

**Regulation of Blood Establishments;  
Fractionators; Plasma for Fractionation and  
Plasma-derived Medicinal Products –  
Developing regional harmonised standards and  
approach to improve access**

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**IPFA Workshop on Improving Access to Plasma and Plasma  
Products in the Southern African Region**

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# Regulation of Fractionation in RSA

- **Blood transfusion services** are regulated in SA by the National Health Act (23, 2003)
  - **Blood components are provided by blood services**
    - Single donor and small pool components prepared from  $\leq 12$  donations or aphaeresis are regarded as “blood components” and not medicines
- **Plasma-derived Medicinal Products** are regulated as medicines in terms of the Medicines Control Act (101, 1965)
  - Regulator requires that Blood Products meet the same quality, safety and efficacy standards as other medicines

# Aims

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- Review and compare the Regulatory Frameworks for Blood Transfusion Services (BTSs) and labile blood components, and manufacturers (fractionators) of PDMPs in South Africa
- Briefly outline the requirements to be a supplier of source plasma to a fractionator
- Personal view on the harmonisation of NRAs in the Southern African Region

# Legislative Framework – BTSs

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**Constitution**

*Bill of Rights*

*Access to health care services*

*Equality*

# Legislative Framework - BTSs

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**National Health Act No 61 of 2003**

# Legislative Framework - BTSs

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## National Health Act No 61 of 2003

### Chapter 8:

- Establishment of one **(coordinated) national blood transfusion service**
  - Grant a licence
  - Licence holder must comply with norms and standards and provide prescribed blood transfusion services
    - Informed consent
    - **Offence for a blood donor to receive any form of financial or other reward for such a donation** except for reimbursement of reasonable costs
    - Use blood or blood product only for medical purposes
    - **Payment reasonably required to cover costs**
  - Minister may **make Regulations** regarding withdrawal, processing, supply, packaging, labelling, records, utilisation, or disposal of withdrawn or imported blood
  - **Appointment and functions of inspectors** of the national blood transfusion service and investigating officers
  - Make **regulations concerning the payment of persons or institutions in connection with blood and blood products**

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**Regulations relating to Blood and Blood Products**

# Legislative Framework - BTSs

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## Regulations Relating to Blood and Blood Products

- Licensing
- Oversight: licence may be suspended or revoked
  - Appoint health officers in DoH
  - **Examine premises or blood or blood product**; demand and examine registers or records, take samples or examine any blood or blood product, place blood product under embargo
  - Report to Director-General any non-compliance
- Blood transfusion service
  - Non-profit, reimbursed for services
  - **Medical practitioner as medical director – take full responsibility** for medical and related activities
  - Recruitment of **donors** according to Standards of Practice
  - **Mandatory testing of donated blood** and blood products
  - **Requisition and administering of blood** and blood products
    - Prescription
    - Identification of recipient and blood sample
  - **Report to Director-General serious or life-threatening reaction or death**
  - Records of donors, donations, statistics and untoward reactions
  - Provide a **clinical consultative service**
  - Comply with the **provisions of the Standards of Practice**
  - Offences and penalties – any person who contravenes or fails to comply: guilty of offence and liable on conviction to a fine or imprisonment not exceeding 10 years



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**Standards of Practice**

# Legislative Framework - RSA

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## Standards of Practice

**Determined by the Minister: authoritative, enforceable**

- **Minimum Standards for the whole chain of processes/procedures and activities from donor to recipient**
  - Collection, storage, processing and issuing of blood and blood products
  - Minimum standards are obligatory
  - Prerogative of blood establishment to introduce standards and criteria over and above those laid down, provided that they supplement the standards and do not modify or are in conflict with them
  - Do not replace detailed specifications and Standard Operating Procedures, but complement the National Health Act and the Regulations underpinning the Act
- Donor, recruitment, selection, deferral, records
- Testing of donated blood, screening algorithm
- Blood and blood components: standards, import and export
- Clinical use: requests, issues, transfusion reactions
- Quality System
- Quality Assurance and Control of Performance; internal and external assessment
- Biosafety and Waste Management

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**Regulations relating to Blood and Blood Products**

