

SECTION THREE

OPERATIONAL ISSUES: DRUGS AND LABORATORIES

CHAPTER VII	Drug Procurement	143 - 154
CHAPTER VIII	Drug Distribution	155 - 160
CHAPTER IX	Laboratory Services	161 - 171

Chapter VII

Drug Procurement

OVERVIEW

A central component of expanded HIV and AIDS care and treatment is the production, procurement and supply of medicines, in particular antiretrovirals. To support the operational plan, the drug procurement system must achieve the following general objectives:

- Medicines must be of the highest quality and appropriate for the treatment regimens outlined in the plan.
- The supply of medicines must be secure and sustainable at a volume large enough to meet the significant demand envisioned.
- Medicines must be purchased at the lowest possible price.
- The sustainable supply should be ensured through local production of antiretrovirals and sustainable financing.

The framework for the procurement of ARVs has been designed to meet these objectives. This framework is also guided by principles of good procurement practices, sound financial management and accountability and compliance with good quality standards.

BACKGROUND AND RATIONALE

Historically the cost of ARVs has restricted access to ARV therapy to a limited number of patients with AIDS. Though the introduction of equivalent generic products has substantially lowered the market price for these medicines, they are still prohibitively expensive for the vast majority of people who need them. The current market for ARVs in developing countries is small and fragmented. As a result, the production system for these medicines is sub-scale and high cost. Producers have not had the demand or predictability that they need to organize efficient production systems.

The South African pharmaceutical market is characterised by high import penetration, with a significant volume of products coming in as finished products, with limited local

generic production.

The current tender process for pharmaceuticals allows for split contracts among suppliers of critical items that address prevalent conditions and priority programmes. This approach enhances continuity and sustainability of supplies.

Medicines that are procured in the country including antiretrovirals should be registered by the Medicines Control Council and must meet standards of quality, efficacy and safety.

This plan takes into consideration the declarations of the SADC Health Ministers agreed to at two meetings held in Pretoria on the 17th June 2000 and in Durban on the 8th July 2000. These related to legislative and regional legal regimes that will ensure the availability of technologies and drugs at affordable prices for treatment, including bulk purchasing of drugs and manufacturing of generic medicines in the region. The first meeting developed principles that would be used in any negotiations with the companies and these are:

- The prime focus of the negotiations must remain on Sub-Saharan Africa where the magnitude of the problem is greatest.
- WHO should become the convening agency for these negotiations in the light of its broad health mandate and the greater opportunity for representivity that it can provide through the World Health Assembly.
- The negotiations should address the overall provision of care for HIV and AIDS-related conditions and must include a consideration of all the elements related thereto viz. health infrastructure, diagnostic kits, pharmaceuticals and the technology that would ensure that these can be safely and effectively administered.
- All proposals should be centred around the principle of sustainability and on this basis, seek to make drugs both affordable and accessible.
- Health ministries should define all research priorities based on local conditions and national objectives.
- Those options open to Member States under TRIPS (parallel importation and compulsory licensing), should not be compromised.
- Member States should not be required to assume the responsibility of ensuring that these products do not leave their markets.

In particular, at the second meeting held in Durban, Ministers reaffirmed that HIV and AIDS is a serious developmental issue and that therapy for HIV and AIDS-related conditions should be delivered through sustainable health systems. Ministers further

directed that a minimum package of services that can be used by SADC countries when negotiating as individual countries or as a collective with pharmaceutical companies should be developed. The package would not focus only on the provision of antiretroviral drugs, but would address issues of HIV and AIDS-related infections in a holistic way, therefore including aspects such as laboratory support, treatment of opportunistic infections, infrastructure, capacity building and monitoring of drugs, especially antiretroviral drugs.

APPROACH

The national procurement of ARVs will operate on several principles. Firstly, the supply of ARVs must be of high quality and suppliers must have the technical know-how to produce specific treatment regimens and a long-term commitment to deliver high quality pharmaceuticals consistently. Manufacturers of the medicines must conform to national and international quality standards and be able to produce adequate quantities of medicines into the future. The procurement of ARVs must also be flexible; as new and better medicines are introduced, or as the treatment regimen of a particular patient is changed over time, adjustments must be made.

Secondly, there must be a competitive market for the production of ARVs. Engaging with a number of competing manufacturers will further drive price reductions. As more suppliers qualify for tenders, it is envisaged that additional competition will create downward price pressure. A number of viable and competing manufacturers will also guarantee security of supply should any supplier fail for any reason.

Thirdly, ARVs must be affordable and legislative provisions exist to ensure access to affordable medicines. One method of promoting low cost medicines is to maximize the volume of demand by aggregating orders within the country and possibly with other countries in the procurement of ARVs. An additional way to promote efficient production is to commit to long-term supply agreements. Both methods enable investments in large-scale production facilities and significant reductions in cost by manufacturers. On the basis of cost analyses, a maximum forward price can be set along a diminishing cost curve. This will further reduce prices with increased total purchasing volume.

Fourthly, the supply of ARVs must be uninterrupted to meet the treatment needs of patients. There is always a risk of failure in the supply chain of pharmaceuticals. It is intended that the procurement plan coordinates a sustainable supply through the participation of viable suppliers, and local production of finished products and active pharmaceutical ingredients.

To achieve these goals, the following processes are planned.

