PIASA
Pharmaceutical Industry Association of South Africa
IMPROVING LIVES WITH QUALITY MEDICINES

APPENDIX 1

SUMMARY OF RECOMMENDATIONS TO MTT

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Several proposals have been made to the MTT which we believe would provide for an efficient and streamlined health products regulatory review system. We request that these be considered while the regulations and guidelines to the Medicines Act are revised:

1. Review and registration of health products.

   Category 1: Full review - the medicine / indication **not** registered by any benchmark health authority (i.e. UK; USA; Canada; EU, Sweden, Netherlands or Australia).

   - Common Technical Document (CTD) application is reviewed by expert committees of the SAHPRA i.e. externally
   - A suggested review period could be *255 working days (equivalent to 1 year)*

   Category 2: Abbreviated review – medicines / indication **approved by one** benchmark health authority (as listed above).

   - A CTD application including assessment reports and approved label from the benchmark regulatory authority is reviewed by SAHPRA i.e. internally
   - A suggested review period could be *175 working days (equivalent to 9 months).*

   Category 3: Verification review - medicines **approved** by **two or more** benchmark health authorities as listed above.

   - A CTD formatted dossier with assessment reports and approved labels from the benchmark regulatory authorities is reviewed by SAHPRA i.e. internally.
   - A suggested review period could be *125 working days (equivalent to 6 months).*

   The following **exception criteria** should apply whereby products should not be accepted for verification review if:

   - Products 1st in class
   - Biological products manufactured by new technology
   - Non-approval by a benchmark health authority. Such products will be reviewed via Category 2 – Abbreviated review.
   - Products that need to be more stringently reviewed (i.e. blood products, vaccines)

   The evaluation reports by the SAHPRA and it committees should be made available to the applicant following review of the dossier as is the case with all major health regulatory authorities.

   The above model can be also be applied to post registration amendments for both package insert and pharmaceutical changes (refer below).

Supplementary data

The submission of supplementary data (Pharmaceutical and Analytical, non-clinical data or clinical data) that becomes available after the application for registration is submitted and requires evaluation as this data could address any possible or perceived deficiencies identified during the evaluation, should be permitted to be submitted at any stage of the evaluation of the health product.

Registration of unscheduled and Schedule 1 (S1) products

For unscheduled and S1 products where the actives are well documented and approved by benchmark regulatory authorities, the evaluation of the health product should focus on safety and quality and not necessarily on efficacy. Emphasis should be placed on the Good Manufacturing Practice status of the manufacturer.

Multiple branded products

Applicant have submitted several applications (same product but different tradenames) to the current MCC / MRA. Currently these are screened, reviewed and registered separately effectively using valuable resources and time of the local health authority.

Recommendation: Applicants should submit a single "parent dossier" of the health product. The parent application must comply fully with requirements for registration i.e. CTD format of application, sample and relevant production documents / descriptions. The parent file should be allocated a unique name with an identifier to indicated that it is a parent file eg A5008 (MF – Master File). Only when the parent file is certified for registration, should the applicant submit the suggested tradenames for the "multiple branded " products.

If the tradenames are approved, an unique registration number will be assigned linking the "multiple branded" products to the parent file number B3/3.2/079 (A5008 MF).

'Multiple branded' applications must comply with the following requirements:

- The 'parent' product must be fully evaluated.
- The applicant must provide an assurance that all quality aspects of the proposed 'clone' product are identical to the 'parent' product, and that the applicant will ensure that the 'multiple branded ' product will comply with all applicable regulatory requirements.
- The application should be accompanied by copies of all labels, product information and patient information leaflet of the 'parent' product and the 'multiple brand'.
- The SAHPRA should compare the labels, package insert and patient information leaflets of the 'parent' to 'multiple' products. If there are changes beyond the product name and identifying details (registration number), the products should be evaluated fully.

Biological and Biosimilar products

A regulatory framework needs to be established for the reviewed of biological and biosimilar products. We suggest a similar process for review as the original new chemical entities i.e. a comprehensive review of clinical (efficacy and safety), bioequivalence and quality data.
Development of individual INN names for all biologicals including biosimilars (e.g. originator INN + qualifier) should be considered. This should help in both decreasing the likelihood of "inadvertent substitution" and increase the ability to identify the manufacturer for post-marketing pharmacovigilance monitoring and reporting
Since minor differences in manufacturing processes for biologics can have a significant impact on product safety and efficacy, separate guidelines for Post –registration to pharmaceutical-chemical aspects of biological and biosimilars products are required as in certain cases, clinical data should be required to support these amendments.
Biologicals should not be generically substituted / interchangeable because of the risk of immunogenicity hence a post-marketing pharmacovigilance monitoring and risk management plans are essential for these products.