**Standards of Practice**

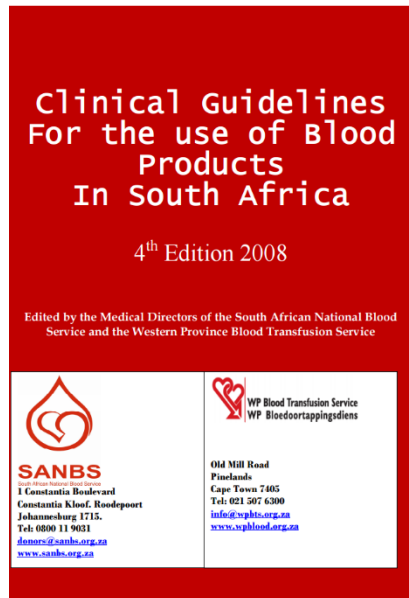
**Blood Transfusion: Clinical Guidelines**

# Clinical Guidelines

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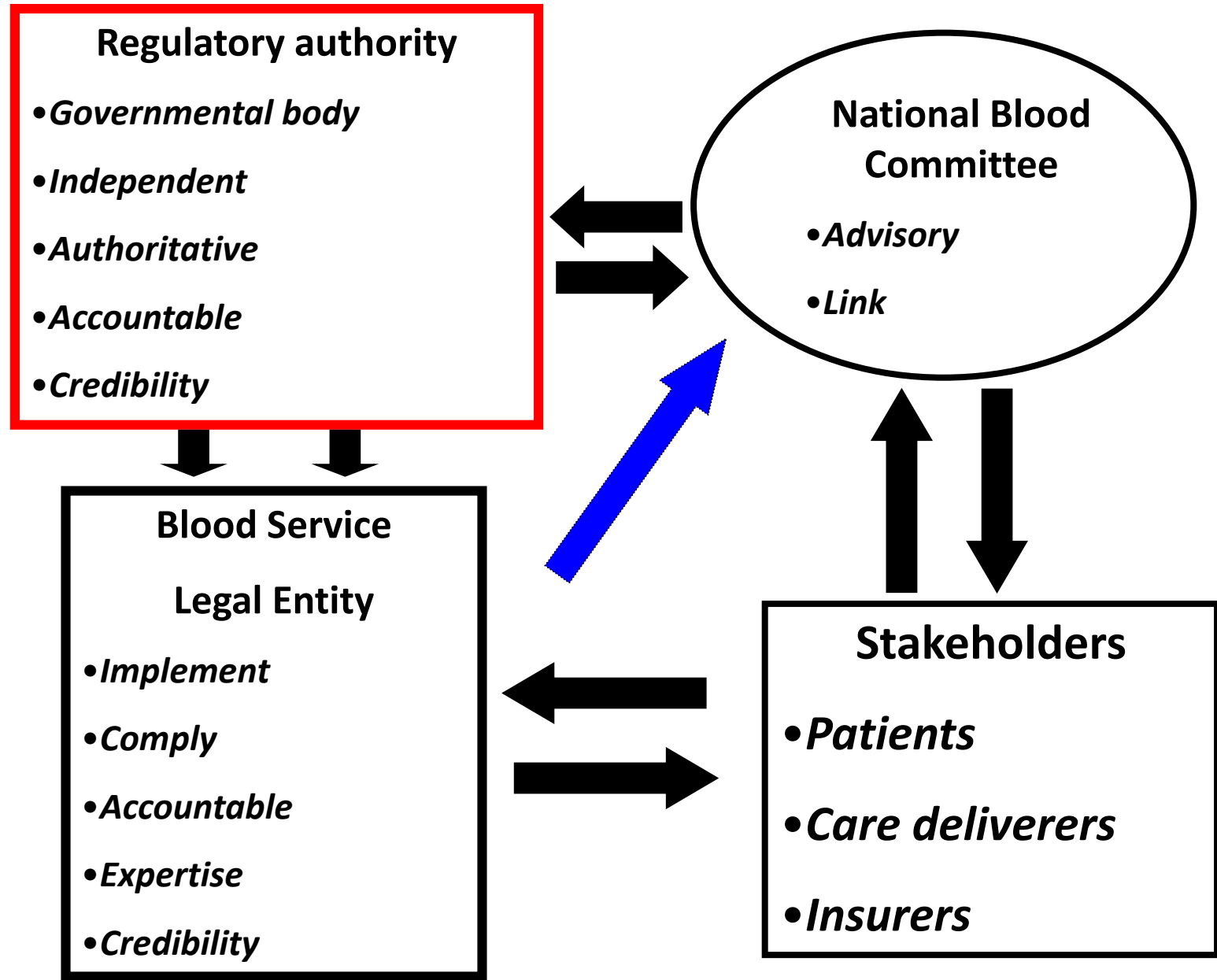
## Contents

