studies of registered medicines are studies where the medical product(s) is (are) prescribed in the usual manner in accordance with the approved medicines regulatory authority package insert. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data.

10.5 Non-interventional studies that are prospective in nature and that involve the collection of patient's data from or on behalf of an individual, or groups of healthcare professionals specifically for the study must comply with all of the following criteria:

10.5.1 The study is conducted with a scientific purpose and there must be:

10.5.1.1 a written study plan (protocol) and

10.5.1.2 written contracts between healthcare professionals and/or the institutions at which the study will take place, on the one hand, and the company sponsoring the study, on the other hand, which specify the nature of the services to be provided and, subject to what is stated below, the basis for payment of those services.

10.5.2 Remuneration provided must be reasonable and of fair market value to the work performed.

10.5.3 Study protocol should be submitted to the ethics committee for review.

10.5.4 Personal data privacy including the collection and use of personal data must be respected.

10.5.5 The study must not constitute an inducement to recommend, prescribe, purchase, supply, sell or administer a particular medicinal product.

10.5.6 The study protocol must be approved by the company's scientific/ medical department, who must also supervise the conduct of the study.

10.5.7 The study results must be analysed by or on behalf of the contracting company and summaries thereof must be made available within a reasonable period of time to the company's scientific service, which service shall maintain records of such reports for a reasonable period of time. The company should send the summary report to all healthcare professionals that participated in the study and should make the summary report available to the MCAupon their request. If the study shows results that are important for the assessment of benefit-risk, the summary report should be immediately forwarded to the medicine regulatory authority. In addition, companies are encouraged to publicly disclose the summary details and results of non-interventional studies in a manner that is consistent with the parallel obligations with respect to clinical trials.

10.5.8 Medical Sales Representatives may only be involved in an administrative capacity and such involvement must be under the supervision of the company's scientific service that will also ensure that the Medical Sales Representatives are adequately trained. Such involvement must not be linked to the promotion of any medicinal product.

10.6 Material issued by companies that relates to medicines but which is not intended as promotional material for those medicines per se, for example corporate advertising, press releases, market research material, financial information to inform shareholders, the stock exchange, should be examined to ensure that it does not contravene the Code or the relevant statutory requirements.

11. PROVISION OF REPRINTS AND THE USE OF QUOTATIONS

11.1 Reprints of articles in journals must not be provided unsolicited unless the articles have been published in a peer reviewed publication in line with good principles of scientific review and publication. When providing a reprint of an article about a medicine, it should be accompanied by prescribing information. If a non-peer-reviewed article is requested by a healthcare professional, a copy may be provided on written request.

11.2 Quotations from medical and scientific literature must accurately reflect the intention and meaning of the author(s). If unpublished, "personal communications" shall not be used unless the company, organisation or individual is able to supply written substantiation upon request.

11.3 Quotations taken from public broadcasts, for example radio, television or the Internet, and from private occasions, such as medical conferences or symposia relating to medicines, must not be used without the formal permission of the speaker unless there is a published record of the proceedings and this is accurately given as a reference.

11.4 Utmost care must be taken to avoid ascribing claims or views to authors when these no longer represent the current views of the authors concerned.

12. DISTRIBUTION OF PROMOTIONAL MATERIAL

12.1 Promotional material should only be sent or distributed to those categories of persons whose need for, or interest in, the particular information can reasonably be assumed.

12.2 A company that is requested by an addressee to cease or limit the volume of promotional material should respect the wishes of the addressee.

12.3 Mailing lists must be kept up-to-date. Requests from healthcare professionals to be removed from promotional mailing lists must be complied with promptly and no name may be restored except at their request or with their permission.

13. SCIENTIFIC INFORMATION SERVICE

Every company must compile and collate information about the medicines they market, and must be able to provide such information to authorities, members of healthcare professions or the general public, where appropriate. This may include information about adverse drug events.

14. CERTIFICATION OF PROMOTIONAL MATERIALS, MEETINGS AND OTHER ACTIVITIES

14.1 Appointment of person (s) responsible as Company Code Compliance Officer for approval of promotional material, meetings or activities.

