COMMENTS ON MEDICINES AND RELATED SUBSTANCES AMENDMENT BILL 2008.

PIASA was actively engaged with the Ministerial Task Team (MTT) and submitted several proposals (October 2006; December 2006 and January 2007), which preceded the legislative amendments. PIASA also submitted comments to the Department of Health (DoH) on the initial draft Medicines and Related Substance Amendment Bill on 16 May 2008. All these submissions are available from the PIASA offices on request. A summary of the key comments / recommendations and proposals are attached as Appendix 1. The DoH published a revised Bill on 2 June 2008 for comment.

PIASA acknowledges the DoH and MTT endeavours to transform the regulatory system into an efficient and effective regulatory authority. This transformation should allow for timely review of clinical trials and the registration of medicines. PIASA in general supports the findings of the MTT report and addresses this below in the context of ensuring the inclusion in the Bill of empowering provisions required to give effect to the MTT recommendations (refer to section 2.2.).

1. POSITIVE AMENDMENTS PROPOSED IN THE AMENDMENT BILL:

   The following proposed amendments are supported by PIASA:

   1.1. The abolition of the Medicines Control Council and the formation of a new juristic structure i.e. South African Health Products Regulatory Authority [Authority].

   1.2. The appointment of a Chief Executive Officer [CEO] with a performance contract for 5 years with the possibility of a further 5 years.

   1.3. The CEO can appoint staff with the required expertise and can contract in any other experts to assist the Authority to carry out its functions.

   1.4. The CEO can appoint committees to investigate and report on any matter within the purview of the Authority.

   1.5. The formal inclusion of foodstuffs and cosmetics for which medical claims are made, complementary health products and medical devices.

   1.6. Codes of Practice for 'relevant' industries and other stakeholders.

   1.7. The improved Appeal Processes against decisions of the Director General (DG) and decisions of the Authority.

2. KEY CONCERNS WITH THE REVISED BILL ARE:

PIASA has three key concerns viz.:

2.1. The two-tiered regulatory review of health products i.e. Certification by the Authority and the Registration of health products by the Minister of Health (MoH).

2.2. The omission of empowering provisions for key regulations.

2.3. The lack of adequate transitional measures.

2.1. The two-tiered regulatory review system i.e. Certification and Registration of health products (ref. section 15 of Act)

Following submissions and presentations to the DoH on the initial bill, the DoH has amended the criteria on "public interest" to be considered by the MoH for registration and ultimately the market access of health products.

However, it remains a concern as this two-tiered approval system creates an additional barrier to entry for health products and will further delay patient access to medicines. The final decision-making power is vested in the Minister of Health over and above the regulatory review of health products undertaken by a juristic body, the South African Health Products Regulatory Authority (Authority) and the Pharmaceutical Economic Evaluation Unit in DoH.

2.1.1. Current medicines regulatory considerations

a. The Medicines Control Council (**MCC** within DoH) reviews the **quality, safety** and **efficacy** of a clinical trials and medicines **registration**.

b. The Pharmaceutical Economic Evaluation (**PEE** within DoH) regulates the manufacturer's Single Exit Price (**SEP**) and in future intends to regulate logistics and dispensing fees (section 22G regulations). International benchmarking {Reg. 5 (2)(e)} of medicine prices is currently under review and it is expected to further reduce the SEP component of medicine pricing. The medicines pricing regulations include provisions for the publication of details where a medicine is found to be *cost-ineffective* by the PEE.

c. **Reimbursement** is a separate process from the registration of a medicine i.e.:
Private sector reimbursement:

- **uninsured** patients have immediate access to registered medicines
- **insured** patients (access is regulated by legislative requirements, clinical and financial/economic considerations relating to a particular medical scheme)
  i. If the medicine is part of a Prescribed Minimum Benefit (**PMB**'s) as defined by the Council of Medical Schemes (**CMS** reporting to MoH), patients access is dependant on whether the medicines appear on a formulary list or not.
     - Formulary listing entails a detailed submission to the medical scheme / administrator. Medical schemes use a number of benefit design, managed care and pharmacy software tools to manage medicines cost both before and after prescription.
     - For non-formulary products, patients and/or their healthcare providers have to follow extensive motivational processes in cases of proven clinical need.
  ii. If the medicine is **not** part of a **PMB**, patient access will depend on the specific benefit option of the patient and the nature of the medicine (e.g. chronic or acute use), and factors relating to whether co-payment is required or if the medical scheme is prepared to reimburse the patient.

Both insured and uninsured patients benefit from generic substitution as stipulated in the Medicines and Related Substances Act, over and above the economic and financing mechanism described.

