# Assessment of Current Needs and Constraints in Southern African Region

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

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# Aim of Presentation

- Problem statement
- Roles of BEs and Fractionator
- Role of Regulator
- Harmonise activities to achieve the goal to satisfy current and future needs
- Suggestions on way forward

# WHA63.12

**SITUATION**

- Unequal access globally to blood products, particularly plasma-derived medicinal products;
- Key limiting factor is an inadequate supply of plasma meeting standards for fractionation;
- Increasing use of blood components in developing countries will make increased quantities of recovered plasma available for fractionation;
- Insufficient regulatory controls and failure to implement appropriate practices in blood establishments results in wastage of plasma in developing countries;

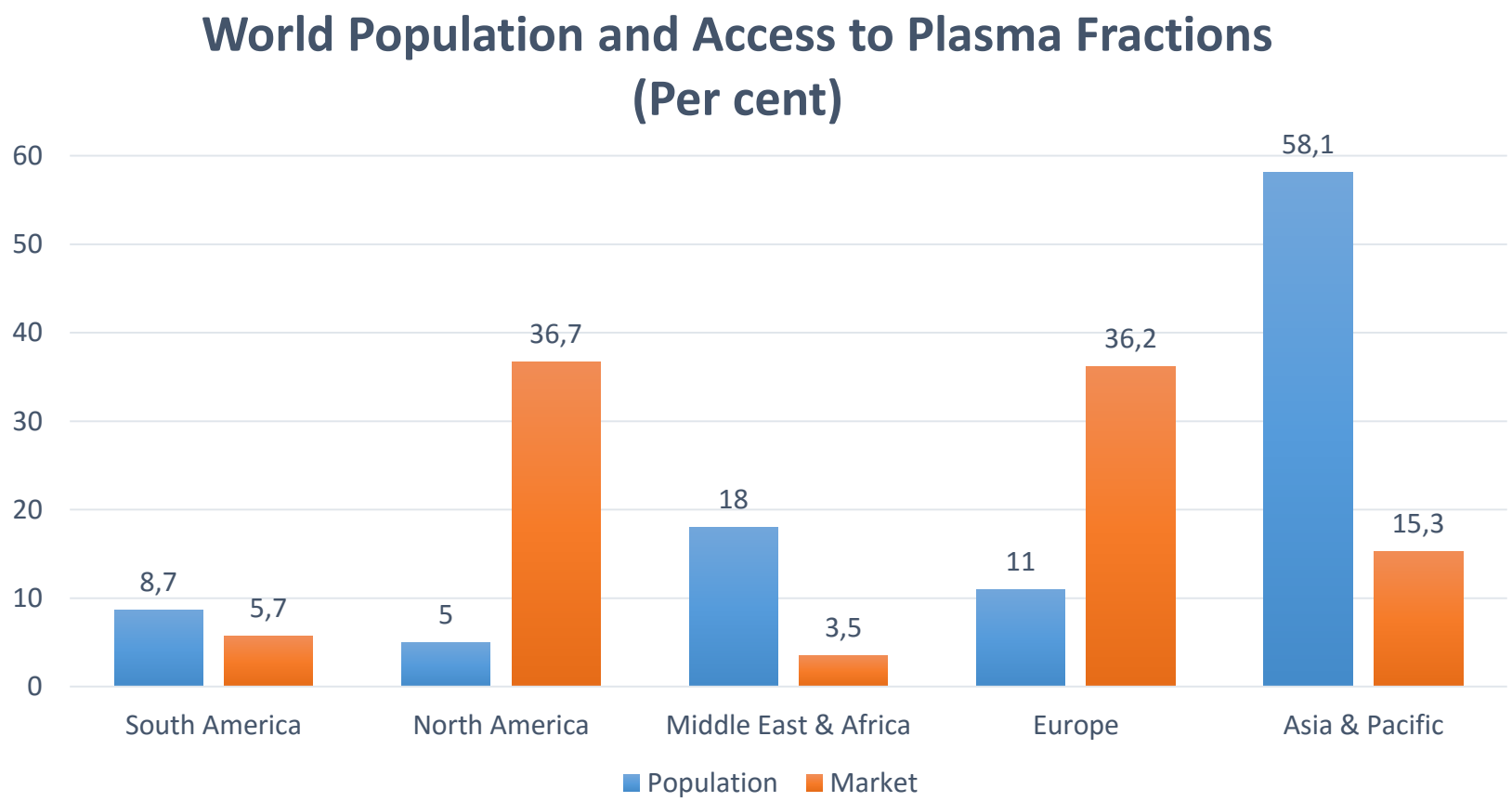
**ACTION**

- Implement nationally-coordinated sustainable blood and plasma programmes according to the availability of resources
- Update national regulations and operation of regulatory authorities across the entire transfusion chain to comply with international standards;
- Establish quality systems, for the processing of whole blood and blood components and good manufacturing practices for the production of plasma-derived medicinal products
- Ensure reliable reporting of serious or unexpected adverse reactions in blood donors and recipients, including transmissions of pathogens

**SUPPORT**

- **REQUESTS the DG:** to develop, provide and disseminate guidance and technical support to strengthen national coordinated blood and plasma programmes to promote these goals.