14.1.1 Promotional material and activities must not be approved nor issued unless its final form, to which no subsequent amendments will be made, has been certified by an individual on behalf of the company i.e. the Company Code Compliance Officer. Company Marketing Personnel and Medical Sales Representatives must ensure they obtain the necessary approval from the Company Code Compliance Officer prior to placing adverts in any publications and/or forums.

14.1.2 The appointed Company Code Compliance Officer should either be the responsible pharmacist and/or a natural person responsible for the enforcement and compliance with the Act.

14.1.3 Each company or individual should have a Standard Operating Procedure (SOP) for the approval process. The SOP and documentation must be available for auditing by the Marketing Code Authority or the medicines regulatory authority according to the medicines regulatory authority's auditing requirements.

14.1.4 Activities which would be subject to certification include, but are not limited to, Continued Professional Development (CPD) or similar professionally-required educational events, the presentation of scientific or promotional material, journal club meetings organised and/or sponsored by the company, etc.

14.1.5 Meetings that fall within the ordinary scope of the day-to-day activities of company Medical Sales Representatives, and/or where the events, parts of the event, a speaker or

an attendee is not sponsored by the company, are not subject to certification.

14.2 **The Certificate**

14.2.1 The Certificate must state that the Company Code Compliance Officer has examined the final form of the material or arrangements for an event and that it is in accordance with the requirements of the relevant advertising regulations and this Code, is not inconsistent with the product registration and the package insert and is a fair and truthful presentation of the facts about the medicine.

14.3 **Recertification of promotional material**

Promotional material that is still in use must be re-certified at intervals of no longer than two years to ensure that it continues to conform to the relevant regulations and the Code.

14.4 **Retention of documentation**

14.4.1 Companies, organisations or individuals shall preserve all certificates and the relevant accompanying information for not less than five years after the final use of the promotional material or the date of the meeting and produce them on request from the MCA or the medicines regulatory authority.

14.4.2 In relation to certificates for promotional material, the material must be preserved in the form certified with information indicating the persons to whom it was addressed, the method of dissemination and the date of first dissemination. It is, however, in the interest of storage space, acceptable to store accurate photographic or other electronic representations of material, information or items.

14.4.3 All documents/material relating to marketing and promotion, including the agenda for the event, irrespective of the nature of the campaign or event, have to be retained for the minimum period.

15. MEDICAL SALES REPRESENTATIVES

15.1 **Training of Medical Sales Representatives**

Each company shall ensure that its Medical Sales Representatives, including personnel retained by way of contract with third parties, and any other company representatives who call on healthcare professionals, pharmacies, hospitals or other healthcare facilities in connection with the promotion of medicinal products (each, a “Medical Sales Representative”) are familiar with the relevant requirements and all applicable laws and regulations related to the promotion and advertising, and are adequately trained and have sufficient scientific knowledge to be able to provide precise and complete information about the medicinal products they promote or services offered.

15.2 **Compliance with codes and laws by Medical Sales Representatives**

Medical Sales Representatives must comply with all relevant requirements of the applicable professional and good practices codes and all applicable laws and regulations, and companies are responsible for ensuring their compliance.

15.3 **Gaining interviews**

Medical Sales Representatives must not employ any inducement or subterfuge to gain an interview. No fee should be paid or offered for the granting of an interview. Donations to charities in return for Medical Sales Representatives gaining interviews are prohibited. Offering or making donations in lieu of hospitality are unacceptable. In an interview, or when seeking an appointment for one, Medical Sales Representatives must at the outset take reasonable steps to ensure that they do not mislead as to their identity or the company that they represent.

15.4 **Organising meetings**

Medical Sales Representatives organising meetings are permitted to provide appropriate hospitality and/or to meet any reasonable, actual costs, which may have been incurred. All meetings have to conform with the provisions of Clause 17 (Interaction with Health Care Professionals).

15.5 **Consideration for healthcare professionals and others**

Medical Sales Representatives must ensure that the frequency, timing and duration of calls on healthcare professionals, pharmacies, hospitals, other healthcare facilities, medical schemes or funders and the like, together with the manner in which they are made, do not cause inconvenience. The wishes of individuals on whom Medical Sales Representatives wish to call, and the arrangements in force at any particular establishment, must be observed.