- Legal aspects
- Ordering administration blood
- Red cell components
- Leukodepletion
- Platelet Transfusion
- Paediatric Transfusion Practice
- Plasma Components and Derivatives
- Alternatives to allogeneic transfusions
- Risks of Transfusions/Adverse Reactions



# Regulatory Structure: Integrating

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# Comments on Regulation of BTS

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- Blood is regulated as a “tissue transplant” and not as a “medicine”
- The regulatory oversight is deficient: no trained or informed inspectors
- The NRA has no real expertise in blood transfusion
- Blood Services are thus self-regulated
  - To international standards
- Accredited by SA National Accreditation System (SANAS): ISO/IEC 17025
- The blood products prepared and issued by the BTS are not registered
- Vein-to-vein service, but the process for BTS ends when blood is issued

# Legislative Framework - Medicines

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# Legislative Framework - Medicines

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**Medicines and Related Substance Act 101 of 1965**



# Legislative Framework - Medicines

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**Medicines and Related Substance Act 101 of 1965**

**Pharmacy Act 1974**

**Consumer Protection Act 2008**

# Legislative Framework - Medicines

## Medicines and Related Substance Act 101 of 1965

- Establish **Medicines Control Council as a juristic person**
  - Work through external experts who are members of Council Committee structures (Biological Medicines; P & A; and Clinical Committees)
  - Evaluate data sets submitted by pharmaceutical industry for purposes of registration
- Provide for the **control of medicines, scheduled substances, and medical devices**
- Provide for the **licensing of certain persons to manufacture, compound or dispense medicines and medical devices**
- Provide for the renewal, suspension and cancellation of such licences
- **Authorise inspectors to perform power or function under this Act**
- Provide for the **registration of medicines**
- Establish a **pricing committee**
- **Make regulations in support of the Act** and its implementation

To ensure the maintaining of high standards of quality in the manufacture and control of medicinal products the ***MCC Guide to Good Manufacturing Practice for Medicinal Products*** has been adopted

- Derived from WHO GMP Guide; EU and PIC/s GMP Guides; European and other relevant Pharmacopoeia

# Legislative Framework - Medicines

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**Medicines and Related Substance Act 101 of 1965**

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**Consumer Protection Act 2008**