Generic applications.

The applicant should provide the patent status of the compound or process in the submission[(a)]. No claims should be approved in the generic package insert beyond the originator's package insert. For expedited review of EDL products, this should be limited to one per applicant and a limited number of generic EDL products.

Data and Paediatric exclusivity[(a)]

It has also been noted that generic products have indications approved that are not approved in the local package insert of the innovator's product. Data exclusivity and data in paediatric patients should be considered by the SAHPRA as a basis for patent extension.

2. Clinical trials

In order to expedite the review of clinical trial applications, we recommend adopting the Medicines Health Regulatory Authority (MHRA – UK) Regulation 18 (3) whereby all clinical trials are submitted to the authority and if no objection is received within 30 days, the trials are considered approved.
We suggest that the SAHPRA adopt this system and have 60 days in which to raise an objection

(a) Not supported by Adcock Ingram

The currently MCC guidelines and application form for clinical trials needs to be revised. The MCC clinical trial guideline provides no information on observational studies while the clinical trial application form is repetitive and not user friendly.

3. **Patient named programme (Compassionate use - Section 21)**

We recommend that the Australian (TGA) Special Access Scheme and Canadian Special Access Programme for providing access to unregistered products is adopted i.e. 3 categories for access.

Category A products:

The doctor notifies the SAPHRA in writing of their intention to use an unregistered medicine for a very seriously ill patient without awaiting approval for a patient who is seriously ill i.e. with a condition from which death is reasonably likely to occur within a matter of months or from which premature death is reasonably likely to occur in the absence of early treatment.

Category B products:

The doctor submits an application for approval to use an unregistered medicine in a particular patient to the SAHPRA. The current Section 21 form should be revised as it is not user friendly and details of the pharmacy dispensing the medication is lacking.

Category C products (orphan drug)

The definition of an orphan medical condition is: "life threatening debilitating disease where the prevalence is 5 in 10 000 persons and there is no satisfactory method of diagnosis, prevention or treatment".

For these medicines, a prescreening evaluation of the medicines is performed by SAHPRA or if already listed as an orphan drug in the EU or US, the compound is allocated a local orphan drug status and made available to patients.

4. **Post registration amendments**

i. Package insert amendments

The term package insert is misleading. It is recommended to change the terminology to Summary of Product Characteristics (SmPC) which is the term used by the European Medicines Evaluation Authority (EMEA) or Product Information (PI) as used by the TGA.

The current MRA guideline on package insert (dated April 2008) is based on the EMEA SmPC guideline dated December 1999. This guideline should be updated in line with the latest EMEA SmPC document dated October 2005.

With regards to changes to the package insert / product information, we recommend alignment with the FDA, Canadian Health Authorities, EMEA and Australian health authorities i.e.

Notifiable changes

The SAHPRA should be notified of all possible side effects, interactions, warnings and contra-indications that could affect the patient.

- If the safety changes have been approved by a *benchmark* country - the applicant should notify SAHPRA. Should no response be received from SAHPRA within 30 working days, the applicant can implement the safety changes.
- If not yet approved by a benchmark country, the applicant should submit to SAHPRA within 30 days of being aware of the issue. If no response is received from SAHPRA within 2 months, the applicant can implement.

Prior approval

Clinical changes to the indications, dosage and composition of the active ingredient (i.e. qualitatively and quantitatively) requires prior approval from the SAHPRA. Other changes eg, storage instructions, packaging, also require prior approval in line with post registration amendment guideline.

Urgent Safety Restriction (USR)

Urgent Safety Restriction – an interim change to product information restricting the indications (s) and / or dosage and or target species of the medicinal product, or adding a contra-indication and / or warning based on new information having a bearing on the safe use of the product. This should be used in the event of risk to the public health. The rapid procedure consists of a notification to the authorities with implementation of the change if no objection is raised within 7 days.