15.6 **Information to scientific service of company**

Medical Sales Representatives must transmit to the scientific service of their companies (Clause 13) any information that they receive in relation to the use of the medicines that they promote, particularly reports of adverse drug events.

15.7 **Information to be provided to healthcare professionals**

When Medical Sales Representatives introduce a medicine to a healthcare professional for the first time, they should provide a copy of the latest approved package insert. On subsequent occasions, such information should be available on request.

15.8 **Follow up on requests for information**

If discussion on a medicine is initiated by the person or persons on whom a Medical Sales Representative calls, the medical representative should make available the information on that medicine referred to in Clause 15.7, as soon as possible after the request.

15.9 **Detailed briefing materials**

Companies may prepare detailed briefing material for Medical Sales Representatives on the technical aspects of each medicine that they

will promote. Briefing material must comply with the relevant requirements of the Code and must be approved by the Company Code Compliance Officer in the company.

15.10 **Company responsibility for Medical Sales Representatives**

Companies are responsible for ensuring that the activities of their Medical Sales Representatives comply with the Code and all applicable laws and regulations.

16. TRAINING

All personnel, including members of staff concerned in any way with the preparation or approval of promotional material or of information to be provided to members of South African health professions and to appropriate administrative staff or of information to be provided to the public, must be fully conversant with the requirements of the Code.

17. INTERACTIONS WITH HEALTHCARE PROFESSIONALS

17.1 **Hospitality/ Venues of meetings and events**

Companies, organisations or individuals are permitted to organise or sponsor meetings and events including Continued Professional Development (CPD). The following should be adhered to:

17.1.1 The merit and focus of the meeting should be clearly scientific and/or educational.

17.1.2 The venue and hospitality should be secondary to the meeting both in time allocation and focus.

17.1.3 The venue should be appropriate and conducive to the scientific or educational objectives and the purpose of the event or meeting.

17.1.4 Hospitality, meals and entertainment should be modest. As a general rule, hospitality must not exceed what the healthcare professionals would normally be prepared to pay for themselves.

17.1.5 Invitations should not be extended to spouses or other guests except if they are healthcare professionals or administrative staff i.e. any costs incurred by spouses or other guests cannot be reimbursed or paid for by the company.

17.1.6 Inappropriate financial benefit or material benefits including excessive hospitality cannot be offered and/or extended to healthcare professionals.

17.1.7 For product launches, no sponsorship or payment of travel and accommodation can be extended to healthcare professionals.

17.1.8 For speakers, payment of reasonable honoraria and reimbursement of out of pocket expenses, including travel are permissible provided it is in terms of a written contract.

17.1.9 CPD meetings:

17.1.9.1 No product promotion is allowed in the CPD meeting room. Company-branded items / promotion are permissible.

17.1.9.2 Speakers should use the INN names of products during CPD events. Companies must make it known to speakers that the use of trade names is not permitted.

17.1.9.3 Product promotional material displayed outside of the CPD meeting room should not be accessible to the general public, if it is not permissible to market such product directly to the public.

17.1.10 For local CPD events and product launches which are held in major cities, reasonable travel arrangements or travel reimbursement can be made to ensure that the healthcare professionals that do not reside/ practice in major cities are able to access the applicable information. *(If this is not accepted by the HPCSA then we recommend the following be included. Then 17.1.7 would hold. If approved then 17.1.7 deleted)*

17.1.11 The criteria for selection of attendees/invitees must be transparent and available to the MCA on request for scrutiny.

17.2 For medical or scientific congress, conferences or seminars held in South Africa, internationally or international meetings organised overseas and held in South Africa.

17.2.1 Meetings organised by pharmaceutical companies, other organisations or individuals at venues outside South Africa, that are educational and scientific in nature and involve South African healthcare professionals are acceptable.

17.2.2 The rationale for any meeting, or sponsorship to attend a meeting, is to be transparent, valid and cogent.

17.2.3 Consideration must be given to the educational programme, overall cost, facilities offered by the venue, nature of the audience, hospitality provided and the like.