The **public sector access** is driven by the needs and economic considerations. The state tendering is regulated by the State Tender Board and allows for the State to obtain medicines at a very reduced price. The therapeutics committees in each province determine which medicines will appear in the list for medicine tenders.

Current Medicines Regulations

1. **Registration of medicines (safety; efficacy and quality)**
   - ✓ **MCC (part of DoH)**
2. **Pricing of medicines (Single Exit Price, logistic and dispensing fees)**
   - ✓ **PEE (part of DoH)**
3. **Reimbursement of medicines (clinical and pharma-economic data**
   - ✓ **Private market: PMB (CMS part of DoH) or not PMB**
   - ✓ **Public sector: Tendering (State Tender board)**

2.1.2. Proposed medicines regulatory environment for medicines

The DoH intends including an additional step in the regulation of medicines thereby potentially delaying patient access to new innovative medicines. The new proposed regulation of medicines is envisaged to be:

a. Certification of medicines (based on quality, safety and efficacy) by the Authority, reporting to MoH

b. **Registration of medicines (public health issues) by the MoH**

c. Pricing Committee (SEP; international benchmarking; pharmaco-economic data; logistics; dispensing fees) reporting to MoH

d. Reimbursement

   i. Private sector via PMB or not PMB's. The proposed amendment to the National Health Act (NHA) is intended to regulate PMB's.

   ii. State tender in public sector

Proposed Medicines Regulations

1. **Certification of medicines (safety; efficacy and quality)**
   - ✓ **Authority (part of DoH)**
2. **Registration of medicines (public health interest)** ←
   - ✓ **MoH**
3. **Pricing of medicines (Single Exit Price, logistic and dispensing fees)**
   - ✓ **PEE (part of DoH)**
4. **Reimbursement of medicines (clinical/pharma-economic)**
   - ✓ **Private market: PMB (CMS part of DoH and NHA) or not PMB**
   - ✓ **Public sector: Tendering (State Tender board)**

Even if the additional approval step (2) is performed in parallel with the certification of medicine, there will be an unnecessary and costly duplication of considerations for both government and the pharmaceutical industry.

The duplication of reviews will include scientific / clinical data, population health needs, health financing and health economics. Many of the criteria listed by the DoH in the proposed Bill are already quite successfully applied, in some form or another, in the following settings:

- The PEE Unit (within DoH), prior to marketing when an SEP is awarded and after marketing on cost-effectiveness or where concerns are raised in relation to a particular medicine's pricing;
- In community pharmacy through the provisions on generic substitution in the Act;
- Individual medical schemes through benefit design, managed care (such as formulary design) and the actual implementation of benefits;
- Provincial Departments of Health through their Therapeutics Committees;
- National Department of Health through national treatment guidelines and lists, such as the Essential Drug List (EDL); and
- the State tender board.

PIASA agrees that issues of health economics are important, but submits that this debate, and the alignment of health financing with South African health needs, has to take place within the context of a roadmap to national healthcare financing, preceded by policy discussion and decisions.

2.1.3 Response to DOH questions on criteria used by other countries for medicines regulation

At the presentation to the DoH (21 May 2008) on the revised medicines amendment bill, the pharmaceutical industry was challenged to comment on the following scenarios in other countries i.e.:

i. *Medicines registered but not permitted to be marketed*

This is the case in the USA where generic anti-retrovirals (ARV's) receive "tentative approval" from the FDA in order to qualify for the Presidents Emergency Plan for AIDS Relief (PEPFAR). The generic ARV is subjected to a full review, and based on a scientific merit, receives "tentative approval". The generic ARV's are not marketed in the USA as the patent protecting the innovator product is still in place and full approval is only granted when the patent protection expires, whereby the generic ARV is allowed to be marketed in the USA.

ii. *"Public interest" considerations*

In Belgium "public health interests are considered as part of re-imbursement of medicines in a national health system. Briefly the process in Belgium is:

- *Registration* of medicines by the regulatory authority based on safety, efficacy and quality aspects of medicine
- *Pricing* is reviewed by the Minister of Economic Affairs based on price comparison with main competitors and mean European Union price.
- *Reimbursement* aspects of "public interest" are evaluated by the Minister of Social Affairs. It does <u>not</u> form part of the registration. A separate dossier is filed for re-imbursement.

This system has proven to be very cumbersome and has delayed market entry and patient access to new medicines.

iii. *Brazilian health care environment*

Healthcare in Brazil consists of a public sector, Unified Health System (SUS) and a private sector (similar to South Africa).

