



Plasma fractionation in South Africa: challenges and successes in meeting international standards

Jeh-Han Omarjee, Willem Andreas Germishuizen, Rangini Chetty, David Stubbings

National Bioproducts Institute, Durban, KwaZulu Natal, South Africa

Contributions: (I) Conception and design: JH Omarjee, WA Germishuizen; (II) Administrative support: JH Omarjee, WA Germishuizen; (III) Provision of study materials or patients: JH Omarjee, WA Germishuizen; (IV) Collection and assembly of data: JH Omarjee, WA Germishuizen; (V) Data analysis and interpretation: JH Omarjee, WA Germishuizen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Andre Germishuizen. 10 Eden Road, Pinetown, 3610, KwaZulu Natal, South Africa. Email: andre.germishuizen@nbisa.org.za.

Abstract: Africa represents a challenge to the provision of plasma-derived medicinal products (PDMPs) as there are many competing health priorities on a continent with limited investment and resources to support some of the poorest nations. To compound this, the availability of suitable plasma, although improving, severely limits better access to PDMP for patients in the region. The National Bioproducts Institute NPC (NBI), as a fractionator in South Africa, illustrates a model of local fractionation which successfully addresses some of the dilemmas faced by lower resourced countries in the broader African context. NBI is a relatively small fractionator in the South African pharmaceutical manufacturing landscape, which is characterised by rigorous local and international regulatory requirements, a volatile currency and restrictive pharmaceutical pricing practices. Further, NBI is confronted by a constantly evolving regulatory and operating environment, a paucity of active raw materials, dynamic market trends and variable patient demand for plasma derivatives, as diagnosis of many of the clinical conditions for which plasma derivatives are indicated, improves. Despite these challenges, NBI remains a sustainable and viable local fractionator, positioned to realise its strategic intent of providing accessible, affordable and a comprehensive range of essential PDMPs to patients in South Africa and the Southern African Development Community region. A key to NBI's success is the strategic partnerships with the South African Blood Transfusion Services (BTS) and other industry associations, as well as a good working relationship with the local regulatory authority, the South African Health Products Regulatory Authority (SAHPRA).

Keywords: National Bioproducts Institute (NBI); plasma derived medicinal products; South Africa; plasma fractionation; Southern African Development Community

Received: 27 October 2017; Accepted: 09 January 2018; Published: 23 January 2018.

doi: 10.21037/aob.2018.01.02

View this article at: <http://dx.doi.org/10.21037/aob.2018.01.02>

Introduction

Human plasma contains more than 1,000 proteins and more than 30 of these plasma protein concentrates are available as plasma-derived medicinal products (PDMP) to treat a range of conditions including haemophilia A and B (Factor VIII and Factor IX deficiency, respectively), primary immunodeficiencies, Guillain Barré syndrome and immune thrombocytopenic purpura (1). Several of these plasma protein concentrates are included in the World Health

Organisation (WHO) Model Lists of Essential Medicines (EML) (2) to guide allocation of scarce healthcare resources in low and middle income countries and ensure the availability of these medicines in public health care (3).

Despite EML listing, sufficient access to safe and effective PDMPs in sub-Saharan Africa remains a challenge as there are many competing health priorities on a continent with limited resources and healthcare investment (4). Other challenges in the African public health landscape include,

inter alia, high burden of disease, limited sophistication of diagnosis, lack of cold chain and inadequate distribution networks, the disconnection between progressive healthcare and regulatory policies and their actual implementation, and the limited availability of human resources in the healthcare sector, especially critical care (5,6).

In June 2012, a workshop for stakeholders was held at the WHO headquarters to discuss the accessibility of PDMPs in the sub-Saharan African area. The discourse focused on the feasibility of establishing local plasma fractionation that would supply sub-Saharan Africa (4,5). Over and above the general challenges that face the continent, several limitations were outlined by African member states that hindered the achievement of goals specifically for local plasma fractionation. These limitations included, inter alia, the lack of a legal framework and strong governmental support to establish a regulatory framework to support a national blood policy. The lack of adherence and compliance to generally-accepted international standards for processing blood donations to ensure recovery of good quality plasma despite the high burden of disease was acknowledged. The absence of National Regulatory Authorities for blood products to enhance the quality of evaluation and regulatory oversight in the area of blood products was highlighted as a weakness. Lastly, the lack of leadership and governance coupled with strong political support for defining clear milestones, selecting dedicated key leaders, and ensuring the commitment of well trained and skilled manpower, and the unavailability of technology transfers required for fractionation plant design, validation and operation were also recognized as limitations (4).

The National Bioproducts Institute NPC (NBI) is a South African plasma fractionator that manufactures, markets, sells and distributes a range of PDMPs to the South African and other regional markets (7). NBI illustrates a model of local plasma fractionation that provides affordable, safe and efficacious PDMPs that comply with international manufacturing and safety standards, notwithstanding the numerous constraints affecting sub-Saharan Africa and specifically South Africa.

This article focuses on the challenges facing plasma fractionation in South Africa to meet constantly changing local and international standards that govern the manufacture of PDMPs, and highlights NBI's approach to successfully overcome these challenges to ensure compliance and availability of affordable and safe PDMPs to patients.

NBI as a model of sustainable plasma fractionation in South Africa

Like many other fractionators, NBI has its roots in local blood transfusion. NBI originally commenced operations in the late 1960s as part of the local blood transfusion service (BTS) and was established in 1994 as an independent pharmaceutical company. NBI's product portfolio of liquid and lyophilized PDMPs includes blood coagulation factors Factor VIII (FVIII) and Factor IX (FIX), albumin, fresh dried plasma, polyvalent intravenous immunoglobulin (IVIG) and anti-D, anti-tetanus and anti-rabies intramuscular immunoglobulin (IMIG) products (7). These products are included in the South Africa Essential Medicines List (8). NBI's PDMP manufacturing processes are based on Kistler and Nitschmann cold ethanol fractionation (9). NBI currently processes approximately 200 kL of plasma annually to meet more than 80% of therapeutic requirements of South Africa and regional markets in terms of range and quantity. Plasma is procured from the local BTS and contributes, on average, more than 50% of production costs. Notably, NBI and the BTS are self-funded using a fee-for-service/product model.

