REGULATORY REQUIREMENTS FOR DRUG PRODUCTS REGISTRATION IN SOUTH AFRICA

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REVIEW ARTICLE

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ABSTRACT

The South African Pharmaceutical market is one of the emerging markets in the world and it is important to study on how to register a drug in the promising pharmaceutical market in Africa. The MCC is the regulatory body which deals with the quality, safety and efficacy of the medicines in South African market which regulates by approving the medicines by very specific process which is unique to South African health system. They have a specific type of CTD for Regulatory submissions which is generally well known as ZA CTD. This article provides the insight on the Drug Registration process in South Africa, the details of data to be submitted to the agency and the pathways of registration an applicant can avail, categories a drug can be registered by MCC, Application fees to be paid to the agency on various types of applications are also dealt.

Keywords: ZA CTD, MCC, AMRP, CTC, MRF.

INTRODUCTION

Guidelines are constantly evolving as a result of scientific developments and harmonisation of the requirements of regional and international regulatory authorities. This article deals with the registration of medicine in South Africa, which is governed by the provisions and requirements of the Medicines and Related Substances Control Act No. 101 of 1965, (hereafter 'the Act') and the Regulations and Guidelines published in terms thereof.

South Africa is a combination of the first world with a large third world component: first world science and technology and third world finances. From the east to the west coast several different climatic zones can be identified, with the east coast being warm to hot and humid subtropical, and the west being desert. Average temperatures range from up to 35° C (extremes up to 46°C) in summer in the lower lying areas to freezing temperatures in winter (average 1°C, extremes to -13° C) in the higher lying areas. For stability studies, climatic zone II should suffice. (1)

The article describes the information required for the registration of "medicines" and for an application to amend a registered medicine.

The Medicines Control Council (hereafter referred as MCC) since 1965,endeavours to regularly update the guidelines to reflect current thinking and keep its technical requirements and evaluation policies in line with "best international medicines regulatory practice." Its main purpose is to check medicines in South Africa are safe, therapeutically effective consistently meet acceptable standards of quality. The medicine regulatory system is highly regarded internationally.

About 750 new medicine applications are received annually by the MCC. There are approximately 330 applicants, of which about 80 have manufacturing and packaging facilities. A unique characteristic is that applicants are required by law to be registered with the SA Pharmacy Council. It is estimated that 80 percent of the population consults with traditional healers before they seek access to conventional medicines. The use of indigenous African medicine is thus quite prevalent and presents medicine regulatory challenges as the materials are obtained from the fauna and flora of the country. (2)

The total value of medicine sold in the country comprises approximately 1 percent of the total world market but, when the use of generic

medicines by the State is taken into account, the generic market is large.

Most multinational companies hold a majority of South African shareholding are operating in South Africa. Due to international rationalization, a significant number of manufacturing facilities has ceased manufacturing operations. Medicines are now increasingly being imported.

ZA CTD (South African CTD) format is clearly discussed including their requirements, specifications and fees payable to the registrar.

It also focuses on *when a product should be registered***:**

This may be:

i) Any of the ingredients of a product is listed in one of the Schedules to the Act;

ii) The product is a medicine by virtue of the definition of a medicine in the Act.

iii) The intended use of a product and the text/words used in promoting the product, even if no claims are reflected on the label, render the product able to register.

To date, more than 20,000 medicines have been approved in the country. Since the establishment of the Medicines Control Council, more than 220 meetings have been held to decide on the registration of medicines.

Regulations in South Africa

The Medicines Control Council (MCC) is a statutory body that was established in terms of the Medicines and Related Substances Control Act, (Act 101 of 1965), to oversee the regulation of medicines in South Africa. It is appointed by the Minister of Health and its main purpose is to safeguard and protect the public through ensuring that all medicines that are sold and used in South Africa are safe, therapeutically effective and consistently meet acceptable standards of quality. The Council, in considering whether a medicine is suitable for use for its intended purpose, assess its relative risk against the benefits.

All medicines for human use are subject to Act 101 of 1965, including complementary and complementary biological medicines. Further, all veterinary medicines must be registered in terms of the Act excluding stock remedies registered in terms of Act 36.

The CTD guidelines, together with the South African Regulatory Guidelines (SARG) provide detailed information about the contents of an application. These guidelines apply to applications to register medicines and all related variations. Applicants should not modify the overall organisation of the CTD. If not contained in the bulk of the documentation, any additional data should be included as addenda to the relevant part, together with additional expert comment that may be provided as a supplement to, or incorporated into, the relevant summary, overall summary or overview. (3, 4)

South African CTD (ZA CTD)

The MCC have distinctive and additional requirements which are imposed upon applicants, so it is generally necessary to supplement the core regulatory data package provided in Europe and elsewhere. The South African CTD (ZA CTD) is sectioned into parts where as it is called as module in ICH CTD.