The above principle has been in practice by the current MCC for post registration approval of pharmaceutical and analytical changes.

ii. Pharmaceutical and Analytical amendments

Many companies operate globally and are often confronted with different decision by local regulatory authorities. These inconsistencies can delay introduction of local changes and result in logistical problems with global implementation. The consequence is that product supply can be affected.

We recommend that the SAHPRA take cognisance of benchmark health authorities approval of post registration changes relating to Pharmaceutical and Analytical changes.

5. **Re-registration / re-certification**

We support the concept of 5 years re-registration / re-certification of medicines however, it should only be implemented once the SAPHRA processes are clearly defined and the SAHPRA have the capacity to manage re-registrations / re-certification. The certification of health products should ensure that the health product dossier is updated in terms of quality and the risk benefit profile.

6. **Adoption of international guidelines and forms / formats of submissions.**

We strongly recommend that the SAHPRA makes an in-principle decision to adopt the International Conference on Harmonisation and European Union guidelines. Furthermore, the SAHPRA should align itself with the CTD format for submissions; Summary of Product of Characteristics (package insert) and the use of the Anatomical and Therapeutic Classification system for medicines. This will facilitate the decision making, consistency of quality and the ability to export products from South Africa.

7. **Patient information Leaflet (PIL) and Scientific Product Information / Package insert (PI).**

We recommend that the current scientific package insert in the packaging of health products is replaced by the Patient information leaflet (PIL). The scientific package insert should be available to health care professional on a central repository.

With a central repository for scientific package insert, the prescriber and dispenser will have access to the all the latest product information required for the safe and effective prescribing, dispensing and administration of medicines.

By having the PIL in the pack and instituting a comprehensive S0 label, the difficulties of the distribution of the PIL will be overcome and patient have the information and knowledge to take their medicine correctly.

This recommendation is again in line with EU, FDA, Canadian and Australian legislative systems. More details of this proposal are available and has been submitted to the MTT.

8. **Advertising of Schedule 2 medicines**

With the publication of Government Gazette No 24727 Regulation 45 whereby Direct-to-Consumer (DTC) advertising of Schedule 2 (S2) substances as prohibited, the Pharmaceutical Industry prepared a submission to the MCC to allow direct to consumer advertising of certain Schedule 2 products. It was suggested to split the two categories viz:

- Molecules that do not have a potential for abuse hence allowed to be advertised directly to the consumer (Section A of Schedule 2),
- Molecules that could have an abuse potential and not allowed to be advertised to the consumer (Section B of Schedule 2).

It should be noted that there are some S2 molecules which should not be advertised in spite of it having no abuse potential. The reason being that it the substances listed below requires close medical diagnoses or management and should not allowed to be advertised directly to the consumer viz: Contrast media; Diarrhoeal – when intended for use in children; Cholestryamine; Nicergoline; Mesna; Mercury salts; Nux vomica; Strychnine

We suggest that the regulation would necessitate the re-wording of parts of Regulation 45 to read as follows:

Regulation 45(2)(a) " Medicines which do not contain a scheduled substance and medicines which contain a substance appearing in Schedule 0 or Schedule 1 **or Section A of Schedule 2** may be advertised to the public; and "

Regulation 45(2)(b) " Medicines which contain a substance appearing in **Section B of Schedule 2**, Schedule 3, Schedule 4, Schedule 5 or Schedule 6 may be advertised only for the information of medical practitioners, dentists, veterinarians, pharmacists and other persons authorized to prescribe or in a publication which is normally or only made available to persons referred to therein; "

8. **Pharmacovigilance**

It is essential that our current guideline on adverse event reporting is updated in line with ICH guideline as compliance is critical.

9. **Conflict of interest**

We are of the opinion that a conflict of interest could be avoided if, consulting services by applicant / market authorization holders of health products are used on policy issues. Applicants / market authorization holders should not be part of decision making process of health products i.e. review any health products dossiers or serve on any of the committees the SAHPRA establishes.

9. **Structure and funding of the SAHPRA**

Regulatory Authority independent of the DoH but reports to MoH has been proposed by PIASA. The regulatory authority needs full time staff and in-house expertise provided that the individuals were adequately remunerated with acknowledgement of the special expertise of professional staff members not related to the public service remuneration levels. Refer to the arrangements made for remuneration of the experts serving on the Council for Medical Schemes.