Appointment of Negotiating Team

The Minister of Health will appoint a negotiating team to implement the procurement strategy recommended in this plan.

The negotiating team appointed by the Minister should be composed of people with the following skills and expertise:

- Knowledge of the tendering process
- Knowledge of procurement and Treasury regulations
- Knowledge of Competition Commission rules and regulations
- Knowledge of the cost and pricing structure and pricing models of the pharmaceutical industry
- Knowledge of the strategic and policy positions of the South African government regarding the pharmaceutical sector
- Knowledge of trade and legal issues

Procurement Mechanisms

There are at least three options by which procurement processes could be put into operation, namely:

- A regular government tender using local suppliers.
- A public-private partnership/initiative.
- International tendering as stipulated in section 1(4) and Regulation 3 of the Medicines and Related Substances Act 101 of 1965.

The Task Team recommends that the regular national government tender procurement pre-qualification procedures be used. In the case of ARV procurement, a substantive

contractual agreement for sustainable supply of medicines would require a longer-term agreement than the standard two-year tender agreement as well as more flexible terms to allow for changes in drug regimens within an existing procurement agreement. This would also enable the department to negotiate diminishing cost curves as volumes increase.

If the usual tender process is unsuitable, ARVs could be purchased through a public private partnership (PPP) with specified suppliers, in accordance with Treasury regulations, led by the Department of Health. The PPP could be established to administer the tendering process for ARVs and to coordinate a sustainable and competitive long-term market for ARV production. While this mechanism allows greater flexibility in the tender process, the establishment of the PPP may involve delays.

International tendering may be considered in accordance with Section 1(4) and Regulation 3 of the Medicines and Related Substances Act 101 of 1965 as amended if such medicine;

- is essential for national health as approved by the Minister,
- can be obtained at a lower price outside the Republic and
- is registered by the Medicine Control Council (MCC)

International tendering or procurement however implies that continuous quality monitoring capacity must be strengthened to ensure that imports are not sub-standard and the possibility of counterfeiting is guarded against.

Pooled Procurement

Coordinating procurement with other countries provides manufacturers the volume required to achieve maximum economies of scale. This would allow for dramatically lower prices, enabling the government to realize one of the core goals of ARV procurement. Enhancing the total size of the ARV market also provides greater opportunity for competition, economic sustainability, and secure supply by multiple manufacturers. Pooled procurement could also be considered within the framework of the SADC Ministers' statement entrenching cooperation in strengthening local production and access to affordable medicines. Though this type of buying group has advantages, it requires careful management of country specific contracts.

Security of Supply and Local Production

To secure the long-term sustainable supply of ARVs, local production should be enabled through transfer of technology and production of active pharmaceutical ingredients (APIs) in South Africa. Local production policy should be aimed at establishing local production capacity that builds on existing realities of our investment drive and development initiatives. The strengthening of the industrial pharmaceutical and technological base in South Africa will respond to the NEPAD initiative and ensures that South Africa assumes an international market role.

Tender Process

The tender process consists of four stages. It is expected that the tender process will take about twelve weeks. A lead-time of two to four weeks may be required after the first orders are placed.

1. Supplier pre-qualification

All suppliers with MCC-approved drugs will be invited to participate in the pre-qualification process. All suppliers will be required to meet national and international standards in order to be qualified to tender to supply South Africa with ARVs. Pre-qualification is open to any manufacturer of ARVs, including companies producing generic, branded, and/or patented medicines. The criteria will include:

- MCC product registration and licensing of suppliers and distributors
- Pre-qualification standards (WHO or MCC approval)
- Financial viability
- Manufacturing quality, capacity and scale
- Cost transparency
- Agreement to price ceilings
- Commitment to establishing integrated production in South Africa
- Compliance with local regulations e.g. Black Economic Empowerment (BEE), Preferential Procurement Act etc.

2. Request for proposal and tendering (RFP)

Consistent with the notion of a partnership, a request for proposals will be developed to ensure procurement needs are met with the least cost and disruption to production. The RFP will establish:

- Product specifications
- Unique identification
- Volume of ARV supply for tender
- Duration of supply
- Substitution of medicines to alternative regimens
- Forward price setting according to a diminishing scale curve
- Annual review of costs of production and future prices
- Currency denomination
- Bid bonds
- Contingencies and risks assumed by each party
- Minimum inventories
- Distribution

3. Contracting

The final stage of the procurement transaction is negotiation, agreement on final terms and completion of the purchase contract.

4. Monitoring and evaluation

Contracts completed under the procurement process must be actively managed, monitored and evaluated for compliance with agreed to performance criteria and cost effectiveness.

Under this process it is envisioned that dedicated amounts of demand, e.g. 100,000 patient-dose-years, will be offered for tender to supply ARVs over a fixed period extending up to five years. To ensure adequate ongoing supply of ARVs by multiple manufacturers the total volume of any tender may be apportioned amongst bidders. During the fixed tender term, one drug regimen may be substituted for another regimen set at a different forward price curve depending on the clinical needs of the population.

SPECIAL CONSIDERATIONS

Regulatory Considerations

For both imported and locally produced medicines, it is important to have a robust regulatory and legal framework for the manufacture, sale, distribution and use of medicines, including ARVs, to underpin the long-term security of supply.