Contents required for Application or Dossier

PART 1: ADMINISTRATIVE INFORMATION

- *Part IA- Administrative Particulars*
- *PART 1B- Table of Content*
- *PART 1C-Labeling*
- *PART 1D- Foreign Registration*

PART 2: BASIS FOR REGISTATION AND OVERVIEW OF APPLICATION

- *PART 2A- Pharmaceutical and biological availability*
- *PART 2B- Summary basis for registration application (SBRA)*
- *PART 2C- Pharmaceutical Expert Report (PER) or Quality Overall Summary (QOS) Quality overall summary*
- *PART 2D- Pre-clinical expert report.*
- *PART 2E- Clinical expert report*

PART 3: PHARMACEUTICAL AND ANALYTICAL

- *Part 3A- Active pharmaceutical ingredient*

- *Part 3B- Formulation*
- *PART 3C- Specification and Control procedure for pharmaceutical ingredients*
- *PART 3D- Containers and Packaging Material*
- *PART 3E- Manufacturing Procedure*
- *PART 3F- Final Product Specification and Control*
- *PART 3G- Stability Data of the FPP*
- *PART 3H- Pharmaceutical Development*
- *PART 3I- Expertise and premises used for the manufacture of a biological Medicine.*

PART 4: PRE-CLINICAL STUDIES

PART 5: CLINICAL STUDIES

Attachment B: Details for package insert:

1. Proprietary name
2. Composition
3. Pharmacological classification
4. Pharmacological Action
5. Indications
6. Contra-Indications
7. Interactions
8. Pregnancy and lactation
9. Dosage and Direction for use
10. Side effects and special precautions
11. Known symptoms of over dosage and particulars of its treatment
12. Identification
13. Presentation
14. Storage instruction
15. Registration number
16. Name and address of the holder of the certificate
17. Date of publication of the package insert (5)

Preparation and Submission of an application form

Application for registration of medicine submitted on Medicine Registration Form (MRF-1) (6, 7)

- Each page of application should be numbered, font size should be at least Arial 10 point black on white and the copies including figures tables, photos should be clearly legible.
- Each part or Sub-Part should contain a Table of Contents.
- Application should be bound on left side as this allow for easy update /addition of pages.
- Cheque and payment submitted in separate envelope attached to the original covering letter.
- Boxes in which documentation submitted to the MCC labelled it contains:
- Applicant name
- Name of the product

The content of box e.g. File nos., Parts, samples, covering letter, Cheque. No of Boxes (1 of 10), Type of application e.g. routine, fast track, Colour sticker indicating screening (Red) and Pre-screening (green)

In the case of fast track registration copy of approval letter attached

Pre-screening (According to attachment A)

Screening according to the screening form MRF-2

Presentation of Screening and Post-screening copies (8)

Part of the application for registration should be duplicated and submitted as prescribed in the screening approval letter with application fee.

Screening Submission

SET 1:

- Covering letter in front of each volume
- Screening fee (Do not include the application fee with the screening fee)
- Completed Pre-Screening check list (Attachment A)
- Completed MRF 2 (Screening Form)

One complete application for registration dossier (MRF1) and the following:

- Inspection report latest
- GMP/WHO certificate
- Certificate of analysis of samples submitted
- One sample smallest pack size
- BMR for same batch samples
- License for manufacturer, packer, laboratory
- Proof of registration of company and authorized person
- Full Submission

SET 2 (P + A)

Completed MRF 2 form

All screening outcome letters and amendments

PARTS 1A to D, 2A (if not biostudy), 2C if applicable, 3A to I

SET 3 (NAMES and SCHEDULING)

Covering letter in each volume

PARTS 1A, C and 3B

SET 4 MEDICINE REGISTER

PARTS 1A, C, 3B

PART 3E and Part 3Fb

SET 5 SCHEDULING (NCE)

Parts 1A, C and 3B

Parts 2B, 2D and 2E

SET 6 CLINICAL AMRP (Abbreviated Medicine review process)

PARTS 1A to D and 2B or 2D and 2E

SET 7 CLINICAL

PARTS 1A to D and 2B or 2D and 2E, 3B 4 and 5

SET 8 BIOSTUDY or Other

Completed MRF 2 form

All screening outcome letters and amendments

PARTS 1A to D, 2A (if not bio study), 2C if applicable, 3A to I, 4 and 5

An acknowledgement letter will be sent to the applicant and evaluation of the application will proceed on receipt of the additional copies. The applicant will not be permitted to communicate directly with the evaluator. All queries and concerns should be communicated through the secretariat.