Local operating conditions are underpinned by the epidemiological profile of South Africa's population and its impact on the safety and availability of plasma for fractionation, the disparity between public and private healthcare, the highly regulated pricing of medicines and affordability of PDMPs in the context of a volatile local currency, as well as the level of sophistication of the local medicines regulatory authority.

Evolving international standards, local regulatory expectations and the drive in the South African market for modern PDMPs compels NBI to modernise its product range and manufacturing technology to align to that of the so-called developed world markets. Further, patient expectations propel NBI towards pursuing first world technology related to product safety, ease of product administration and extension of therapeutic half-life of products, for example FVIII (10,11), while at the same time maintaining the affordability of its products.

However, the development of a new product can be arduous in the context of capacity constraints, escalating demand that dissuades lengthy production down time, clinical trial requirements, and high capital costs. Therefore, to contend with these formidable challenges and meet customer demand, NBI engages in technology transfers and subsequent acclimatisation of its products

to local conditions rather than undertaking its own new product development. To this end, modernisation of NBI's production processes and product range aims to optimise yields and maximise output, thereby reducing the impact of additional capital and other expenditure on production costs.

Access to sufficient quantities of safe and quality raw materials and/or intermediates is essential for ensuring continued supply of NBI's products to patients. Consequently, as the local and regional PDMP market expands, NBI is compelled to locate and secure additional sources of plasma for fractionation and intermediates to supplement the plasma purchased from the local BTS. Notably, the stringent plasma safety and quality requirements, coupled with the rigorous and lengthy approval process for new raw material sources adds another challenge to NBI's operating environment.

NBI remains reasonably agile and appropriately adapts and positions itself to continue anticipating and responding to changes in its regulatory and operating environment, despite the various challenges to meeting regulatory and international standards which are further elucidated below.

Challenges facing local plasma fractionation

Regulatory environment

Plasma derivatives in South Africa are governed by pharmaceutical manufacturing regulations. NBI is licensed as a manufacturer of PDMPs in terms of the Medicines and Related Substances Act 101 of 1965 and is registered locally as a Manufacturing Pharmacy, in terms of the Pharmacy Act 53 of 1974. The South African Health Products Regulatory Authority (SAHPRA) (formerly known as the South African Medicines Control Council, or MCC) is the national regulatory authority that applies standards that control the manufacture, distribution, sale and marketing of medicines (12).

The SAHPRA has been a member of Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) since July 2007 (13), and an observer of the European Pharmacopoeia Commission since July 2013. These international instruments facilitate constructive co-operation and exchange of information and mutual recognition of inspections with regard to current good manufacturing practice (cGMP) between South Africa and participating pharmaceutical inspection authorities (14). Hence, the environment governing all aspects of production

of PDMPs from the raw materials to the fractionation processes and the distribution and administration of final products to patients is highly regulated to meet international cGMP standards.

Due to its alignment with other participating health agencies and countries of the PIC/S, the regulatory expectations of the SAHPRA is akin to international standards with professional views abiding by the PIC/S guideline and first world manufacturing, automation and process analytical technology (13). This mutual recognition and harmonisation of the regulatory requirements therefore makes it imperative for NBI to meet these international standards by acquiring relevant first world technology and expertise in cGMP in the field of plasma derivatives.

As an observer of the European Pharmacopoeia Commission, the SAHPRA follows the European Pharmacopoeia (Ph. Eur.), and NBI is therefore governed by the various Ph. Eur. monographs on PDMPs. Any changes to these monographs therefore need to be evaluated and duly incorporated by NBI, as appropriate (15).

Management of dossier changes

NBI is mandated to notify SAHPRA of any change to its raw material suppliers, quality control (QC) analytical tests, manufacturing processes, product formulations and specifications for assessment. A change to a registration dossier in South Africa is known as an "amendment" (14,16). The nature of the amendment in terms of the probability that the change will impact the quality or performance of a dosage form, prescribes the category in which it is evaluated. This consequently determines the filing mechanism, the approval timeline (if any) and the documentation requirements that must be satisfied (14).

Major changes to an approved registration file in South Africa are assessed under the Type C category. Amendments of this type are considered to have a significant impact on the quality and performance of a dosage form, and therefore written approval from the SAHPRA is required prior to implementation. This is the highest category of change and is analogous to the type II classification used to assess major variations in the European Union (EU). In the EU, a Marketing Authorisation Holder (MAH) typically anticipates approval of a type II variation after 60 days (14). However, in South Africa, evaluation and subsequent approval of Type C changes is excessively lengthy and, based on NBI's experience, may take as long as 2 years.

Currently in South Africa there is no renewal

process as available in the EU, which further restricts the opportunities available to file minor updates to the dossier (14). However, such amendments are captured in the “Amendment Schedule”, located under the Common Technical Document (CTD) section 1.2.1 (17), and list all changes made to the dossier from the date on which the registration certificate was granted through to the present day. One of the challenges facing South African pharmaceutical companies is the dossier conversion from the existing format to the more comprehensive CTD format, as mandated by the SAHPRA.

In summary, effective management of product registrations by the national regulatory authority is critical for pharmaceutical companies to deliver much needed medicines to the patients in good time. However, the lengthy approval timelines, coupled with the requirement for harmonisation of dossier content to the CTD format, and the international expectations by the national regulatory authority presents a significant challenge to NBI in seeking to achieve on-going compliance of its product portfolios in the dynamic market and meeting the needs of its customers.