Regulatory Context for Supply

Like all medicines, ARVs must meet the normal standards for drug regulation and approval. All suppliers must include the following criteria for tendering:

1. Establish a legal presence in South Africa, i.e. appoint and designate a natural person who resides in the Republic to be responsible under local law
2. Use premises licensed for warehousing and distribution by the Director-General: Health
3. Gain approval as a pharmacy with the Pharmacy Council. From May 2004 the Medicines Control Council (MCC) will be responsible for licensing manufacturers, wholesalers, distributors, importers, and exporters.
4. Register the product with the MCC.

Accelerated Registration Processes

It is important to reduce administrative delays in the registration and approval of any new medicines that may improve health outcomes and mitigate drug resistance. All medicines procured must be registered by the MCC. Registration with the MCC is a thorough and occasionally time-consuming process. Fast track procedures are in place for expediting MCC approval.

Intellectual Property Considerations

All ARVs on the market are still under patent protection. The maintenance of intellectual property rights is essential to foster innovation and industrial development, however, the costs of patented medicines may prevent equitable access to essential medicines. The introduction of ARVs to the care and treatment of HIV and AIDS must comply with South African medicines law, patent law, and international obligations under the Trade Related Intellectual Property Rights (TRIPS) agreement. There are several ways in which access within existing laws can be facilitated.

Voluntary licenses

In cases where medicines can be obtained at a lower price, generic manufacturers can apply for voluntary licenses from patent holders. The disadvantage with voluntary licenses is that they are granted by the patent holders, who may or may not cooperate. Secondly, prices generally do not fall substantially where there is only one generic on the market. Prices come down with more competition. Thirdly, voluntary licenses may have strings attached e.g. royalties or restrictions with regard to whom products can be sold to.

So far, only one generic company has been granted a voluntary licence by two patent holders. This option may not be very useful as it is weighted heavily on the goodwill of the patent holder who may also have an interest in a viable market share. There are two further options to ensure a sustainable and affordable supply of necessary medicines as outlined in 2 and 3 below.

Compulsory licenses

The Patent Act provides for granting of a compulsory license by the Patent Commissioner, where demand for a patented ARV is not being met to an adequate extent and on reasonable terms. International legal norms provide further guidance regarding the granting of compulsory licenses. In cases of national emergency or where a product is for public non-commercial use, TRIPS allows the use of a patented product without the authorization of the patent holder. The detailed operation of this provision in the case of HIV, TB, and malaria has been reaffirmed and elaborated by the World Trade Organisation (WTO) Council for TRIPS. Most recently, the WHO has declared access to antiretroviral treatment by HIV and AIDS sufferers a global health emergency. A legislative amendment to the Patent Act to introduce compulsory licensing in the case of national emergency and public non-commercial use would be one way to further reinforce the comprehensive legal environment to enable broad access to affordable medicines and to facilitate secure and sustainable local supply.

The underpinning principle in the granting of compulsory licenses is that the patent holder is abusing his/her patent rights by maintaining an unaffordable price. This therefore implies that there must be negotiation with the patent holders to lower prices to an affordable level. The advantage with this option is that it opens the market to any generic

manufacturer. The disadvantages are that it may take a few months (three to four) to set it up and the patent holders may appeal to the Patent Commissioner on the basis of their not abusing their patent rights e.g. by granting voluntary licenses or bringing their prices down through the preferential price framework. This may therefore lead to protracted negotiations, appeals and delays.

Parallel importation

To enable the supply of more affordable medicines and to protect the health of the public, the Minister of Health may grant a permit that allows parallel importation of medicines. In this case, the Minister may determine that patent rights relating to a medicine patented in South Africa do not apply and the medicine can be imported. This provision is applicable and better invoked where the patent holder is abusing his/her patent rights by maintaining unaffordable prices. If parallel importation is invoked, it must be clearly demonstrated that there is no other option to access affordable medicines. Though this provision is at the behest of the Minister of Health, it may have wider trade related implications. It may also have a negative impact on the prevailing South African manufacturing capacity. The Doha and Cancun discussions however lessen this risk. The Department has all along been stating that this would be a last resort, after having exhausted all other negotiations to make medicine affordable. If this provision is invoked, communication in this regard is necessary. Secondly, parallel importation would be open to other players, beyond government in line with administrative justice and fairness. This implies that the monitoring arm of the Medicine Regulatory Authority must be vigilant and ensure that sub-optimal products are not imported into the country.

Regulation 7 of the Medicines and Related Substances Act stipulates that the permit granted by the Minister under this provision will be valid for two years and proof of registration of the product in the country of origin by a regulatory authority recognized by the MCC must be furnished. The person seeking a permit must also furnish documentary proof of the lowest price at which the medicine is currently sold in South Africa as well as the price at which it will be sold in South Africa. To ensure safety and efficacy, all parallel imported drugs must be registered with the MCC.

The principles outlined above, which aim at making medicine more affordable, will be extended to all essential medicines, in the spirit of the minimum package as stated by the SADC Ministers.

ADMINISTRATIVE STRUCTURE

Interdepartmental Leadership

An interdepartmental group will be established to oversee the implementation of the ARV procurement system. The Pharmaceutical Policy and Planning Cluster within the Department of Health will manage day-to-day operations in coordination with the Negotiating Committee. The Cluster will be responsible for managing tenders, aggregating provincial orders, placing order directly with suppliers, and ensuring that appropriate payment systems are in place.