Export report on chemical-pharmacological, pharma-toxicolgical and clinical documentation should be given.(8)

Bio study

Comparison of the therapeutic performance of two pharmaceutical products containing the same API, or action moiety is a critical means of assessing the possibility of using either the innovator or a multisource pharmaceutical product.

Bioequivalence studies for immediate release dosage forms should be done under fasting condition.

Bioequivalence studies for modified release dosage forms should demonstrated any influence of food in order to exclude any possibility of dose dumping hence both fed and fasted studies are required. (9)

Drop-out and withdrawal

Sponsors should enter a sufficient number of subjects in the study to allow for possible drop-outs or withdrawals.

Pathway of Registration

- Application for registration of medicine should be submitted on Medicines Registration form (MRF1)
- A. Each page of the application should be numbered and the printing should be in a font size with a legibility equivalent to at least Arial 10 point black on white and the copies including tables, photos should be clearly legible.
- Have a header reflecting the HCR, Product name, dosage form and strength.

  Note: Pages should be numbered according to the MRF 1 except for pack insert and PIL.
- Each PART or SUBPART should contain a table of content.
- The application for registration should be properly bound on the left side as this allow for easy update or addition of pages. Binding is left to the discretion of the applicant. The binding should enable the easy handling and evaluation of documents without it coming apart. The dossier should therefore be bound in units not exceeding 4 cm.
- Copies of both screening and final submission covering letter in addition to all screening outcome letters should be bound to the application dossier.

- Cheque and proof of payment should be submitted in separate envelop attached to the original covering letter.
- The boxes in which the documentation is submitted to the MCC should be clearly labelled.
- If expedited review (Fast track) registration a copy of approval letter should be attached.
- On the receipt at MCC all application for registration will be subject to Pre-screening according to the checklist, attachment A.
- On successful pre-screening the application will be logged onto the system and allocated a screening number. A letter of acknowledge receipt of the application and receipt of the screening fee will be issued to the applicant.
- If the applicant does not comply with the pre-screening requirement the application will be returned to applicant.
- After successful pre-screening the application will be subjected to screening according to the screening form MRF2.
- The screening outcomes i.e. hold or returns as incomplete will be communicated to the applicant together with reasons.
- The ACCEPTED screening outcomes the required application fee and the number of copies will be communicated to the applicant. (at this point the application number will also be allocated. Applications for which expedited review has been approved should be clearly marked.)
- The correct number of copies of application and additional documents required for evaluation of the application should be submitted. (This date will be regarded as the date of submission of the application for registration.)

Fees

(i) New Chemical Entities or highly technological products, which have been processed by the abbreviated registration process (first strength, first dosage form): R30000 per application;

(ii) Strengths and dosage forms other than those referred to in sub-paragraph (i): R15000 per application;

(iii) New Chemical Entities, including highly technological products, (first strength, first dosage form): R30000 per application;

(iv)Strengths and dosage forms other than those referred to in sub-paragraph (iii): R20000 per application;

(v) Biological products (pharmaceutical, analytical and bioavailability evaluated): R30000 per application;

(vi) Generic products (pharmaceutical, analytical and bioavailability evaluated) and all other dental and radio pharmaceutical products (first strength, first dosage form): R12500 per application;

(vii) Strengths and dosage forms other than those referred to in sub-paragraph (vi): R6500;

(viii) Screening fee on receipt of an application: R1050;

(ix) Evaluation of additional submitted clinical data: R1900;

(x) An application in terms of Section 15C of the Act: R12500.

(xi) 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.

Review and approval by MCC

Evaluation procedures are of following types. They are,

Expedited review process (fast-track)

Speed up the registration process for specific medicines Include-

I) has important therapeutic benefit

II) Required urgently to deal with key health problems

Abbreviated Medicine Review Process (AMRP)

- ✓ To limit the evaluation time of pharmaceutical products. (if the evaluation report is readily available)
- ✓ Only new chemical entities registered with one or more of the authorities with which the Council aligns itself will qualify for AMRP.