17.2.4 As with any meeting, it should be the programme that attracts delegates and not the associated hospitality or venue and all entertainment and events have to be subordinate in time and nature to the sponsored meeting, congress, conference or seminar.

17.2.5 Payment of registration fees, travel and accommodation must be made to the professional associations/organisers and not directly to the healthcare professional or appropriate administrative staff, unless proof is received that the amounts spent are in the name of the sponsored person and which corresponds to each and every line item as per the agreed sponsorship. No payment may be made to the professional/staff for time spent at the event.

17.2.6 Sponsored speakers may receive reasonable honoraria.

17.3 **Sponsorship of meetings at patient support groups**

Patient support group meetings and events may be sponsored provided that proper records are kept and that no product promotion takes place.

17.4 **Transparency**

When meetings are sponsored by pharmaceutical companies, other organisations or by individuals, the fact must be disclosed in the papers relating to the meetings and in any published proceedings. The declaration of sponsorship must be sufficiently prominent to ensure that readers are aware of it at the outset.

17.5 **Stand-alone entertainment, leisure, social or cultural events with healthcare professionals**

17.5.1 Meetings organised for patients, general public, individual or groups of doctors, other healthcare professionals and/or for administrative staff that are wholly or mainly of an entertainment, leisure, social or sporting nature is not permitted.

17.5.2 No stand alone entertainment or other leisure, social or sporting activities may be planned, arranged or funded by pharmaceutical companies as these are unrelated to the promotion of scientific or educational objectives.

17.6 **Other interactions with healthcare professionals**

17.6.1 Consultancy services

The engagement of a healthcare professional to provide genuine consultancy or other genuine services to a company is permitted. Healthcare professionals that provide consulting services to a company and are still practicing their profession must declare their employment arrangement with the company whenever they write or speak in public about a matter that is the subject of the employment or any other issue relating to that company. Such arrangement must be formalised in a written agreement.

17.6.2 No direct payments to healthcare professionals for any other services

17.6.2.1 Payments may not be made to doctors or groups of healthcare professionals, either directly or indirectly, for rental for rooms or other services.

17.6.2.2 Healthcare professionals involved in *bona-fide* and if relevant, peer reviewed research, are not subject to the Code.

17.6.3 Certification of Meetings

For the purposes of certification envisaged in Clause 14, the following details have to be retained:

17.6.3.1 Details of the programme, both scientific/education and entertainment/ hospitality, if any,

17.6.3.2 Invitations, the choice of venue(s),

17.6.3.3 Documentation as to the rationale for the meeting or sponsorship,

17.6.3.4 Participant selection processes and criteria,

17.6.3.5 The anticipated costs associated with the event, as well as that associated with all entertainment and hospitality. Records of actual costs will be retained by the company's finance department and be available for auditing purposes.

18. INDUCEMENTS, GIFTS AND PROMOTIONAL ITEMS, COMPETITIONS

18.1 Inducements

There should be no personal enrichment of healthcare professionals or other healthcare providers. No gift, benefit in kind, rebate, discount, kickback or any other pecuniary advantage shall be offered or given to members of the health professions, administrative staff, government officials, or the general public as an inducement to prescribe, supply, stock, dispense, administer or buy any medicine, subject to the provisions of Clause 18.2. No donation should unjustifiably enrich healthcare professionals performing a health related service.

18.2 Gifts and promotional items

Occasional gifts and promotional items to healthcare professionals and appropriate administrative staff are acceptable provided that they are:

18.2.1 Inexpensive and of minimal intrinsic value i.e. within the cost limit set from time to time by the MCA.

18.2.2 Not for personal use e.g. no entertainment CD's / DVD's, electronic items for entertainment, tickets to attend sporting events or other forms of entertainment.

18.2.3 Educational and/or scientific value, benefit the patient and/or be relevant to the practice.

18.3 Promotional items

It is permissible to brand promotional items. The minimum information for a medicine as required under Clause 5 does not have to be included on a promotional aid provided that no promotional claims are made. The following information may be included on such items:

18.3.1 The name of the medicine.

18.3.2 An indication that the name of the medicine is a trademark.

18.3.3 Relevant company name, company logo and/or product logo.

18.4 Cultural courtesy gifts

An inexpensive gift not related to the practice of medicine, the value of which will determined by the MCA, may be given as a maximum of 1 gift per year to healthcare professionals, in recognition of significant national, cultural or religious days. The maximum value of the gift must be in line with the value of general gifts.