Quality Assurance

Quality assurance (QA) for all companies registered by the MCC is administered by the MCC. The MCC inspects premises, determines Good Manufacturing Practice (GMP) standards, and recalls defective products. For purchased medicines, random product sampling is required. At present there is a need to strengthen the QA laboratory facilities at two centres, based in Cape Town and Johannesburg.

PROGRAMME ASSESSMENT

The effective management of the ARV procurement process requires routine, detailed analysis of the procurement portfolio and processes themselves. This review should include:

- Monitoring and evaluation data
- Review of market dynamics for ARVs
- Procurement patterns and irregularities
- Total volumes of procurement
- Analysis of prices paid
- Analysis of any hidden costs
- Management costs, times and other metrics
- Contractual performance

- Management of supplier relationships/ performance

Chapter VIII

Drug Distribution

OVERVIEW

An efficient and secure process for storage, distribution and appropriate utilisation of antiretroviral medications (ARVs) will be put in place in the public health system to ensure a reliable supply of medicines at all levels of distribution to avoid “stock-outs” and to prevent shrinkage and re-exportation.

To meet these two aims, the drug distribution process will include:

- Inventory management, patient prescription information and financial management systems at the national, provincial, and local levels.
- Secure storage facilities at the central, provincial, and local levels.
- Efficient and secure transport between central warehouse facilities, provincial pharmaceutical depots and public health service points.
- Training of pharmacy personnel to implement inventory management practices.
- Improved packaging to support inventory control (and to improve patient adherence).

BACKGROUND AND RATIONALE

Each province operates its own drug depot that provides drug storage and distribution services to the public health centres in the province. There are a total of 11 provincial drug depots, including one per province, except Western Cape and Eastern Cape, which each have two. Some have strong security mechanisms and inventory-tracking information management systems in place, while others do not. Those that do not have these systems experience higher rates of theft and stock-outs.

It is estimated that in the public health sector, a significant amount of pharmaceutical products procured is lost during the process of distribution and storage. While some of this high shrinkage risk can be attributed to the product being damaged or stocked inappropriately in the drug depots or the service point pharmacies, or during the process of

delivery, the majority is attributed to theft of product. Because of the very high market value of ARVs in Europe and the United States, and because of the lack of availability of the medicines in other African nations with a high prevalence of HIV and AIDS, large-scale theft for re-exportation presents a serious risk.

APPROACH

Provincial Level Depots

Drug storage

This Programme will need to ensure that existing Standard Operating Procedures at the provincial level depots are followed. ARV medicines will be managed administratively as “Schedule 5” medicines, with some additional requirements:

- An up-to-date register with a detailed listing of all products received and distributed, as well as every prescription dispensed.
- Inventory storage in a secure location, with access restricted to the person designated as responsible for the Schedule 5 stock (e.g. pharmacist, manager, specified ARV handler). The definition of a secure location is, at minimum, a padlocked room that is caged, (caged ceiling, four walls) and has a concrete floor and for pharmacies is either a caged room or a locked box.
- Order processing at depots may only be handled by the depot pharmacist, manager or specified ARV handler.
- Whether the delivery service is a government-owned system or an out-sourced courier service, the delivery service will be required to sign the shipment in and out directly in the presence of the depot pharmacist, manager or specified ARV handler. Contracts will have to be put in place between the provincial depots and their delivery services to ensure proper service, including the introduction of severe penalties in the event that an order is mishandled by the delivery service.
- Rooms where ARVs are stored will need to have air conditioning. Some ARVs, such as paediatric formulations in syrup form, will need refrigeration.

In any location where stock is stored and distributed, audits will be required every three months.

Inventory management

To ensure proper supply of ARVs to the public health service points, provincial depots will be required to process and ship an order within two business days (48 hours) of receipt. In addition, for exceptional cases where there is a local emergency, mechanisms

will be put in place that should allow orders to be processed and shipped within four hours.

Given the volume of medicines that are likely to be ordered, the number of service points, and the need for rapid turn-around, it will be necessary to place and track orders electronically within three to five years. IT systems in each provincial depot will need to be upgraded over the initial years of the programme to include high-speed Internet connectivity, and symbology-based technologies for electronic parcel tracking. Symbology-based technologies that identify the drug, the source, the destination and the patient through a patient identification number will enable the department to meet the drug handling requirements without all the manual record keeping. There still will be paper based tracking systems in facilities that do not have computer systems or reliable access to electricity.

Within five years, it is expected that this upgrading will be completed and each provincial warehouse should have one IT person on staff to maintain the ordering and processing system. An additional investment in an advanced inventory tracking system at the central procurement, provincial depot and local health facility levels should also occur to improve visibility into the drug supply at the national, provincial and local levels, and prevent stock-outs. The system should contain the following functionality:

- When stock runs low at the service points, the system will notify the provincial depot and/or the manufacturer that more stock needs to be sent.
- When the stock runs low at the provincial depot level, the system will trigger a notification to the manufacturer that more stock needs to be sent.
- In the event that stock runs low at a provincial depot and the main manufacturer is not able to supply the order, even with the contingency supply requirements, the system will: 1) check the stocks of other provincial depots to see if they are overstocked, and trigger re-route of some of that stock to the provinces that are under stocked; 2) send an order to a secondary set of manufacturers asking for an expedited supply of the medicines.