Plasma for fractionation

Access to plasma for fractionation

Presently the South African BTS are self-regulated and guidelines for blood establishments pertinent to plasma production for fractionation are contained in the Standards for Practice for Blood Transfusion, albeit in less detail than provided in developed countries. To overcome this and to ensure good quality plasma is produced by the BTS, NBI's specification for the supply of fresh frozen plasma (FFP) clearly determines the required characteristics for the supply of plasma to NBI and is based on international guidelines for plasma for fractionation. Further, NBI provides regular guidance and audits the BTS to control and monitor the quality and safety standards to satisfy its requirements. Over many years, this process has led to a positive and constructive working relationship between NBI and the BTS and contributed to the strengthening of infrastructure of the national blood system in South Africa to support the concepts normally associated with plasma fractionation. Positive improvements to the system took place on many levels, including: (I) cooperative cold chain management to improve plasma quality and maximize plasma availability; (II) adoption of a closed system for plasma extraction to reduce the risk of contamination; (III) introduction of blast plasma freezing to improve the quality of FFP for fractionation

and therapeutic use; (IV) strengthening of GMP process control and status management; (V) joint initiatives for risk mitigation; and (VI) enhanced information technology systems.

Improved health care in South Africa has led to an increased demand for blood, blood components and PDMPs (18). The market growth translates into a defined quantity of active raw materials which need to be procured as FFP. In Europe and the US, excess plasma not required for transfusion is directed to the manufacture of PDMPs (3). Leading plasma fractionators acquire blood collection centres to vertically integrate into their active raw material supply chain, allowing the industry to support increased growth in worldwide PDMP market by increased plasma collection mainly through plasmapheresis (19). However, NBI has no control over the local supply of plasma for fractionation as the South African BTS, i.e., the South African National Blood Services (SANBS) and Western Province Blood Transfusion Services (WPBTS), are independent organisations, and NBI is therefore dependent on the incremental increase in recovered plasma availability as a result of blood collection (20). Further, augmented plasma collection through plasmapheresis is not currently available in South Africa. NBI will therefore have to import FFP or partly processed fractions of plasma, called plasma intermediates, from other PDMP manufacturers to supplement the limited increase in plasma collections by BTS. Similarly, hyperimmune plasma, used to manufacture immunoglobulins for passive immunisation against Rabies, Hepatitis B, Tetanus, Varicella zoster and antenatal anti-D prophylaxis, is not readily available and NBI has to supplement local supply to ensure a strategic stock at all times, using qualified international suppliers.

NBI follows a rigorous qualification process to provide assurance of the safety and quality of its active raw materials, including an audit of the facilities and documentation such as the plasma master file (PMF), which should contain a certified copy of the supplier's license to operate as a BTS and any other relevant accreditation. In addition, local suppliers of plasma for fractionation must be licensed in terms of Chapter 8 of the National Health Act 61 of 2003 (21). Only plasma of human origin, collected by a licensed BTS from healthy blood donors by either whole blood donation or plasmapheresis, is acceptable for fractionation. The supplier has to comply with local standards of practise for blood transfusion and relevant guidelines such as the Council of Europe Recommendation of 29 June 1998 “On the suitability of blood and plasma donors and the screening

of donated blood in the European Community (98/E463/EC)” (22); Recommendations of the Council of Europe “Guide to the preparation, use and quality assurance of blood components” as amended (23), and the World Health Organisation Expert Committee on Biological Standardisation (24). Reference must also be made to the WHO Guidelines on Good Manufacturing Processes for Blood Establishments (25) to establish a reliable quality assurance system for the whole chain of blood collection. In addition, reference should be made to the Commission Directive 2004/33/EC of 22 March 2004, which provides recommendations on technical requirements for blood and blood components (26). Further, the guidelines adopted by the CPMP, in particular “Note for Guidance on Plasma Derived Medicinal Products” (27), which cites the requirement for a PMF, has to be adhered to. An updated PMF and/or information required to populate the PMF, has to be submitted to NBI on an annual basis.

It must be noted that the world-wide availability of surplus plasma for fractionation and intermediates can be sporadic, providing a challenge to identify, qualify and register additional non-South African suppliers for both FFP and intermediates, when coupled with the long lead time to obtain approval from the SAHPRA. Additionally, the volatile South African currency is impeding as imported materials are more expensive and significantly contribute to the cost of manufacture of PDMPs in South Africa. In 2010, at the World Health Assembly, a development programme called the Achilles Project was introduced (5). The WHO convened regional meetings that deliberated on blood safety and regulatory requirements and mechanisms to access recovered plasma from African countries in quantities that would ultimately satisfy the growing need by NBI and others for more active raw materials (5). It was envisaged that the work of the Africa Society for Blood Transfusion (AfSBT) to improve the quality systems and structures in BTS in the SADC and other African countries in the region (28) in the short-term could also provide additional revenue for the BTS concerned and lead the way to NBI procuring plasma from new sources as well as supplying PDMP back to these countries. In practice, the cost of compliance with NBI plasma specifications, availability of funding for the various BTS infrastructure development, transport and logistics to NBI and supply contract duration have resulted in slow progress with the project. Although there are several countries progressing well with the process of being accredited, to date, only plasma from Namibia has satisfied all the requirements for the provision of plasma for

fractionation.

Plasma safety

Transfusion-transmitted infections (TTI's) remain a formidable problem in Africa, including South Africa. The transmission of blood-borne infectious agents is well understood as a potential major risk associated with PDMPs. Therefore, several robust safety measures are in place to ensure the safety of plasma for fractionation.

At the outset, the BTS follow an integrated blood safety policy to ensure the safety of blood and plasma supply of the country (29). Significant efforts are expended on the education, recruitment, selection and retention of safe blood donors including education on lifestyle risk reduction for prospective and active blood donors (28). All donors at risk of exposure to human immunodeficiency virus (HIV), Hepatitis B (HBV) and C (HCV) infections, as well as syphilis and other transfusion transmissible infections, are deferred from donating. In addition, all blood in South Africa is collected exclusively from voluntary non-remunerated donors. These risk mitigation measures have been proven to be effective and robust over many years (30,31).