18.5 Competitions

Competitions should fulfill the following criteria:

18.5.1 The competition is based on medical/ product knowledge or the acquisition of scientific knowledge;

18.5.2 The prize is relevant to the practice of medicine, dentistry or pharmacy; and

18.5.3 Individual prizes or educational items offered and within the cost limit set from time to time by the MCA.

18.5.4 Entry into a competition must not be dependent upon prescribing, ordering or recommending of a product and no such condition shall be made or implied.

18.6 Donations and grants to charities

Financial donations or other appropriate donations to registered charities or other institutions may be made if properly recorded and approved by the responsible person(s) in each company or organisation. Donations, grants and benefits in kind to institutions, organisations or associations are only allowed provided:

18.6.1.1 They are made for the purpose of supporting healthcare or research;

18.6.1.2 They are documented and kept on record by the donor/grantor; and

18.6.1.3 They do not constitute an inducement to recommend, prescribe, purchase, supply, sell or administer specific medicinal products.

18.6.2 Donations must not be paid directly to healthcare professionals.

18.6.3 Companies are encouraged to make available publicly, information about donations, grants or benefits in kind made by them as covered in this section.

18.7 Corporate Social Investment

18.7.1 Donations to meet identified corporate social responsibility projects may also be made if judged on its merits, approved by the responsible person(s) in each company or organisation and documented.

18.7.2 Corporate social investment is excluded from the operation of the Code in so far as such donations do not induce the overall over or under utilisation of a medicine.

19. RELATIONS WITH THE GENERAL PUBLIC AND THE MEDIA

19.1 Medicines must not be advertised to the general public if they are prescription only medicines.

19.2 Information that is made available to the general public either directly or indirectly about medicines must be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading or disparaging with respect to the safety of the product. Statements, representations or tie-off lines must not be made for the purpose of encouraging members of the public to ask

their doctors to prescribe a specific medicine. Clause 19.1 does not prohibit education or information relating to substitution of a medicine or information on safe use, storage of a medicine in general.

19.3 Requests from individual members of the public for information or advice on personal medical matters must be refused and the enquirer should be recommended to consult with his or her own healthcare professional.

19.4 Companies are responsible for information that is issued by their public relations agencies about their products.

19.5 Patient education ("help-seeking advertisements') directed at general public is acceptable, provided that it:

19.5.1 Does not contain the name of the specific medicine.

19.5.2 Does not make or allude to a medicinal claim.

19.5.3 Does not provide any risk information.

19.5.4 Lets the public know that treatment exists for a medical condition.

19.5.5 "For more information, refer to your doctor or pharmacist (or healthcare professional)" is mentioned.

20. SAMPLES

The supply of samples is not permitted to extend beyond the conditions as prescribed under the Medicines Act.

21. THE INTERNET

21.1 Access to promotional material directed at the South African public provided on the Internet in relation to Schedule 2 to Schedule 6 should be limited through a password protection scheme to healthcare professional and appropriate administrative staff only.

21.2 Information or promotional material covered by Clause 21.1 about medicines which is placed on the Internet outside South Africa will be regarded as within the scope of the Code if it was placed there by a South African company, or an affiliate of a South African company, or at the instigation or with the authority of such a company and it makes specific reference to the availability or use of the medicine in South Africa.

21.3 Medicines covered by Clause 21.1 may be advertised in a relevant, independently produced electronic journal intended for healthcare professionals or appropriate administrative staff which can be accessed by non-healthcare professionals.

21.4 Package inserts for medicines covered by Clause 21.1 above may be included on the Internet and be accessible by members of the public provided that they are not presented in such a way as to be promotional in nature.

21.5 It should be made clear to an Internet user when he/she is leaving any of the company sites, or sites sponsored by the company, or is being directed to a site, which is not that of the company.

22. COMPLIANCE WITH UNDERTAKINGS

When an undertaking has been given in relation to a ruling under the Code, the company concerned must ensure that it complies with that undertaking.