The medicines regulatory review is as follows:

- *Registration* of medicines registered by National Agency of Sanitary Surveillance (i.e. the regulatory authority), based on quality, safety and efficacy
- *Price* proposal is assessed by Medicines Market Regulation Chamber which is represented by the MoH, Treasury, Justice and Development. The price of medicines for the public sector is 25 % lower than the private

sector price while generics are 35 % lower than the innovators. Homeopathic, herbal and *some* over the counter medicines are not included in this price control scheme.

- ***Re-imbursement*** is performed by the Health Economic and Technology assessment unit (CITEC). CITEC gives **recommendations** for incorporation by the public and private sector i.e.:

  - Public sector has funding lists which are subject to treatment guidelines. The national medicines list includes a National List of Essential medicines and Exceptional / High cost medicines for long term use.

  For new medicines to be incorporated in the public sector funding lists, the pharmaceutical industry must submit their requests to CITEC based on scientific and health-economics grounds. The CITEC determine whether the government will, or will not, pay for the medicines and provide them to public sector patients.

  - Private sector: National Agency of Supplementary Health regulates access reimbursement to "in-hospital" procedures and medicines.

The registration of medicines and pricing re-imbursement are separate and independent processes.

The consequences of the Brazilian model:

- Since 2006, 107 medicines submission have been made to CITEC and only **4** medicines approved.
- Since Brazil's constitution states that all citizens must have appropriate health care, patient have made applications to the court in order to exercise their rights to get access to new medicines.

iv. *The International Conference on Harmonisation (ICH)*

ICH is a joint initiative involving both regulators and industry as equal partners in the scientific and technical discussions of the procedures which are required to ensure and assess the safety, quality and efficacy of medicines.

ICH is comprised of six Parties as well as three Observers and the International Federation of Pharmaceutical Manufacturers & Associations. The Six Parties are the founder members of ICH which represent the regulatory bodies and the research-based pharmaceutical industry in the European Union, Japan and the USA. The Observers are WHO, European Federation of Pharmaceutical Industries and Associations and Canada (represented by Health Canada). As part of the Southern Africa Development Community (SADC), the current MCC has been invited as a permanent representative on the ICH Global Co-operation Group (GCG), a sub-committee of ICH. The GCG serves as a forum for the discussion of harmonisation topics and practices.

World-wide regulatory authorities have adopted the ICH guideline and base the registration of medicines solely on the safety, efficacy, and quality of health products.

In countries with a national health financing system, government reimbursement is an entirely separate process from registration and does not deny patients access to the medicines should they be able to afford the treatment. Hence patients and healthcare providers have the immediate benefit of new registered health products.

2.1.4 Comments on the listed criteria for registration of medicines by the MoH

PIASA does not support the proposed two-tiered registration process, and its comments below on the specific criteria should not be construed as endorsing this process. It should be noted that if any, or all of this is implemented, there will be substantial practical and cost implications, which may, in the end, be counter to the intention of increasing patient access to affordable healthcare.

(i) "***public health interests*** *including* ***national epidemiological*** *trends* "

- It should be noted that national epidemiological data on the burden of disease in South Africa is not readily available for many therapeutic areas. PIASA notes and supports the establishment of a National Health

Information System by the Department of Health. It submits that, in future, data generated through this system will be extremely valuable in the current evaluations, as outlined above, and would enhance the move towards a national health insurance system.

However, national epidemiological data requirements as found in the proposed registration process may be unavailable, or only obtainable at considerable cost, which would be likely to impact the price of medicines. Furthermore, epidemiological data is not relevant to all health products within the scope of the Medicines Act (e.g. complementary, foodstuffs and cosmetics with medicinal claims).

- Issues of public health interest should be outlined in government's health policy and not legislated. It is important for all stake holders to know up front what issues of public health interests are relevant and applicable before submitting a medicine for registration to the Authority. This will avoid unnecessary effort and wastage of scarce resources by both the pharmaceutical industry and DoH.

In our opinion, we do not believe that "public interest" even if clearly defined, can be evaluated in a transparent and efficient manner without the DoH establishing another structure. This structure will require additional resources (both financial and human) and will further delay patient access to medicines and potentially increase the cost of medicines.

(ii) ***economic interests*** *in relation to health policies*

- **Economic issues** should relate to an appropriate review of pharmaco-economics, within the broader context of health economics. This means that although an individual product is "cost-effective," other factors such as downstream costs, and related care needs such as more visits, tests and hospitalisation and the financing mechanisms of institutions and individuals, should be considered.