In recognition of the risks associated with all donations, the BTS ensure that every unit of blood is tested for HIV-1, HBV, HCV and syphilis. State of the art testing, referred to as individual-donation nucleic acid amplification testing (ID-NAT), is used to detect the presence of HIV-1, HBV and HCV in donated blood. This method of testing was introduced in 2005 and has significantly reduced the risk of transmission of especially HIV and HCV (32). As an added safety measure, serology testing is also performed for HIV- 1 and 2, HBV and HCV (and syphilis) as there has been occasional cases of donors who were able to suppress viral replication to the extent that only their antibody tests were positive (33,34). The epidemiological profile of various infectious diseases in the South African donor population and their impact on the risk of transmission through transfusion is summarised in *Table 1*.

Since implementation of ID-NAT by the BTS and with active lookback programs in place, confirmed transmission of any of HIV, HBV and HCV infections has been less than 1 in 10 million transfusions in South Africa (34). Indeed, the ID-NAT testing implemented by the BTS, employing world class testing systems, has markedly improved plasma safety in South Africa. It must also be noted that the multi-faceted measures introduced to improve quality and safety of plasma added significantly to the cost of the manufacture of PDMPs.

Table 1 Prevalence estimates and the risk of transmission of various major diseases affecting the South African donor population

Disease/pathogen	Epidemiological considerations	References
HIV/AIDS	HIV/Acquired Immunodeficiency Syndrome (AIDS) is a prominent health concern in South Africa. The total number of persons living with HIV in South Africa increased from an estimated 4.72 million in 2002 to 7.03 million by 2016	(35-37)
	Introduction of ID-NAT for HIV has reduced the infectious window period for HIV from about 19 days to an estimated 4.6 days. The worst case theoretical residual risk of a transmission occurring is estimated to be 1:143,226 donor exposures, which must be considered in the context of the high background prevalence of HIV in South Africa	(32)
HBV	HBV is endemic in South Africa, with a large proportion of the population having been exposed to the disease prior to ever needing a transfusion. Around 1 in 185 first time donors have been exposed to the disease prior to ever needing a transfusion	(31)
	ID-NAT reduced the window period for HBV transmission from 38 to 24.3 days, which is much longer than the window period for HIV. The worst case theoretical residual risk for HBV remains relatively high at 1:20,642 donor exposures	(32)
HCV	Hepatitis C is uncommon among South African blood donors with only 1 in 2,700 first time donors having been previously exposed to HCV	(32)
	ID-NAT dramatically reduced the window period for HCV from 65 to 2.8 days with a calculated residual risk of 1 in 21 million donor exposures	(32)
Variant Creutzfeldt-Jacob Disease (vCJD)	vCJD was first recognised in the United Kingdom in 1996, and it has been confirmed that vCJD may be transmissible through blood transfusions	(38,39)
	The BTS of South Africa introduced deferral criteria for donors who may possibly be asymptomatic carriers of this condition. This is an extremely rare condition and there has been no confirmed case of transfusion transmitted vCJD in South Africa	(40)
Other infectious diseases	PDMP's have also been associated with the transmission of Hepatitis E (HEV) (41), Parvovirus B19 (42,43) and Hepatitis A (HAV) (44). It is therefore recommended that plasma fractionators further reduce non-lipid enveloped viruses (45,46)	(41-46)
	Screening for non-lipid enveloped viruses in blood donations is not performed at the local BTS. Hence, NBI employs a set of different test algorithms using NAT to remove non-enveloped viruses and reduce the burden to the fractionation process but consequently increase the cost per litre of plasma	

Affordability of implementing required changes

Local pricing regulations

In South Africa, as in many other countries, health legislation is an important enabler of the implementation of health policy. Since 1995, South Africa has been engaged in a constant process of public health law reform. The goal of the National Drug Policy (NDP) in South Africa is to ensure an adequate and reliable supply of safe, cost-effective drugs to all citizens of South Africa and the rational use of drugs by prescribers, dispensers and consumers (18). The NDP introduced an Essential Drugs Programme, which included an Essential Drugs List and standard treatment guidelines which created a foundation for the basic health

care package of the National Health System for universal primary care. Presently, 90% of the products manufactured by NBI are listed on the WHO SA Essential Medicines List (7). However, in South Africa, access to medicines is often disparate between rural and urban areas, with limited access for patients living in rural areas. As an example, unequal distribution of clotting factors among different provinces in the public healthcare sector emphasises the disparities in the public and private healthcare systems, with patients in some provinces having access to clotting factors at levels well below the World Federation of Haemophilia (WFH) recommended dose of one unit per capita (47,48).

To improve access to healthcare in South Africa, the NDP had as its objective the development of a pricing plan

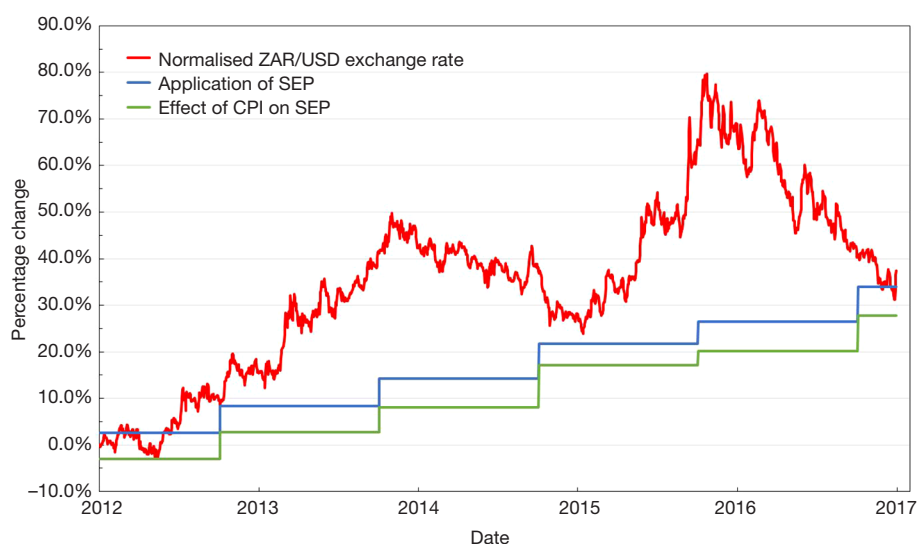


Figure 1 The cumulative increase of year-on-year SEP adjustments and the impact of CPI, in relation to the percentage change in the South African Rand/USD exchange rate from 2012 to 2017.