Based mainly on the expert reports of the Pharmaco-toxicological and clinical data

- The first review process first is purely administrative and occurs within 2 weeks of submission.
- The second review is both scientific and ethical and has two separate cycles:

1. Review by evaluator and the Clinical Trials Committee (CTC)

Submission cycles end approximately every 8 weeks. Submissions may be made at any time during the submission cycle but must be submitted a minimum of 6 weeks before the first scheduled CTC meeting i.e. by the end of the submission cycle as indicated on the attached table.

Submission dates are 'cast in stone' and no late submissions are allowed. Neither are incomplete submissions accepted, all required documentation must accompany the submission document. Should documents be outstanding, the application will be held over to the next review cycle. As the number of submissions per cycle is usually very large, it is well worth the effort to submit at least 7 to 14 days before the end of the submission cycle date. Although every effort is made to review all application dossiers submitted, submissions received on the due date at the end of a cycle risk not being reviewed at all during that particular cycle.

All submissions are reviewed firstly by an appropriate evaluator who takes his/her comments to a meeting of the CTC. The CTC meets 6 weeks before the full MCC meeting.

At the CTC meeting, the evaluator's comments are discussed, concerns raised by the other members of the CTC are addressed by the evaluator and the agreed upon queries and category for approval (see category listing below) are then compiled by the secretariat and sent by fax to the applicant. These queries are usually received within approximately 10 working days after the CTC meeting. Applicants are given 7 calendar days in which to respond. Responses are both hard and electronic copies (on a CD). The responses to the queries are then forwarded to the evaluator for review and approval.

Applications which receive up to a 2B rating are deemed to have minor queries, which, if acceptable responses are received by the evaluator, will ensure that the trial is approved and the category awarded by the CTC is ratified at the Medicines Control Council meeting. Ratings of Category 3 and over, indicate serious deficiencies in the protocol design or scientific rationale for the study and may require resubmission and review over the next submission cycle. (10)

An application receiving a Category 4 indicates that expertise outside of the CTC is being sought to ensure thorough review of the proposal. Categories 5 and 6 are self-explanatory in the table below.

Table 1: MCC approval categories

MCC APPROVAL CATEGORIES	
Approval code	**Explanation**
1a	Approval
1b	Ethics committee Approval outstanding
2a	Outstanding issues can be dealt with "in house"
2b	Outstanding issues must be checked by original reviewer
3	Original reviewers reports back to full committee
4	Referral for specialist
5	Rejection of Application and requires Full Resubmission if to be reconsidered
6	Rejection because of missing

	component(s)

The following documents /information are required for the submission:

A completed application form (CTF-1) with the following attachments / information:

1. *Protocol in Word*
2. *Patient Information Leaflet and Informed Consent Document*
3. *Certificate of insurance*
4. *Certificate/s of analysis*
5. *A Financial Declaration*
6. *Investigator's brochure*
7. *Registration status*
8. *Details of submissions to any other regulatory authority*
9. *Details of the monitor for the study*
10. *A summary of the monitoring plan*
11. *The amount of study medication to be imported to complete the trial*
12. *person responsible to the regulatory authorities for the trial*
13. *rationale for the sample size*
14. *Details of serious / adverse event reporting*
15. *Supply, handling, labelling, manufacturer and dispatch of medication*
16. *Any additional material*
17. *Any relevant publication/s*

Reports required after study commencement:

A six-monthly Progress report is required by the MCC. Data is captured for the 6 month period after the approval date for the study and each 6 month period thereafter until study close out.

The approval document can therefore be generated at any time after confirmation by the evaluator that the responses received were acceptable, and does not have to wait for the following scheduled MCC meeting.

CONCLUSION

It describes Registration cycles of New Drugs & Generic Drugs in the South Africa and also provides recommendations for applicants preparing a dossier for the Registration of Medicines for easy and fast track marketing authorizations submissions to the Medicines Control Council (MCC).

It is a legal requirement that data submitted for evaluation should substantiate all claims and should meet technical requirements of quality, safety and efficacy of the product for the purposes for which it was intended.

Guidance to the applicant in meeting the requirements of the Act. It is acknowledged, however, that in some instances scientific developments may dictate alternative approaches.

When a deviation from a guideline is decided on, a detailed motivation giving the reason(s) for the deviation and justification for the alternative approach should be included in the expert report submitted with the application. Applicants should always refer to the current version of the relevant Guidelines for the Registration of Medicines before completing the application form.

It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications. Thus it has covered Drug Registration Procedures in South Africa and explained different modules of the Common Technical Document (either NDA or Generic.)

ACKNOWLEDGEMENT

I take this opportunity to express my deep sense of gratitude to IJDRA Journal for publishing my Article.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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