These investments in information technology will not only improve the system to manage ARVs, but should improve inventory tracking for the entire drug distribution network.

Pharmacies at the Public Health Service Point Level

There are pharmacies in all of the district hospitals and most of the community health centres. In order to accommodate the ARV Programme, investments in infrastructure and human resources will be required for up to 90 percent of these sites.

Site Accreditation

Every health facility pharmacy that wishes to dispense ARVs will need to be accredited. Minimum standards will include, but not be limited to, the following:

- Implementation of the Standard Operating Procedures for receiving, storing and dispensing Schedule 5 medicines, including the security standards described for provincial depots.
- A minimum level of buffer stock (at programme initiation, this will be four weeks' supply; by the end of year 5, it decreases to two weeks).
- A registered pharmacist on-site.

Physical Plant Upgrades

Most public health pharmacies will have to upgrade their facilities to deal with the demands of storing and dispensing large amounts of ARVs. Site upgrades will include an expansion of storage facilities for Schedule 5 medicines and investments in the IT infrastructure to allow for online order placement and prescription information collection and management. In addition, pharmacies will need adequate rooms for patient counselling. This should strengthen pharmaceutical care throughout all services rendered.

Prescription Tracking

A significant portion of the population moves between their homes and a separate place of work. To ensure uninterrupted access to needed medications, it will be important for individuals to be able to get prescriptions filled as they move throughout the country. Therefore, a system needs to be in place to track prescriptions throughout the country. A software module will have to be added to the inventory management system discussed in the provincial level depot section to track patient movement throughout the system (see Chapter XI, *Patient Information Systems*). This will improve tracking and follow up for all patients on chronic medication, including TB patients.

SPECIAL CONSIDERATIONS

Contingency Stock Plans

In order to minimize potential disruptions to ARV programme implementation, a contingency stock plan has been considered. Drug manufacturers will be required to keep a two month supply of stock on hand in their local warehouses. This requirement will help to minimize the chance of stock-outs in the country while at the same time lessening the storage demands of the provincial depots and public health pharmaceutical facilities.

Packaging to Optimise Adherence

The provincial depots have a role to play in the packaging of ARVs to improve overall drug adherence. For example, using a system that is already in place in a few of the provincial depots, packaging all the separate ARVs from a single regimen into one box or bag can greatly improve the dispensing and administering of the drug. As the IT systems improve, printing the name of the prescription recipient on each package at the warehouse or depot before it arrives at the local pharmacy will greatly improve the security and accurate dispensing of the medicines at the pharmacies. This also allows for the introduction of direct-shipping options to prescription recipients. As the number of individuals on ARVs increases over time, consideration might be given to the development of capacity to provide the type of individualized, large-volume packaging that is required through contracts with local suppliers. This can be extended to other high value items and specialised treatment regimens.

ADMINISTRATIVE STRUCTURE

In order to ensure the proper implementation of the drug distribution component of the ARV programme implementation, the Pharmaceutical Policy and Planning Cluster will manage the following structures:

- The Committee for Medical Provisioning (COMED) will determine the standard operating procedures as they relate to inventory management, security, and distribution of all medicines including ARVs to all public health pharmacies.
- The Heads of Pharmaceutical Services Forum will assess training programmes and materials, and ensure proper budgets are in place to deliver on the drug distribution plan.

- The Pharmaceutical Policy and Planning Cluster will oversee the pharmacy accreditation process, developing a strategy to ensure that accreditation can happen in a timely manner. Other activities will include development of standards for tracking and tracing of medicines

PROGRAMME ASSESSMENT

The Pharmaceutical Policy and Planning Cluster will assess the programme on an ongoing basis, to ensure that set goals are met. Specifically, at depot level, the goals are to:

- Keep shrinkage of ARVs below 0.5%.
- Process orders within 48 hours.
- Maintain a minimum of 6-week stock at the provincial depot level.

At the pharmacy level, the goal is zero stock-outs and shrinkage below 0.5%. Manufacturers will be measured based on meeting expected lead times, the quality and completeness of orders, and the maintenance of a continual 6-week stock in local warehouses.

At facility level, the ultimate goal is to ensure that records of patients' medication profiles are kept to facilitate counselling on drug use, follow-up of patients on chronic medication that default, reporting of adverse events and adverse reactions and to link all pharmacy activities to a patient information system.

Chapter IX

Laboratory Services

OVERVIEW

Laboratory diagnosis of HIV infection, staging of disease progression, and monitoring of therapies, including management of antiretroviral toxicities and the response to therapy are essential components of HIV care and treatment. The significant current expense of these tests mandates a careful assessment of the required tests and their use. Price negotiations with suppliers are ongoing.

The laboratory services established as part of this programme incorporate the best available evidence and international guidelines in order to establish a judicious laboratory plan. Moreover, the high volumes that will be required to support the HIV and AIDS care and treatment programme make significant reductions in the price of CD4 and viral load tests likely.

The guiding principles of the laboratory services component of the ARV treatment programme are:

- To support best practices of patient care.
- To monitor for the development of drug resistance.
- To establish evidence-based, cost-effective and sustainable laboratory services.
- To expand currently available capacity within the NHLS to offer best support to the clinical services.