# Inequality of Access to PDMP (excluding Recombinant Factors)




Source: Patrick Robert, MRB, 2011

# FVIII Usage: Africa and Globally (2006)

| Country | Economy | IUs/capita | IUs/PWHA |
|---|---|---|---|
| South Africa | Upper middle | 0.59 | 20 028 |
| Zimbabwe | Low | 0.24 | 10 556 |
| Senegal | Lower middle | 0.0029 | 354 |
| Nigeria (2005) | Lower middle | 0.0004 | 1 563 |
| Lesotho | Low | 0.18 | 22 906 |
| Kenya (2004) | Low | 0.03 | 2 416 |
| India | Low | 0.008 | 854 |
| Cuba | Upper middle | 0.02 | 866 |
| Brazil | Upper middle | 1.19 | 32 525 |
| USA | High | 5.32 | 135 378 |
| Germany | High | 6.78 | 138 101 |

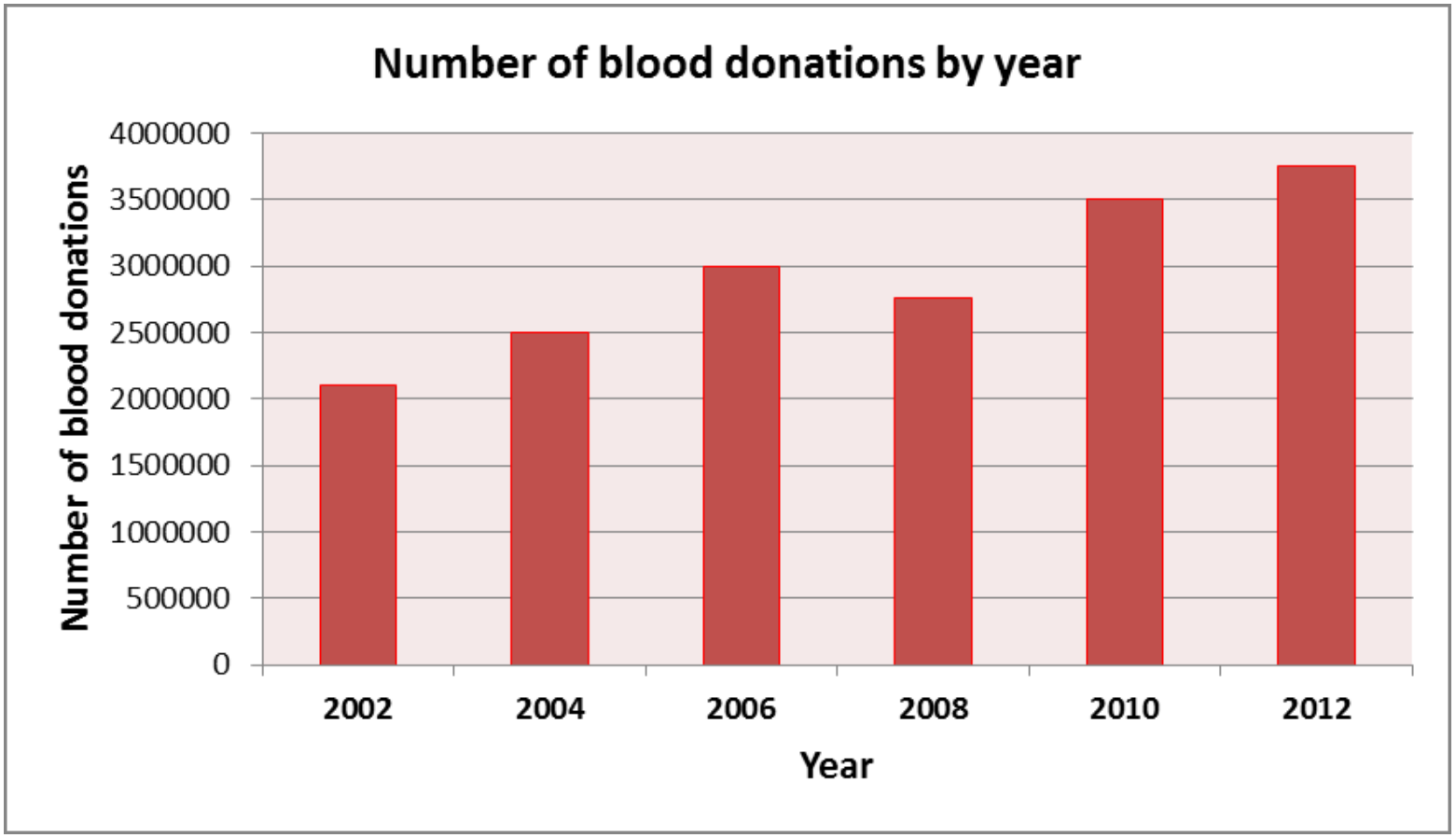
Source: Stonebraker et al: Haemophilia (2010), 16:33