for medication used in South Africa, for both the private and the public sectors (48). Following this, the amended Medicines and Related Substances Act was introduced to legislate the process with two inter-related sections—section 18A banning bonusing and effectively preventing pharmaceutical manufacturers from offering discounts and/or rebates to patients or healthcare providers and Section 22 G, which created a Pricing Committee (49).

The Single Exit Price (SEP) mechanism was introduced for all medicines in the private healthcare sector in South Africa, stipulating regulated maximum annual price increases (50,51). The implementation of SEP effectively meant that the private sector had to adjust from a free market to a regulated market where prices have to be motivated for and all discounts discarded, ensuring transparent pricing practices for the industry (52). The SEP became a fixed maximum price at which local manufacturers such as NBI and importers had to sell medicine without an opportunity for offering discounts. Cumulative year-on-year SEP increases since 2012 are shown in *Figure 1*.

The SEP mechanism has been in place for several years, but some related legislative processes remain stalled. Of particular significance is the introduction of international benchmarking for medicine prices, and the National Health Insurance implementation processes remain contested, with the legislative component still poorly developed (6).

Volatile local currency

NBI relies on imported reagents, raw materials, intermediates, consumables such as single use technology, as well as PDMP manufacturing expertise and other services. Further, new analytical and process equipment or PDMP process technology implemented in response to local and international regulatory changes are typically imported, and invoiced in US dollars (USD). Between 2012 and 2016, the South African Rand (ZAR) depreciated on average by 38% against the USD from about R10/USD to about R13.5/USD placing significant pressure on the price of imported and locally-manufactured medicines (49). *Figure 1* shows the percentage depreciation of the ZAR against the USD, relative to the exchange rate in the beginning of 2012. Imported medicines cost more to procure and distribute locally, while the depreciation of the currency increases the cost of production of locally-manufactured medicines, including PDMP's manufactured by NBI. In addition to the overall depreciation, the local currency also fluctuates significantly, with a peak of almost 80% during the 2012 to 2016 period, thus complicating planning and budgeting processes.

The Consumer Price Index (CPI) provides an indication of the rising cost of materials and services procured locally, which adds to the production costs. The annual increase in SEP should account for these external influences on production costs to ensure local manufacturers remain

competitive and sustainable; however, the SEP mechanism is not flexible enough and the increases in the SEP over the past 5 years was insufficient to compensate for the erosion of profit margins due to the weaker local currency and high local inflation rate. The SEP increased from 4.8% in 2016 to 7.5% in 2017 (6,53), while the CPI increased from 4.6% in 2015 to 6.3% during the same period (6,54). The annual SEP increase and its offset by the CPI for the period from 2012 to 2017 are compared to the percentage change in the ZAR/USD exchange rate in *Figure 1*.

The depreciation of the value of the local currency combined with a high inflation rate results in further increases in production costs, while the disparate SEP consequently limit sales prices and thus margins, effectively limiting the profitability of PDMP production in South Africa.

Non-regulatory drivers of changes to products and manufacturing processes

Advances in PDMPs over the past few decades resulted in major improvements in the quality of life of patients, for example improvements in FVIII replacement therapy in the treatment of haemophilia A (55-57). This progress has, however, occurred with considerable increases in cost (58) such that some advanced therapeutics are available only in the developed world and a lack of adequate treatment modalities exist in the developing world (59,60). The presence of strong patient advocacy groups in the developed world has driven and accelerated approval of PDMPs (11). Patient representatives in South Africa belonging to the South African Haemophilia Foundation (SAHF) and Primary Immunodeficiency Network of South Africa (PiNSA) collaborate with patient advocacy organisations in developed countries namely Plasma Protein Therapeutics Association (PPTA) and International Plasma Fractionation Association (IPFA) and are well versed in product development in plasma derived medicinal products. Consequently, expectations by South African patient interest groups are increasingly towards first world technology. This drive in the South African market for modern PDMPs places pressure on NBI to modernise its product range and align to that of the developed world.

Similarly, growing clinical demands for immunomodulatory therapies prompted further process improvements in the last few years to avoid some or all typical ethanol fractionation steps, increase IgG recovery, replace the traditional low pH/pepsin to reduce anti-

complementary activity, and improve viral safety with more efficient procedures (61), and these are adopted by the fractionation industry. Where appropriate, NBI also considers these improvements of its manufacturing processes.

Pharmacopoeial changes to product specifications

A significant driver of change at NBI is updates to international standards. From time to time, monographs are updated with the latest analytical techniques or product specifications. An example of a recent specification change that affected NBI's PDMPs is the amendments to Ph. Eur. monographs on immunoglobulin, following a series of product recalls from the EU and US after increased thrombo-embolytic events (TEE) observed by certain IVIG products (62). The TEE-related adverse events prompted manufacturers, including NBI, and regulatory agencies to scrutinize existing IVIG manufacturing processes for their capacity to generate thrombogenic substances. The Ph. Eur. publication, *Human Normal Immunoglobulin for Intravenous Administration*, Monograph 0918, was revised to state that products should exhibit no thrombogenic (procoagulant) activity, as follows:

“The method of preparation also includes a step or steps that have been shown to remove thrombosis-generating agents. Emphasis is given to the identification of activated coagulation factors and their zymogens and process steps that may cause their activation. Consideration is also to be given to other procoagulant agents that could be introduced by the manufacturing process” (63,64).