The National Health Laboratory Service (NHLS) will take responsibility for the laboratory services as required to support the HIV and AIDS care and treatment programme. Although the NHLS has a strong infrastructure base, additional infrastructure and capital equipment expenditure will be required to support the programme's laboratory needs, as will targeted improvements in sample collection, specimen transport, laboratory training, and information systems. Initial working capital will be required to support initial implementation operations. The NHLS could contract out work to the private laboratories

as a contingency measure.

The NHLS operational plan is outlined at the end of this chapter, following a brief summary of the laboratory services to be provided under the care and treatment plan and a brief discussion of additional laboratory issues relevant to the HIV and AIDS care and treatment programme.

BACKGROUND AND RATIONALE

Laboratory Services to Support HIV Care and Treatment

A set of diagnostic assays is central to HIV care and treatment, in accordance with national and international guidelines:

- HIV diagnostic tests (rapid tests, ELISAs, and infant diagnostics)
- CD4 counts
- Viral loads (currently by quantifying HIV RNA. Other technologies may become available.)
- Toxicity assays (such as FBC and ALT)
- Resistance monitoring
- Diagnostics for opportunistic infections

Clinical Monitoring Protocol

The NHLS laboratory services will follow the requirements dictated by the ARV treatment clinical protocols (see Chapter I, *Prevention, Care and Treatment*). The protocol for clinical monitoring of HIV disease has been evolving since the mid-1990s, when antiretroviral drugs to treat HIV infection and new laboratory assays - particularly viral loads - were first introduced. While there is consensus on some issues, there is as yet no well-established protocol for laboratory and clinical monitoring. Recent guidelines were set forth by the World Health Organization and by the United States Public Health Service, but revisions of these recommendations are expected in the near future. In order to remain vigilant of new developments in monitoring, the Department of Health will develop periodic updated guidelines for the ARV treatment programme. (See Chapter I, *Prevention, Care and Treatment*, and Chapter XII, *Monitoring and Evaluation*.)

CD4 Count and Viral Load

The CD4 count assay is the cornerstone of HIV disease monitoring. CD4 counts provide an assessment of the immune system in HIV-infected patients and are used to track both the decline in immune function in untreated patients, and the rise in immune function following the initiation of ARV treatment. A CD4 count below 200 cells/mm³ will be the major laboratory determinant of entry into ARV treatment until further evidence indicates otherwise, and CD4 counts will also determine the need for specific interventions to prevent opportunistic infections.

To perform these tests the NHLS will require significant investment in laboratory infrastructure, capital equipment and ongoing operational expenditures. Based on current projections, a cumulative total of between 14 and 20 million CD4 counts will be performed after the first five years of the ARV programme. To meet these targets, infrastructure and equipment to support CD4 count testing will need to be developed in all NHLS regions. Of the NHLS sites selected for CD4 testing, capacity is currently available in Cape Town, Durban, Johannesburg and Bloemfontein. To meet targets, CD4 laboratories will be established in Nelspruit, Polokwane, Umtata, Ngwelezana, and Port Elizabeth. New sites in Newcastle, Port Shepstone and Tshepong could be established by the fifth year of the programme to handle the projected increased needs.

Specimen transport capacity to ensure timely delivery of samples to the designated CD4 laboratories will be upgraded where necessary. Overall CD4 testing capacity will need to be expanded approximately six to eight-fold after five years. Training will have to be expanded to equip the new technical staff required (see the outline of the NHLS operational plan below).

Viral load assays measure the amount of HIV present in the plasma of an infected individual. They serve three functions: as a marker of progression from HIV infection to AIDS; as a measure of the response to ARV treatment; and as a sentinel indicator for development of treatment failure, possibly due to drug resistance. The assays are technically complex to perform, and require sample separation within eight hours of collection and subsequent sample refrigeration. Based on current projections, a cumulative total of approximately three million viral load assays will be performed after

the first five years of the programme.

Of the NHLS sites selected for viral load testing, capacity is currently available in Cape Town, Durban, and Johannesburg. To meet targets, viral load laboratories will be established in Bloemfontein, Umtata, Ngwelezana and Polokwane, as well as one additional site to be determined based on need. To maximize cost effectiveness and thus reduce costs to the DoH, viral load and CD4 testing will remain centralized as far as possible, particularly in the first five years of the project, or until the technology changes sufficiently to permit cost effective service to be offered closer to the point of service.

The NICD would form an additional facility to handle any specimen demand in excess of current capacity. A detailed table of facilities upgraded to perform these two assays by year is included in the summary of the NHLS operational plan.

South Africa's CD4 and viral load volumes will likely expand the global market for these assays by 50-100 percent. In order to minimize the budgetary impact, significant price reductions can be achieved through strategic partnerships with international manufacturers of the CD4 and viral load testing equipment and reagents. These partnerships should involve not merely volume discounting, but innovative ways to reduce the costs of production and distribution and guarantee supply, and the development of local manufacture of consumables or reagent kits will be explored. Such partners may be used to fast track new technology for African and global use. Commercial partners should be selected on their ability to provide the highest quality equipment and test kits using protocols designed for resource-constrained settings, at affordable pricing.

Toxicity Monitoring/Pharmacovigilance

The existing infrastructure of the NHLS is sufficient to handle the routine assays used for toxicity monitoring, particularly given the anticipated upgrades to several previously disadvantaged district and central laboratories, and to specimen transport capacity that will take place within the ambit of this project. As the programme expands additional infrastructure development of district laboratories and service sites for routine haematology and chemistry is anticipated, particularly in provinces where current peripheral laboratory capacity is limited.