**Regulations and Guidelines pertaining to  
Statute**

# Legislative Framework - Medicines

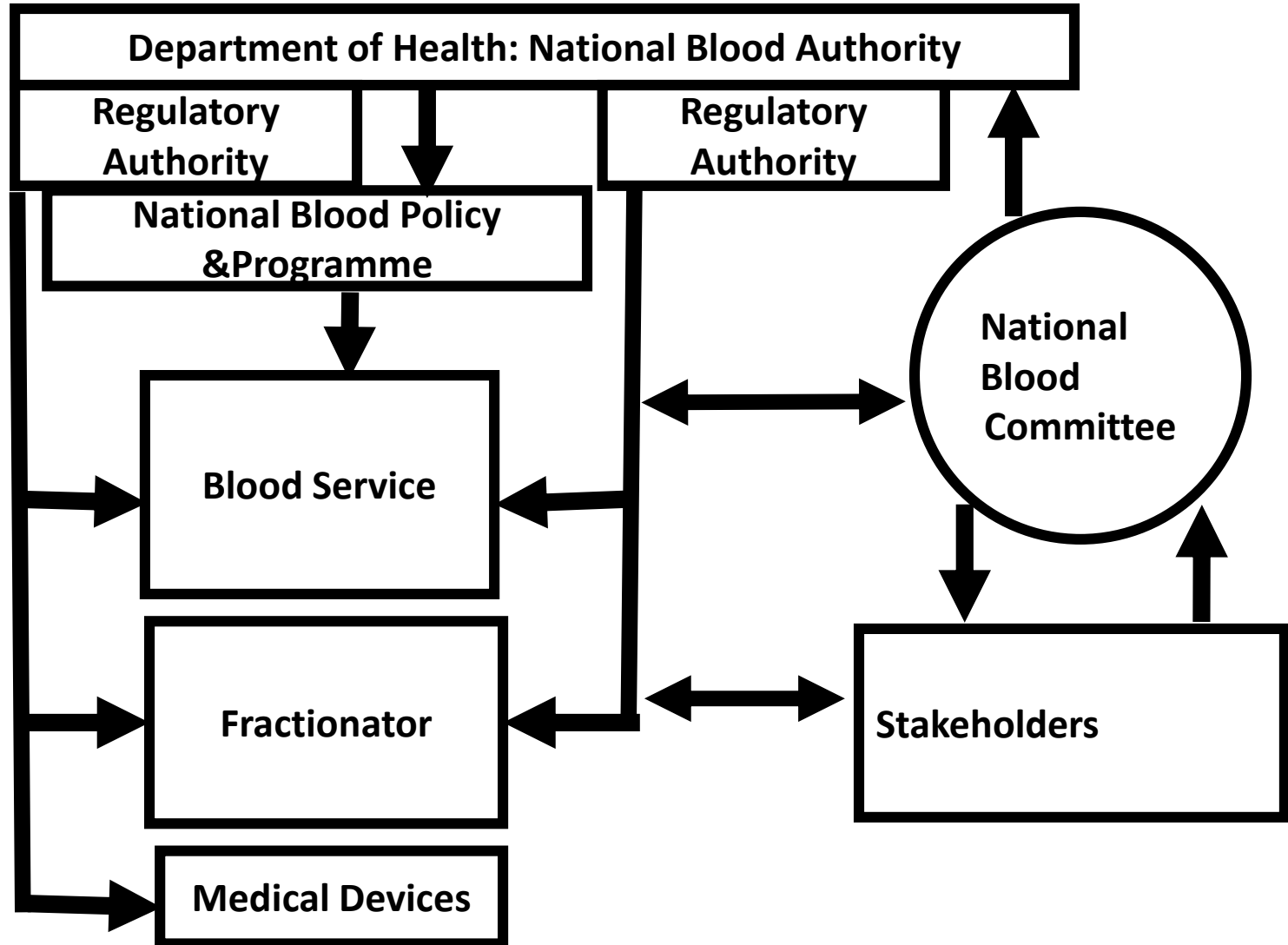
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## Regulations and Guidelines pertaining to Statute

- **Licence to manufacture medicines**
- **Application to register a medicine**
- **Application for amendment to a registered medicine**
- **Conduct of clinical trials**
- Categories and classification of medicines
- **Adverse drug reactions**
- **Guidelines:**
  - Biological Medicines include, but may not be limited to the following:
  - Plasma-derived products
  - Vaccines;
  - Biotechnology-derived medicinal products (rDNA products)
  - Biosimilars

# Legal Framework

**LEGISLATION: ACT OF PARLIAMENT**



# Regulation of Fractionation in RSA

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Some distinctive issues that must be noted and considered

- Source of materials
- Risk of transmitting viral and other diseases
- Viral and pathogen inactivation and removal
- Antibody formation
- Some features of therapeutic response

Plasma is sourced from surplus plasma collected during blood donations from registered RSA BEs

- in special well-motivated circumstances pooled plasma may be imported

# Regulation of Fractionation in RSA

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- **Blood Donors: low risk**
  - Voluntary, non-remunerated
  - Plasmapheresis donors
  - Low prevalence of transfusion transmissible diseases and agents in the donor population
- **Screening for transmissible agents**
  - Range of tests; sensitivity
  - NAT: Individual donation; small pools; final product
- **Plasma Master File**
  - **Traceability** of every donation
  - Epidemiology of TTIs
  - Systems and policies in place to sequestrate potentially contaminated pools
  - **Risk management**; residual risk in plasma vs. virus inactivation capacity of processes
- **Appropriate Haemo- and Pharmacovigilance** systems to identify TTIs
- **Blood Service or facility** from which plasma is sourced must be accredited and conform to highest quality standards
- **Import and export of plasma**
  - There must be policies and systems in place
  - Import of plasma for not-normal source as per registration for specific uses evaluated in terms of quality and safety, its usage authorised and a permit/license issued

# Evaluation of an application to register a PDMP

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- Evaluation of plasma-derived medicinal products comply to the same quality and other standards as other drug products and are according to MCC Guidelines
  - GMP compliance and GMP certification are required
- Dossiers are submitted in the ICH CTD format
  - Module 1 requires information specific for SA
  - Module 2: Quality overall summary
  - Non-clinical and clinical summaries
    - Demonstrate Efficacy and Safety
  - Module 3
    - Quality: Body of data on API and FPP
    - Addresses Raw Materials, including plasma
  - Module 4
    - Non-clinical study reports
  - Module 5
    - Clinical study reports