# ACTIONS INSTITUTED

- 51st session of WHO Committee for African Region adopted strategies to promote implementation of WHA 63.12
- Achilles Project: In June 2012 and in October 2012 stakeholders and WHO discussed the feasibility of local production of plasma for fractionation and how to best deal with the recovered plasma as API
  - Build on RSA experience as a model of fractionator/BE cooperation in an epidemiological challenging environment
  - Identify two other countries in sub-Saharan Africa to serve as model for the implementation of a like programme
  - Cost-benefit analysis in blood services and investigate opportunities for technology transfer and potential fractionation of plasma
- AfSBT: *Surplus Plasma for Fractionation (Johannesburg; November 2012)*
- WHO Workshop on Blood Regulatory Systems. *Building national capacity for improving access to blood products (Johannesburg; September 2013)*
- WHO Essential Medicines List 2014:

  *Blood Products of Human Origin and Plasma Substitutes*
  - **Blood and blood components: *FFP, Platelets; Red Blood Cells; Whole Blood***
  - Plasma-derived Medicines: Human Immunoglobulins; Blood Coagulation Factors VIII and IX
- AfSBT Step-wise Accreditation Programme structured, funded and implemented

# WHO AFRO Region: Donations per year




**45% Requirements in 2012**

# Blood Safety in WHO Afro Region

| Indicator | 2006 | 2010 | 2014 |
|---|---|---|---|
| VNRD:80-100% | 45% | 44% | 79% |
| Donor recruitment programme (≥10/1 000) | 11% | 11% | 20.4% |
| National Blood Policy<br>Implemented | 30%<br>55% | 56%<br>67.4% | 97.5%<br>75.6% |
| Regulatory System | 25% | 26% | 54.7%<br>(Implemented: 22%) |
| Adequate Funding<br>Budget/cost recovery | 38% | *"Low funding"* | 81%<br>(52% cost recovery) |
| Screening: 100%<br>(HIV; HBV; HBC) | 95%; 83%;<br>59% | 97.7%; 83%;<br>83.7% | 97.6%; 92.8%;<br>90.5% |
| Blood components | RBC 73% & Pl<br>57% | RBC 88%; Pl 68%<br>FFP 68% | RBC/Pl/FFP: 62% of all donations |
| Cold chain | 39% storage;<br>24% transport | 74.5%;<br>51.8% | N/A |

# Key Findings: Discard plasma

| | Total annual collections (approximate) | Estimate of potential recoverable plasma (litres) | |
|---|---|---|---|
| | | **100%** | **50% repeat donors** |
| Kenya | 230 000 | 37 950 | 18 975 |
| Malawi | 50 300 | 8 300 | 4 150 |
| Namibia | 25 000 | 4 125 | 2 063 |
| Tanzania | 230 000 | 37 950 | 18 975 |
| Uganda | 220 000 | 36 300 | 18 150 |
| Zambia | 110 000 | 18 100 | 9 500 |
| Zimbabwe | 80 000 | 13 200 | 6 600 |
| | **TOTAL** | **155 925** | **77 963** |

Mvere (2012): adapted
Chipare (2012): adapted
Assumptions: 220 mL per unit whole blood
25% of plasma used within country

# Models to satisfy need for PDMP

**Import PDMP**

- Satisfy local needs
- Meet quality, efficacy and safety needs
- Country plasma does not qualify for fractionation (GMP standards)

**Utilise local plasma for contract fractionation**

- Contract fractionation models
  - Sell plasma to fractionator and purchase PDMP to satisfy needs
  - Pay a processing fee to fractionator and use PDMP in the country
  - Criteria in terms of plasma volumes, continuity of supply, product portfolio (at least 3 products) and contract terms should be developed and evaluated
- Examples of contract fractionation programmes
  - France: Brazil, Morocco, Tunisia
  - Australia: Hong Kong, Malaysia, New Zealand, Singapore, Taiwan