The clinical monitoring protocol calls for laboratory assays to monitor the toxicities of the antiretroviral medications. These include monitoring for the development of liver toxicity after the initiation of the first ARV regimen, and testing for anaemia and cholesterol abnormalities for patients receiving the second regimen. These assays are technically simpler (and therefore less expensive) than CD4 and viral load testing, and are currently performed routinely by the NHLS. In addition, it is anticipated that other tests to monitor potential toxicities not identifiable through routine screening will be clinically indicated for a subset of patients (such as pancreatitis, lactic acidosis, and glucose intolerance). The ability to perform these assays on an as needed basis has been budgeted into the laboratory component of the programme, based on projections of the frequency of ARV side effects. (See Chapter XIII, *Pharmacovigilance*.)

APPROACH

The availability of high quality laboratory services is an essential component of the HIV and AIDS care and treatment programme. There are a number of key principles that apply. Testing will need to be performed using the best international standards. Investment in high quality laboratory infrastructure will have to be made to monitor patient safety, response to therapy and eligibility for ARV therapy. This investment will also improve access to laboratory services nationally. Although national standards will proscribe certain tests, these tests will need to be available as clinically indicated. In addition, price negotiations should be conducted to achieve lower prices for higher volumes of tests being performed.

National Health Laboratory Services (NHLS) Operational Plan

The NHLS will provide the laboratory services for the ARV programme within the resources available to it. This is in accordance with legislation currently in effect in South Africa. Should the NHLS infrastructure prove inadequate for the workload, work could be contracted out to the private pathology sector by the NHLS. In reviewing its capacity to meet the needs of the programme, the NHLS has identified seven priority areas for development:

- Enhancing laboratory infrastructure to support CD4 count and viral load testing.

- Improving specimen transport infrastructure in currently under-serviced areas.
- Improving information technology and laboratory information systems to facilitate transfer of patient details and results between clinical service sites and the laboratories. This will also permit improved data mining capability.
- Upgrading district hospital infrastructure where necessary for basic laboratory assays and specimen processing.
- Expanding laboratory staff training to support increased need for viral load and CD4 testing, quality assurance and information technology.
- Implementing dried blood spot technologies for support of VCT external quality assessment (EQA).
- Identifying and supporting research priorities in affordable HIV related diagnostics, monitoring and surveillance.

Support for the NHLS in each of these priority areas is included in the operational plan and outlined briefly here.

Laboratory Infrastructure to Support CD4 Count and Viral Load Testing

Implementation of the ARV treatment programme nationally will require expansion of central laboratory facilities extending into all regional divisions of the NHLS. The facility expansion plan will be reassessed regularly by NHLS in coordination with the Department of Health, particularly in the first phase of the programme when uptake may be variable across the provinces. By increasing capacity at existing facilities and diverting specimen transport, the NHLS can flexibly meet unexpected increases in demand. By the third phase of the programme, sufficient capacity should exist in each province to meet local/regional CD4, viral load, and toxicity testing needs.

Specimen Transport Infrastructure

CD4 counts and particularly viral load assays have unique specimen handling constraints, further complicating laboratory operations. A comprehensive plan to identify geographic areas and existing laboratories needing specimen transport upgrades has been conducted by the NHLS. Areas in need of additional transportation resources (including four-wheel drive vehicles) will be prioritised, in order to ensure that laboratory services are equitably distributed and do not hinder programme implementation. Specimen transport should be monitored and addressed on an ongoing basis by the NHLS. In addition, technologies to reduce the impact of specimen transport issues, such as dried blood spots for viral load

assays and point-of-care diagnostics, will be developed, evaluated, and implemented as they become available.

Information Technology (IT) and Laboratory Information Systems (LIS)

The existing laboratory information system in place at NHLS laboratories will be expanded to meet the needs of the ARV treatment programme. This will facilitate improved turn-around-times. Data mining will also be possible within the existing Laboratory Information System (LIS). Computer hardware and licensed software will need to be brought into several existing peripheral laboratories, to improve the interface with the rest of the NHLS. Implementation of the IT expansion also encompasses system installation and LIS training for laboratory personnel. The existing LIS infrastructure will also be utilised by the NHLS to monitor laboratory ordering practices and laboratory costs, as well as regional uptake of laboratory services. (For further details, see Chapter XI, *Patient Information Systems*, and Chapter XII, *Monitoring and Evaluation*). This data will be communicated to the DoH. Demographic details and laboratory results may also readily be accessed in NHLS data repositories for additional analyses.

District Hospital Infrastructure

In addition to the creation of additional central laboratories for CD4 count and viral load testing, several district hospitals may be upgraded to enable CD4 count and viral load testing based on demand. While essential laboratory assays (such as HIV ELISAs, FBCs, or liver enzymes) are already well established and generally sufficient for the needs of this project, upgrades will be implemented where necessary. Such upgrades will need to be undertaken in order to ensure that laboratory services are available in geographical settings appropriate to demand across the country.