# Requirements for Plasma for Fractionation

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## Based on

- WHO recommendations
- EU Directive
- Council of Europe Standards
- BP
- MCC Guidelines

## Process to approve BE as plasma supplier

- Fractionator
  - Paper audit that as a minimum requires compliance with certification by the NRA and National Standards for Blood Transfusion
  - Audit requires compliance with a quality management system across the full collection-plasma-patient chain
  - Physical audit focuses on whether facility complies with principles of GMP
  - Segments on plasma units for pooling and NAT testing
  - Electronic system to issue units to fractionator and suitable PMF
  - Physical audit done to demonstrate that there is compliance with GMP standards
- MCC
  - This information is supplied to MCC who will decide whether to approve the BE as source of plasma
  - All levels of the operation may be audited by MCC inspectorate
  - The NRA makes final decision on acceptance of the BE as a source of plasma

# Plasma Master File

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- Starting materials must comply with GMP and specific requirements for PDMP
- **Source materials**, means of collecting these, and their control
  - Common information from collection to plasma pool relevant to manufacture of all intermediates, including cryoprecipitate, and all excipients relevant to the manufacture of medicinal products
  - State medicinal products for which the PMF is valid
  - Quality assurance for collection (overall safety strategy)
    - Establishments where blood/plasma is donated
    - Suitability of donors and criteria for donor selection (includes first time donors)
    - Donation screening (and testing of pools) for viral markers by validated methods
    - Epidemiological Data: annual update
    - Calculation of Residual Risk and measures to reduce the risk
    - Post-collection information system
  - Conditions of storage, inventory hold and transport of plasma
  - Traceability of every donation from donor to finished product and vice versa
  - Updated annually and should be re-submitted for approval
- **Aim to demonstrate that the strategy robustly ensures that all measures taken through the collection to transport chain work together to provide a safe plasma pool**

# Restructuring: SA Health Products Regulatory Authority (SAHPRA)

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- Draft legislation paving way for a new regulatory body for medicines
- Makes provision for a Board appointed by the Minister
- Will cover wider scope of products beyond medicines: medical devices, in vitro diagnostics, traditional medicines, complementary and alternative medicines, and cosmetics
- Envisages recognition of input by other regulators in the statute
- Draft Regulations have just been published for comment
- Capacity building programmes
- eCTD
- Recognises that globalisation is a reality and efforts towards harmonisation should be strengthened

# Personal thoughts: Regional Harmonisation

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- There should be communication between the NRAs of the Region: possibly at the level of and be facilitated through the Southern African Development Community (SADC):
  - Protocol on Health (1999): *coordinate regional efforts on epidemic preparedness, mapping prevention, control and where possible the eradication of communicable and non-communicable diseases. Education and training, efficient laboratory services*
  - SADC Pharmaceutical Business Plan (2007-2013): *aims to ensure availability of essential medicines and to improve sustainable availability and access to affordable, quality, safe, efficacious essential medicines including African Traditional Medicines*
- WHO should support and encourage the advance and harmonisation of blood regulatory systems through regional community and political structures
  - Common standards: roadmap to achieve GMP taking into account that this may be stepwise
  - Facilitate export and import of plasma across borders
- AfSBT could play a role to develop harmonised standards: regional acceptance of standards of the AfSBT Accreditation Programme
- NBI could play a role by discussing regulatory requirements of source plasma with regional NRAs
- The success of such an initiative will rely heavily on commitment, available resources and developing and implementing a properly structured project plan.

# Conclusions

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- Different regulatory systems for blood services and labile blood products and fractionators and PDMPs
- Blood is regulated as a “tissue” and PDMPs as “medicines”
- Medicines Regulatory Authority (MCC) is well structured and the regulatory system conforms to international standards. Manufacturers and suppliers of source materials must conform to GMP
- Blood services in South Africa operate according to the highest international standards, but although the regulatory framework in legal terms is appropriate, it does not function well and the BTSs are “self-regulatory”
- There is a need to harmonise regional standards and develop systems that would allow the import and export of plasma to allow equitable access to PDMPs