The affordability of treatment to medical scheme plans or the country should not prevent medicine access as individual patients may decide to fund certain treatments out of pocket. Increased medicine access may lead to enhanced competition and price reductions and could lead to further and better access.

Currently, economic reviews take place within the ambit of the pricing regulations separately from benefit design and managed care reviews undertaken by medical schemes as outlined above.

- **Economic interest** with regard to industrial and trade policies should be addressed by other government departments such as the Department of Trade and Industry and the Treasury. An example of economic interest could be the protection of the investment in manufacturing facilities by local companies against the awarding of tenders for anti-retroviral's to foreign companies who may be able to offer the product at a lower price.

  However, this is an issue within the realm of national and international trade policy, as well as an issue within the powers awarded to Tender boards and legislation under the control of National Treasury. Therefore, should this be a concern, the medicines registration process is not the correct vehicle to address this issue.

(iii) *whether the product is* ***supportive of national health policy*** *and goals in the long term;*

- The DoH has the power to set national policy and standards for health in South Africa. It therefore has the power to buy and recommend certain products, if they are supportive of such policies.

- Medical schemes have similar powers relating to the clinical and financial needs of its members. For pure "private" patients, access to treatment cannot be curtailed by excluding market access through registration on these grounds.

(iv) *whether the product is likely to significantly improve access to health care for* ***vulnerable groups within society***;

- Generally **vulnerable groups** have access to health care within the State health care system. Therefore access to medicines in the public sector is dictated by government policy and the powers it has in terms of procurement legislation.

(v) *the experience of* ***other countries*** *concerning the marketing, distribution and use of the product;*

It is not clear as to which or how many countries' information will be required for this review. For the SEP of new medicines and medicines already on the market, pricing information from several countries is already required by the PEE Unit (within DoH).

(vi) *generally whether the public would be best served by such registration*".

It is unclear how the manufacturer of any medicines would have to prove this, what information is expected from medicine manufacturers and the importance of this requirement from a health policy point of view.

2.1.5. Implications of the two-step registration process

In the absence of legislated provision for timelines for the regulatory review of medicines, the process as proposed could place the recommended outcome of the MTT Report (efficient and timely registrations of medicines) at risk. Apart from demanding additional human and financial resources, and in some cases duplicating analyses conducted elsewhere, this second step in the registration

process could place serious constraints on access to healthcare. Medicines which might have been available, and which would have introduced greater competition in the market, may not be allowed market access.

Private patients, who may have resources to fund more expensive technologies, would not be able to access these, which, in turn, would exclude the potential for such products to become less costly through enhanced market access.

Medical schemes would be limited in the potential choices of products for inclusion in formularies and the benefit of post-market access competition on grounds of cost-effectiveness and affordability. With fewer innovative medicines, there will ultimately be fewer generics available. In the end, both healthcare needs, and the interest of science, may be detrimentally affected by this second step-review.

For many products, the benefit risk ratio is more clearly defined following the post market approval and after patient utilisation. The initial approved indication of medicines might benefit a limited patient population but additional new indications for use which are developed later in the medicines life cycle, could benefit a large patient population. If market access is denied early on in the regulatory process, patients might never have access to new therapeutic usages of the medicine.
New ARV's medicines are initially developed for salvage patients and then as front line or backbone therapy. The newer ARV's medicines which could serve the South African public well in the future might never be registered if these provisions are implemented as their initial "public health interest" is limited and "*would not serve the broader public interest"* as defined by the DoH.

Even if a medicine meets the criteria, patients will be denied access to medicines until the review of "public interest" is completed.

In the interest of providing patient and healthcare providers with new innovative medicines, medicines regulatory approval should be based on scientific and

clinical data, and the process should be efficient and completed within a reasonable time frame.

The DoH should facilitate access to medicines in order to improve the health status of vulnerable groups within society, using powers it has in terms of national standard-setting and procurement, as well as implementing various aspects relating to financing models for lower-income persons, such as the envisaged state-sponsored medical scheme and low-income medical schemes, in view of a future national health insurance system. The pharmaceutical industry has in the past indicated its willingness to contribute to such systems through, for example, an access subsidy.

In summary

PIASA acknowledges that the MoH has the right and duty to take note of any issue affecting public interest. However, it remains concerned that the DoH has not quantified nor defined the cost implications of this two-tiered regulatory systems and the potential impact it will have on patient's access (both private and public sector) to new innovative medicines, and the knock-on effect on the generics industry. It is also concerned that this prominent change has not formed part of the MTT recommendations and has therefore not been subjected to substantive debate and discussion.