Laboratory Staff Development

The laboratory expansion also necessitates a significant expansion in the numbers of trained laboratory personnel, particularly with respect to CD4 and viral load testing. Technical laboratory training for laboratory technologists and technicians is currently coordinated through the NHLS, the professional registration bodies, and technical training institutes. Training capacity will be enhanced by the establishment of a national training centre at the NICD (National Institute for Communicable Diseases) campus in

Johannesburg. Educational and training efforts will be coordinated with the appropriate certification boards and will be determined by the laboratory-specific human resource needs in each region. Training manuals and short courses on laboratory techniques associated with the ARV treatment programme have been developed and are currently available through the NHLS. In addition, the companies supplying equipment and reagents for the viral load testing should offer equipment and assay-specific training. (For further details, see Chapter V, *Human Resources and Training*).

Dried Blood Spot Technologies for VCT External Quality Assessment

As support for the VCT needs associated with the ARV treatment programme, an external quality assessment (EQA) programme for rapid HIV test kits will be developed. This EQA programme will take advantage of advances in dried blood spot (DBS) technology. Specimens collected as dried blood spots for EQA at service sites and VCT centres can be collected, stored, and shipped to the NICD laboratories for EQA cheaply and reliably. Establishment of an expanded EQA Programme will include improvements in basic infrastructure, additional training for laboratory staff, training for VCT site staff on DBS sample collection, and capital equipment and reagent purchases, including DBS punch elution equipment and DBS packets for VCT sites.

Research

A research programme focused on operational questions central to the ARV programme and on the development of affordable technologies for HIV laboratory services will need to be established within NHLS. Research will include developing methods for improving laboratory services. The research agenda should include resistance monitoring, strategies for optimal ARV laboratory monitoring, and clinical utility of assays at each time point during treatment, the appropriate laboratory evaluation at the initiation of therapy, and the development of new, inexpensive methods for CD4 count and viral load determination. Further details of the research programme can be found in Chapter XIV, *Research Priorities*.

SPECIAL CONSIDERATIONS

Laboratory aspects of Voluntary Counselling and Testing (VCT)

The VCT programme will be an important point of entry into the ARV treatment programme. The existing VCT programme now encompasses 1,625 sites and nearly 5,000 trained VCT counsellors. With the introduction of antiretroviral therapy, it is anticipated that demand for VCT services will increase significantly. Coordination between the ARV treatment programme and the VCT programme will be established to ensure that there is appropriate procurement of HIV testing kits and ready supply at VCT sites. In addition, the NHLS will expand their external quality assessment (EQA) programme for the HIV rapid test kits now in widespread use throughout the VCT initiative. Moreover, contingency plans to address either excess demand or low uptake of ARV treatment programme services need to be coordinated between the VCT and ARV treatment programmes. This may require increased HIV ELISA testing capacity within the NHLS.

Resistance monitoring

As the affordable range of antiretroviral drugs available for use against resistant virus is limited, ensuring that development of drug resistant HIV in patients receiving ARVs is minimized is a high priority of this programme. Resistance monitoring has been established as part of the monitoring and evaluation of this programme, as well as a high priority for research (see Chapter XII, *Monitoring and Evaluation*, and Chapter XIV, *Research Priorities*). The National Institute for Communicable Diseases can support the research needs for resistance testing, which is technically complex. The Department of Health will be responsible to review and report regularly on developments in the field of resistance monitoring, including opportunities for price reductions and the establishment of guidelines for the use of resistance assays.

Opportunistic infection diagnostics

Several laboratory tests are commonly ordered in the context of HIV care to diagnose HIV-related opportunistic infections. Current capacity exists within the NHLS to support these assays, including cryptococcal antigen tests, tests for cytomegalovirus, hepatitis and herpes viruses, and others. The Department of Health, in coordination with the NHLS, will undertake periodic review of OI diagnostics.

Infant diagnostics

Standard HIV antibody test kits (i.e. rapid tests and antibody ELISAs) cannot reliably diagnose HIV infection in infants until approximately 18 months of age. Assays that may be used to determine whether an infant born to an HIV-infected mother is infected prior to 18 months of age include P24 antigen serology and HIV DNA PCR. While available in many laboratories within the NHLS, these assays are not always in routine use. Strategies for infant diagnostics are currently coordinated by the PMTCT programme. It is recommended that a Paediatric Monitoring Task Force be established, and charged with coordinating protocols for infant diagnostics and monitoring with the PMTCT programme and the NHLS.

ADMINISTRATIVE STRUCTURE

The National Health Laboratory Service (NHLS) will implement the laboratory component of the ARV programme.

Because of the cost of laboratory testing and the scope of laboratory services in the ARV programme, the laboratory component represents a significant fraction of the overall budget, despite the development of a monitoring protocol that attempts to minimize unnecessary testing without compromising clinical care. Strategic partnerships with suppliers that include centralized purchasing, predictable volumes and innovative cost reduction initiatives are expected to lead to cost reductions in the necessary equipment and reagents. Procurement plans will be coordinated with NHLS and the Department of Health as the project progresses. These may change with time depending on changes in pricing structures and availability of new technologies.

PROGRAMME ASSESSMENT

The SMT will monitor the laboratory costs of the ARV treatment programme on a regular basis, and will meet regularly with NHLS executives to review data on laboratory utilization, turn-around times, patient friendliness, costs, and new diagnostic assays. The Department of Health will assess the protocols used for initiating ARV therapy and for monitoring patients receiving ARVs on an ongoing basis, including reviewing laboratory

monitoring protocols, based on new developments in HIV laboratory technologies and evolving international guidelines.