**Benefits**

- Sustainability of BEs enhanced: surplus plasma utilised rather than discarded
- Quality system of the blood service is enhanced: quality and safety of all blood components all processes benefit from moving towards GMP

**Regulatory framework** of both the plasma supplier and fractionator should be "compatible" and allow cross-country movement of plasma and PDMP

# Potential Benefits of Contract Fractionation

| NBI Average Yield: | IU/g/L | |
|---|---|---|
| FVIII | 210 | IU |
| IVIG | 4,3 | g |
| Albumin | 23 | g |
| FIX | 191 | IU |

| | Plasma supplied by BE | | |
|---|---|---|---|
| **Finished Product** | **4 000 L** | **10 000 L** | **20 000 L** |
| **20% 50 mL Albumin** | 8 364 | 20 909 | 41 818 |
| **FVIII (500 IU)** | 1 561 | 3 903 | 7 807 |
| **IV IG** | 2 774 | 6 935 | 13 871 |
| **FIX (500 IU)** | 1 455 | 3 638 | 7 276 |

# Justification for Regulation

- Regulatory Authority uses variety of tools to assure that safety and quality standards are satisfied at every level
  - Licensing and registration of the facility
  - Reviews of dossiers related to products, operating procedures, and personnel
  - External accreditation against international standards may be supportive
  - Trained inspectors do physical inspections and audits to ensure compliance with standards: focus is on quality systems, records of process validation, quality control testing, compliance with SOPs, handling of deviations
- Regulatory Authority must have power to enforce actions: license, legal actions such as warning letters, seizure, import detention, injunction and prosecution

# Process Control: Plasma

- Stringent process control steps: plasma separated from whole blood or collected by apheresis
  - Generally plasma suitable for FFP would satisfy the standards for plasma for fractionation
  - Deviations from best practice may affect plasma or PDMP quality
  - Plasma quality is a relative term: different requirements for stable products (albumin) or labile end-products (coagulation factors)
    - Plasma for coagulation factors: standards for freezing and storage; plasma FVIII levels good indicator for plasma quality
- Standards of collection and processing of blood are generally codified as GMP

# GMP for Blood Establishments

***WHO: Guidelines on good manufacturing practices for blood establishments; Recommendations for the control and regulation of human plasma for fractionation***

- Quality management
  - QA; Product quality review; Quality risk management; change control; deviation handling; corrective/preventative actions; internal audits
- Human resource management
- Documentation
  - SOPs; records; document control
- Premises and equipment
- Qualification and validation
  - Equipment; manufacturing processes; test systems to screen for TTIs; assay performance
- Management of materials and reagents
  - Receipt and quarantine; storage; traceability; supplier management
- Manufacturing
  - Donor selection; epidemiological surveillance of donor population; component preparation; laboratory testing; release; storage; distribution; transport
- Contract manufacturing, analysis and services

***WHO: Assessment Criteria for National Blood Regulatory Systems*** includes assessment for compliance with GMP

# NAT Screening

- Not essential and not a solution for all countries
- Depends on country and health priorities
  - Is the international standard
  - Based on risk assessment: viral load; window period risk; viral inactivation and clearance capacity of manufacturing process
- Possibility of collaborations in regions should be considered
- Minipool NAT screening introduced by fractionators
  - Cost-effective
  - Must be validated
- Ethical issue: Must be able to trace donor and inform the donor and BTS of a positive test result

# Legislative Framework - Medicines

**Constitution**

***Bill of Rights***

***Access to health care services***

***Equality***

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

**Pharmacy Act 1974**

**Consumer Protection Act 2008**

**Regulations and Guidelines pertaining to Statute**

# Legislative Framework - BTSs

**Constitution**

***Bill of Rights***

***Access to health care services***

***Equality***

**National Health Act No 61 of 2003**

**Regulations relating to Blood and Blood Products**

**Standards of Practice**

**Blood Transfusion: Clinical Guidelines**

# Regulation BTSs in Southern Africa

- In Southern Africa the regulation of BTSs are not regulated and licenced as manufacturers of biological medical products under GMP
- This does not preclude a BTS to achieve this standard, but there is a discord between regulatory requirements and standards and the aims of the BTS
- Accreditation to an international, regional or country standard by a recognised Accreditation System is supportive, and may be an instrument to facilitate the transition to GMP

# MCC: Evaluation of application to register a PDMP

- Evaluation of plasma-derived medicinal products comply to the same quality and other standards as other drug products
  - **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