Manufacturers were given until 1 July 2012 to comply. The Ph. Eur. Monograph 0338, *Human Normal Immunoglobulin*, was also updated (64), with implementation on 1 January 2013.

Skills shortage

Pharmaceutical and plasma fractionation companies by their nature require a highly skilled workforce. Within South Africa, there is a reliance on pharmacists who play a significant role in the health care sector, from research and development, manufacturing of medicines, promoting and ensuring regulatory compliance and oversight, to dispensing and providing clinical information. Accordingly, their role in the manufacture of medicines, including PDMPs, is a regulatory requirement in accordance to the Pharmacy Act 53 of 1974 (65). The roles and responsibilities of

the Responsible Pharmacist and Industrial Pharmacists are explicated in Annex 16 of the Guide to Good Manufacturing Practice for Medicines in South Africa (66). South Africa's pharmaceutical industry has a significant skills shortage, lacking at least 12,000 industrial pharmacists in order to meet international standards (67). Consequently, NBI has limited access to skilled industrial pharmacists as it is difficult to attract graduates to the plasma fractionation field. In addition, skills in plasma fractionation and aseptic processing in South Africa are deemed to be scarce. To overcome this NBI often engages with international plasma fractionation experts for assistance and support.

In terms of general health care, there is a disparity in availability and distribution of human resources between urban and rural areas, and between the public and private health sectors in South Africa (6). The shortage of key medical personnel is a pressing challenge to the South African public sector, where there is a lack of trained and experienced staff to identify and treat patients with PDMPs. Indeed, despite the many steps taken to improve the availability and distribution of human resources for health in South Africa, there is still much to be achieved (47).

Successes of local fractionation

The success of NBI as a local fractionator can be attributed to its strategic intent and core values, and that its policies are complemented by committed leadership and stewardship, regular engagement with stakeholders, and a duty of care towards the patients that it serves. A key factor that allows NBI to be self-sufficient and sustainable in the production of PDMPs is the close working relationship with the BTS of South Africa, i.e. SANBS and WPBTS. The mutual understanding of the plasma quality requirements for fractionation allows NBI to purchase sufficient quantities of safe plasma in an epidemiologically challenging environment.

Through partnerships with the SAHPRA and IPFA and membership of Parenteral Drug Association (PDA), the International Society for Pharmaceutical Engineering (ISPE) and other relevant organisations, NBI is kept abreast with the latest safety concerns, changes to international standards and regulatory requirements, and new product developments. Based on these inputs, NBI is constantly reviewing its operations and products to ensure compliance with all the international and local requirements and modernizes its manufacturing processes and product offerings accordingly.

Conclusions

NBI remains agile and appropriately adapts and positions itself to continue anticipating and responding to changes in its regulatory and operating environment. In doing so, NBI ensures that it complies with the regulatory requirements and expectations of the national regulatory authority, that it adheres to international best practice with respect to plasma fractionation, and that it remains a sustainable organisation optimally positioned to serve the needs of patients in South Africa and the region.

Acknowledgments

We thank Khatija Suleman for providing information on the regulatory aspects in South Africa and Andrea Muller for providing information on the South African National Health Care system.

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Thierry Burnouf) for the series "Plasma Fractionation" published in *Annals of Blood*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/aob.2018.01.02>). The series "Plasma Fractionation" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the manuscript and ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