All health regulatory authorities approve medicines on the basis of safety, quality and efficacy. Price regulation and reimbursement is a separate process and does not hinder broader patient access. Therefore, PIASA respectfully requests that the DoH seriously reconsider the additional "public interest" review by the MoH as patient access to new medicines could be denied or further delayed.

2.2. The omission of empowering provision for enabling regulations

PIASA has submitted proposals to the MTT in an effort to improve the efficiencies and progress of the regulatory authority (refer to Appendix I – for an executive

summary of PIASA recommendations). It should be noted that several of PIASA's suggestions have been mentioned in the MTT's report(ref to MTT report).

However, in order to allow implementation of the recommendations of the MTT, additional, clearly mandated regulations are needed to ensure an efficient and transparent system. This will also ensure that the new Authority has a clear and unchallengeable mandate and programme of action i.e. it will not be ultra-vires and therefore subject to challenge. It will also allow the new Authority to plan its regulatory programme appropriately, i.e. know which sets of regulations will be required, and how these should be dovetailed with existing regulations, and allow for public comment and discussion, without causing delays or un-implementable provisions.

We suggest that the following enabling provisions are considered by the DoH in terms of regulation 35 viz.:

- Provisions for empowering the Authority to do various types of reviews, and to, accordingly, enter into agreements with other countries on recognising aspects of their system or the outcomes thereof.(Chap.9-pg85)
- Provisions for a transparent system that allows for the progress of a submission to be traced within the Authority. (Chap.10-pg94)
- Provisions for the Authority's Quality Management System (Chap.9-pg90)
- Provisions for publication of the Authority's Performance Report(Chap.9-pg81)
- Provisions to ensure good governance of the Authority (this also means that decision-making processes should be clear, as well as who the "controlling mind" of this juristic person will be(Chap.9-pg85)
- Provisions for data protection(Chap.9-pg92)
- Provisions for prescribed timelines for the review and evaluation of submission to the Authority (both health products registrations(Chap.9-pg80) and clinical trial applications(Chap.9-pg87)
- Provisions for enforcement of the Codes of Marketing Practice(Chap.9-pg131) and for compliance to be a condition for the licensing of all health products, the licensing

and accreditation of all marketers of health products, as well as a condition for the registration of medicines.

- Provisions for additional regulations under section 18A to regulate the elimination of perversities in the industry(Marketing Code Committee recommendations on Legal Gaps to be addressed – Appendix II)
- Provisions for alignment of the pharmacological classification of health products as per the World Health Organisations (WHO) Anatomical and Therapeutics Classification system(PIASA proposal to MTT)
- Provisions for the alignment of the prescribing information (currently termed package insert) with the European Summary of Product Classification(PIASA proposal to MTT).
- Provisions for the patient information leaflet (PIL) to be inserted into the packaging of any health product and the scientific product information (PI) to be made available to healthcare professionals. (PIASA proposal to MTT)
- Provisions for the alignment of information and application forms with those of the International Convention on Harmonisation(Chap.9-pg81).

In addition to the DoH transforming the regulatory authority and the processes within the structure, the need to address the shortage of necessary qualified skills and resources remains a concerns. In this regard, PIASA is more than willing to partner with government in their efforts to address this skills shortage.

2.3. Transitional measures

2.3.1. There is no provision for health products that have been submitted to the MCC prior to the promulgation and implementation of the intended amendments and where the review process is not completed. Provision must be made for completing the approval / rejection of such products.

2.3.2. The status of exemptions in terms of section 36 (which has been deleted) e.g. S0 medicines exemption from Section 18 A and 22G; labelling exemptions etc., needs to be clarified.

2.3.3. The manner in which the current MCC and the MRA will be transformed into the new SAHPRA needs to be clear, in order to avoid a repeat of the problems experienced with the SAMMDRA Act.

2.3.4. Relationships with existing laws, such as the Foodstuffs Act and the Hazardous Substances Act, have to be clarified.

2.3.5. Step-wise implementation of the provisions of the amended Act to ensure that the new Authority is not overwhelmed by the magnitude of the task ahead. PIASA recommendation is to focus on the application of the new processes to orthodox medicines initially and once that system has been implemented and is running smoothly to introduce controls of complementary medicines, medical devices and traditional medicines one at a time.

CONCLUSION

PIASA is supportive of the revised Medicines and Related Substance Bill with the proviso that:

a. There is only **one step** for review of health products based on the safety, efficacy and quality of health products.
b. The Act has **empowering provisions** for key regulations to avoid a situation where regulations are ultra vitres
c. **Transitional measures** are clearly defined and comprehensive.