# Plasma Master File

- **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
    - Estimate of residual risk for viral contamination of plasma pools
    - Post-collection information system
  - Conditions of storage, inventory hold and transport of plasma
  - Traceability of every donation form donor to finished product and vice versa
  - Updated annually and should be re-submitted for approval
- **Aim to demonstrate that the process is robust and ensures that the measures taken in the collection-to-transport chain provide a safe plasma pool**

# NBI: Requirements for Plasma for Fractionation

*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 submitted to MCC
  - 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

# Regulation by NRA: Summary

- Regulation of blood and blood derived products is intended to protect donor health and to ensure the quality, safety, and efficacy of the products
- The essential elements of the regulatory programme include a national coordinated blood transfusion system functioning under an appropriate and competent regulatory authority with powers of injunction
- Products are regulated under defined standards including GMP
- Quality and safety are monitored through an approvals process, inspections and safety reporting

# Regulation by NRA: Summary (2)

- Internationally recognised best practices for blood collection and processing are widely available
  - In general, “Fresh Frozen Plasma” meets international standards for plasma for fractionation
- Blood establishments in a given country may not be able to implement everything that is described in published blood standards, however:
  - Could be implemented step-wise by regulator setting goals
  - Blood quality measures can be added incrementally
  - Implementation process may be supported by an Accreditation System with appropriate standards
    - AfSBT Stepwise Accreditation Programme: Accreditation Step 3

# Challenges

To establish, implement and support sustainable blood and plasma programmes towards self-sufficiency in low-income countries

- Limiting factors
  - Regulatory oversight of blood services
  - Comply with the requirements for the collection, processing quality control of blood and blood components
  - Comply with the requirements, to the GMP standard, for the production, control and regulation of recovered or source plasma for fractionation
  - Lack of financial and human resources
- Consider in the context of country health priorities and country economic status

# Possible Way Forward

- Develop a Regional database
  - Country: needs for PDMP ; plasma available for fractionation
- NBI should state its capacity for current and future manufacture of PDMP, product range, quality standards for source plasma, minimum plasma available for contract fractionation
- Regional BEs should engage in discussions with NBI on issues regarding contract fractionation
- NRAs should be strengthened, and address
  - Incremental introduction of GMP in a step-wise fashion by NRA setting goals and using Standards of Practice and Accreditation Standards as point of departure
  - Issues of regulation of BEs as manufacturers of biological medicines under GMP
  - Register labile blood products as medicines
  - Assure that surplus plasma complies with GMP standards
  - Regional NRAs should be harmonised to enable export and import of plasma across borders and Regional Standards of Practice

# Possible Way Forward (2)

- WHO should facilitate strengthening of NRAs, blood product regulation, and implementation of GMP in blood services
- AfSBT Stepwise Accreditation and Educational Programmes should be fully supported and utilised as important resources to achieve GMP
- Develop a coordinated realistic regional plan with a few, simple easily measured and understood indicators to measure progress against objectives (targets) to evaluate the effect of policy actions and plans, and to identify areas for increased attention

# Conclusions

- The African BEs have made considerable progress to provide sufficient safe blood in their countries
- Competent NRAs should oversee BEs and enforce blood standards in the Region
- BEs should be regulated as manufacturers of biological medicinal products under GMP
- The Regional Standards should be harmonised to permit export and import of plasma across borders
- Wastage of surplus plasma can only be avoided by production of plasma to recognised GMP standards and using it for fractionation

# Conclusions

- Countries should do a need assessment for PDMP and estimate the surplus plasma that could be used for fractionation
- The Regional Fractionator should state capacity for manufacture of PDMP and the quality standards for plasma as a starting material
- The Regional NRAs, BEs and Fractionator should develop a coordinated realistic regional plan, with a few, simple easily measured and understood indicators to measure progress against objectives (targets) to evaluate the effect of policy actions and plans and to identify areas for increased attention
- The AfSBT Stepwise Accreditation Programme is an important tool to promote and facilitate capacity building to achieve GMP

# Word of Caution

***Law of Unintended Consequences***

- Unrealistic demanding regulatory requirements for BEs and standards for plasma used for fractionation may compromise the viability and sustainability of BEs and increase plasma wastage
- Introduction of GMP and regulation of labile blood components as medicines: do not break what works

***Law of Diminishing Returns***

- There is an inverse relationship between returns of inputs and the cost of achieving these
  - Cost of GMP and PDMP availability

***Johann Wolfgang von Goethe***
***1749-1832***

**Knowing is not enough; we must apply. Willing is not enough; we must do.**

**Everything is hard before it is easy**