- Bertolini J, Hayes T. Plasma for Fractionation. In: Bertolini J, Goss N, Curling J, editors. *Production of Plasma Proteins for Therapeutic Use*. USA: John Wiley & Sons, Inc., 2013:423-37.
- World Health Organisation. Expert Committee on Biological Standardization, sixty-seventh report (WHO Technical report series; no. 1004) Annex 3. Guidance document. Management of blood and blood components as essential medicines. Geneva: WHO Publications, 2017. Available online: http://www.who.int/bloodproducts/brn/ManBloodEM_GL_WHO_TRS_1004_web_Annex_3.pdf
- Strengers PF, Klein HG. Plasma is a strategic resource. *Transfusion* 2016;56:3133-7.
- World Health Organisation. Improving access to safe blood products through local production and technology transfer in blood establishments. Geneva: WHO Publications 2017. Available online: http://www.who.int/phi/publications/improving_access_safe_blood_products/en/
- World Health Organisation. Sixty-Third World Health Assembly. Geneva: Resolutions and Decisions Annexes. Geneva: WHO Publications, 2017. Available online: http://www.who.int/nutrition/topics/WHA63.23_iycn_en.pdf?ua=1
- Health Systems Trust. 20th edition South African Health Review 2017. Available online: <http://www.hst.org.za/publications/south-african-health-review-2017>
- National Bioproducts Institute. Available online: <http://www.nbisa.org.za/>
- World Health Organisation. Standard treatment guidelines and essential drugs list for South Africa. Pretoria: The National Department of Health, South Africa, 2017. Available online: <http://apps.who.int/medicinedocs/documents/s18259en/s18259en.pdf>
- Kistler P, Nitschmann H. Large scale production of human plasma fractions. *Vox Sang* 1962;7:414-24.
- Mahlangu JN, Gilham A. Medical and Scientific Advisory Council of the South African Haemophilia Foundation. Guideline for the treatment of Haemophilia in South Africa. *S Afr Med J* 2008;98:126-40.
- Shapiro AD. Long-lasting recombinant factor VIII proteins for hemophilia A. *Hematology Am Soc Hematol Educ Program* 2013;2013:37-43.
- South African Ministry of Health. Report of Ministerial Task Team on Restructuring of Medicines Regulatory Affairs and Medicines Control Council and recommendations for New Regulatory Authority for Health Products of South Africa. Available online: <https://www.gov.za/sites/www.gov.za/files/Report%20of%20Ministerial%20Task%20Team%20on%20Restructuring%20of%20Medicines%20Regulatory%20Affairs%20and%20Medicines%20Control%20Council%20and%20recommendations%20for%20New%20Regulatory%20Authority%20for%20Health%20Products.pdf>
- Gouws J. Inside PIC/S: South Africa's accession to PIC/S. Available online: <http://www.pharmtech.com/inside-pics-south-africas-accession-pics>
- Chorley C. Current Challenges in South African post-approval CMC landscape. *Regulatory Rapporteur* 2014;11:4-7.
- Wicks S. Ensuring the Quality of Biologicals. Internet. Available online: <http://www.biopharminternational.com/ensuring-quality-biologicals-0>
- South African Department of Health Medicines Control Council. Amendments 2.08 Amendments July 2012 v6. South African Department of Health; 2012. Available online: http://www.mccza.com/documents/28d5c6c22.08_Amendments_Jul12_v6_showing_changes.pdf
- South African Department of Health Medicines Control Council. Pharmaceutical and Analytical CTD/eCTD, 2.25 PA CTD August 14. South African Department of Health; 2014. Available online: http://www.mccza.com/documents/751d10ba2.25_PA_CTD_Aug14_v4.pdf
- Rispel L. Analysing the progress and fault lines of health sector transformation in South Africa. In: Padarath A, King J, Mackie E, et al., editors. *South African Health Review 2016*. Durban: Health Systems Trust, 2016.
- Flood P, Wills P, Lawler P, et al. Review of Australia's plasma fractionation arrangements. Chapter 3. The world fractionation industry. *Common wealth of Australia, 2007*. Available online: [https://www.health.gov.au/internet/main/publishing.nsf/Content/B3B4E1D741764DD2CA257BF000193A6F/\\$File/Chapter%203.pdf](https://www.health.gov.au/internet/main/publishing.nsf/Content/B3B4E1D741764DD2CA257BF000193A6F/$File/Chapter%203.pdf)
- South African National Blood Service. Integrated Annual Report 2017. Available online: <https://sanbs.org.za/wp-content/uploads/2017/10/SANBS-Annual-Report-2107-compressed.pdf>
- South African Department of Health, Centre of Human Rights. Government Gazette Republic of South Africa. Chapter 8 of the National Health Act Vol. 469. University of Pretoria, Cape Town South African Department of Health; 2004:1-48.
- Council of European Communities. Council

- Recommendations of 29 June 1998 on the suitability of blood and plasma donors and the screening of donated blood in the European Community (98/463/EC). Official Journal of the European Union 1998
23. Council of Europe/European Directorate for Quality of Medicines & Healthcare (EDQM). Guide to the preparation, use and quality assurance of blood components. Recommendation No. R (95) 15. 19th Edition. Available online: https://www.edqm.eu/sites/default/files/list_of_contents_19th_ed-blood-quality.pdf
 24. World Health Organisation. WHO Expert Committee on Biological Standardization. (WHO Technical Report Series 840). Forty-third Report. Geneva: WHO Publications. Available online: http://apps.who.int/iris/bitstream/10665/39048/1/WHO_TRS_840_%28part1%29.pdf
 25. World Health Organisation. Guidelines on good manufacturing practises for blood establishments. (WHO Technical Report Series, No. 961). WHO Publications. Available online: <http://apps.who.int/medicinedocs/documents/s18652en/s18652en.pdf>
 26. Commission Directive 2004/33/EC of 22 March 2004 implementing Directive 2002/98/EC of European Parliament and of the Council as regards certain technical requirements for blood and blood components. Official Journal of the European Union 2004. Available online: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004484.pdf
 27. European Agency For The Evaluation Of Medicinal Products. Evaluations Of Medicines For Human Use. Committee for Medicinal Products for Human Use (CHMP). Guideline on the Scientific data Requirements for a Plasma Master File (PMF) Revision 1, Ref. EMEA/CPMP/BWP/3794/03Rev.1. London, 2006.
 28. Africa Society of Blood Transfusion. Standards Step-Wise Accreditation Programme. 2014:1-40.
 29. South African National Blood Service. Integrated Blood Safety. South Africa: South African National Blood Service, 2011.
 30. Mandisodza AR, Charuma H, Masoha A, et al. Prevalence of HIV infection in school based and other young donors during the 2002 and 2003 period. *Afr J Med Med Sci* 2006;35:69-72.
 31. Tagny CT, Mbanya D, Tapko JB, et al. Blood safety in Sub-Saharan Africa: a multi-factorial problem. *Transfusion* 2008;48:1256-61.
 32. Vermeulen M, Lelie N, Sykes W, et al. Impact of individual-donation nucleic acid testing on risk of human immunodeficiency virus, hepatitis B virus, and hepatitis C virus transmission by blood transfusion in South Africa. *Transfusion* 2009;49:1115-25.
 33. Okulicz JF, Lambotte O. Epidemiology and clinical characteristics of elite controllers. *Curr Opin HIV AIDS* 2011;6:163-8.
 34. South African National Blood Service. Integrated Annual Report 2016. Available online: <https://sanbs.org.za/annual-reports/>
 35. South African National Blood Service. HIV Residual Risk Based Hierarchical Blood Issuing. South Africa, Constantia Kloof: South African National Blood Service; 2011. SANBS CP-MLD-001.
 36. Shisana O, Rehle T, Simbayi LC, et al. South African National HIV Prevalence, Incidence and Behaviour Survey. Cape Town, South Africa; 2012.
 37. Statistics South Africa. Statistical release P0302. Mid-year population estimates. 2016. Available online: <https://africacheck.org/wp-content/uploads/2017/02/2016-midyear-population-estimates.pdf>
 38. Ludlam CA, Turner ML. Managing the risk of transmission of variant Creutzfeldt Jakob disease by blood products. *Br J Haematol* 2006;132:13-24.
 39. Committee for Medicinal Products for Human Use. CHMP position statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products EMA/CHMP/BWP/303353/2010. London, United Kingdom: European Medicines Agency, Sciences Medicines Health, 2010.
 40. Chamberland ME, Alter HJ, Busch MP, et al. Emerging infectious disease issues in blood safety. *Emerg Infect Dis* 2001;7:552.
 41. Committee for Medicinal Products for Human Use. Reflection paper on viral safety of plasma-derived medicinal products with respect to Hepatitis E virus EMA/CHMP/BWP/723009/2014. London, United Kingdom: European Medicines Agency, 2014.
 42. Blümel J, Schmidt I, Effenberger W, et al. Parvovirus B19 transmission by heat-treated clotting factor concentrates. *Transfusion* 2002;42:1473-81.
 43. Wu CG, Mason B, Jong J, et al. Parvovirus B19 transmission by a high-purity factor VIII concentrate. *Transfusion* 2005;45:1003-10.
 44. Soucie JM, Robertson BH, Bell BP, et al. Hepatitis A virus infections associated with clotting factor concentrate in the United States. *Transfusion* 1998;38:573-9.
 45. European Agency For The Evaluation Of Medicinal

- Products. Evaluations Of Medicines For Human Use. Committee for Proprietary Medicinal Products (CPMP). Note for Guidance on Plasma-Derived Medicinal Products CPMP/BWP/269/95 rev.3 2001. Available online: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003613.pdf
46. World Health Organisation. WHO Expert Committee on Biological Standardization Fifty-second Report (WHO Technical Report Series, No. 924). Annex 4. Guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood plasma products. Geneva: WHO Publications, 2004. Available online: http://apps.who.int/iris/bitstream/10665/42921/1/WHO_TRS_924.pdf
 47. Healthcare P. Challenging Rare Disease Landscape for Drugmakers. Available online: <https://www.bmiresearch.com/articles/challenging-rare-disease-landscape-for-drugmakers>
 48. Skinner MW. Haemophilia: provision of factors and novel therapies: World Federation of Hemophilia goals and achievements. *Br J Haematol* 2011;154:704-14.
 49. Gray AL. Medicines Pricing Interventions-the South African Experience. *Southern Med Review* 2009;2:15-8.
 50. Bodhanian M. Pharmaceutical sector presentation for private health sector Indaba. Johannesburg: Pharmaceutical Industry, 2007:20.
 51. Advanstar Communications. Managing the market - distribution and logistics. *Pharm Tech Europe* 2009;21:47-8.
 52. Pretorius D. The impact of the implementation of single exit pricing for pharmaceuticals in South Africa: University of Witwaterstrand, 2011.
 53. South African Department of Health. Database of Medicine Prices. Available online: <http://www.mpr.gov.za/PublishedDocuments.aspx#DocCatId=21>
 54. Statistics South Africa. Statistical Release P0141. Consumer Price Index. 2017.
 55. Franchini M, Tagliaferri A, Mannucci PM. The management of hemophilia in elderly patients. *Clin Interv Aging* 2007;2:361-8.
 56. Gianotten WL, Heijnen L. Haemophilia, aging and sexuality. *Haemophilia* 2009;15:55-62.
 57. Mannucci PM, Schutgens RE, Santagostino E, et al. How I treat age-related morbidities in elderly persons with hemophilia. *Blood* 2009;114:5256-63.
 58. Rogoff EG, Guirguis HS, Lipton RA, et al. The upward spiral of drug costs: a time series analysis of drugs used in the treatment of hemophilia. *Thromb Haemost* 2002;88:545-53.
 59. Bird A, Isarangkura P, Almagro D, et al. Factor concentrates for haemophilia in the developing world. *Haemophilia* 1998;4:481-5.
 60. O'Mahony B, Black C. Expanding hemophilia care in developing countries. *Semin Thromb Hemost* 2005;31:561-8.
 61. Radosevich M, Burnouf T. Intravenous immunoglobulin G: trends in production methods, quality control and quality assurance. *Vox Sang* 2010;98:12-28.
 62. European Medicines Agency recommends suspension of Octagam in all EU Member States. CHMP recommendation based on risk of thrombo-embolic reactions. EMA/CHMP/591722/2010. London, United Kingdom: Agency of European Union, 2010.
 63. Council of Europe, European Pharmacopoeia Commission, European Directorate for the Quality of Medicines Healthcare. Monograph on human normal immunoglobulin for intravenous administration (0918). Strasbourg: European Directorate for the Quality of Medicines and Healthcare, 2010.
 64. Council of Europe, European Pharmacopoeia, Commission European Directorate for the Quality of Medicines Healthcare. Monograph on human normal immunoglobulin (0338). Strasbourg: Council Of Europe: European Directorate for the Quality of Medicines and Healthcare, 2010.
 65. South African Pharmacy Council. Pharmacy Act No. 53 of 1974. Pretoria, South Africa: South African Pharmacy Council, 2011:1-32.
 66. Department of Health Medicines Control Council. Guide to Good Manufacturing Practice for Medicines in South Africa 4.01 SA Guide to GMP June v5 Pretoria, South Africa: Department of Health, 2010:1-158.
 67. Ndenze B. SA has a huge pharmaceutical skills shortage. Available online: <https://www.timeslive.co.za/news/south-africa/2017-06-28-sa-has-huge-pharmaceutical-skills-shortage/>

doi: 10.21037/aob.2018.01.02

Cite this article as: Omarjee JH, Germishuizen WA, Chetty R, Stubbings D. Plasma fractionation in South Africa: challenges and successes in meeting international standards. *Ann Blood* 2018;3:6.