



BRIGHAM AND
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CASES IN GLOBAL HEALTH DELIVERY

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CONCEPT NOTE

The Global Health Supply Chain

Esther, a mother of three children living in rural Kenya, was distraught. George, her three-year-old son, had been suffering from a high fever for 48 hours; he slept fitfully but constantly, having no energy to respond to his siblings' attempts to distract him with toys. The community health worker had diagnosed George with malaria and advised Esther that she could acquire both antimalarials for George as well as a bednet to protect all of her children at the village drugstore. Esther's visit to the drugstore was unsuccessful; it was stocked out of both antimalarials and bednets. The woman behind the counter had no idea when the next shipment would arrive. It could be as early as that afternoon or as late as next week. Esther walked five kilometers to the nearest village and found a man in the open-air market selling drugs out of a basket he carried on his arm as he moved through the crowd. Esther declined to buy his antimalarials after she watched him sell the same pills to the previous customer as a cure for typhoid. Esther returned home and spent a sleepless night trying to comfort George, whose fever seemed to be getting higher.

Esther woke up with the sun the following morning and borrowed a neighbor's bicycle to travel 20 kilometers to a larger village that had a number of options for purchasing drugs. The licensed pharmacy had the antimalarials, but the cost was four times higher than the last time she had purchased them for her daughter three months ago. The pharmacist also reported that there were no bednets to be found in the entire province—that a district health officer had told him that there was a large supply in the capital city, but they seemed to be stuck in the Central Medical Stores. She thanked the pharmacist and headed to the open-air market. She was sure that one of many vendors setting up small stands, where they sold a variety of goods in addition to medicines, would have the drugs that would cure George and that she would not be forced to make a choice between George's health and affording food for her family.

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In general, a supply chain consists of all parties involved, directly or indirectly, in fulfilling a customer request.¹ The supply chain parties can include raw materials suppliers, manufacturers, transporters, wholesalers/distributors, and retailers. The combined efforts of the various parties determine the cost-effectiveness and responsiveness of the supply chain in satisfying customers.

The wide variety of parties, relationships, products, and requirements involved in the supply chain make it a complex, dynamic system. This system can be characterized as a network that supports three types of flows: materials, information, and finances. The supply chain system can also be characterized by

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the various functions and processes that occur to enable these flows. Over time, the concept of supply chain management (SCM) has emerged to incorporate a scope beyond traditional logistics functions like transportation and warehousing to include upstream activities, such as raw-material sourcing and manufacturing, and downstream activities like customer service. Some organizations have extended supply chain management even further to play active roles upstream in product design and development and downstream in marketing and sales.

In global health, SCM can be a daunting task involving intricate forecasting, negotiating for price reductions, transporting sensitive cargo over thousands of miles, untangling the red tape of customs regulations, and maintaining trained personnel. The flow of drugs, in particular, needs to be monitored through every step, as there is a constant danger of losing goods to thievery and corruption. Although the actual methods and approaches vary from project to project and country to country, this note provides a general reference for the essential components of the process (see **Exhibit 1** for an overview of the global health supply chain). While this note describes the global health supply chain using the functional process view—using the broad areas of manufacturing, procurement, and distribution—it is important to consider the flows that span these activities, since the overall system effectiveness depends on integrated management across the supply chain.

Manufacturing

In the later stages of a lengthy discovery and development process for pharmaceuticals, medical devices, and other health commodities, the manufacturing process for these products is established. The effort and cost to perfect and certify manufacturing processes for these products can be significant. Manufacturers must also manage the upstream procurement of raw materials required to produce the product. For example, the *Artemisia annua* plant is the sole source of artemisinin, which is the essential ingredient for the ACT treatments recommended for malaria. In this case, the manufacturer must manage raw-material supply that requires long cycles of agricultural production.*

Countries and health programs may purchase commodities directly from manufacturers or indirectly through procurement agents. The price, quality, and legality of a given product are often affected by who manufactures it. At a high level, this divides the pharmaceutical market into two sectors: generic and innovator (or branded) drugs. In the generic sector, success depends on being cheap enough to keep manufacturing and other costs down, big enough to dominate distribution channels to wholesalers, and fast enough to move in and out of markets as opportunity ebbs and flows.² One of the largest determining factors in the price of a drug is whether there are manufacturers that produce the drug as a generic.

Generic suppliers provide approximately 63% of the antiretrovirals (ARVs) that go to Sub-Saharan Africa; and, on average, these generic companies charge about one-third of the price charged by patent-holding companies. Sometimes the difference is even more dramatic. When Cipla started producing the ARV triple therapy combination, Triomune, the price of a month of treatment in Uganda fell from USD 500 per month to USD 28 per month. Triomune is made of three drugs from three separate originator firms.[†] As a generic manufacturer, Cipla was able to combine products and create a combination therapy in a way that branded firms cannot.³ Roughly 96% of the ARVs procured are first-line drugs, most of which come from generic firms, while second-line drugs make up the remaining 4% and are supplied almost entirely by patent-holding companies. Of the generic drugs imported to Sub-Saharan Africa, 85% come from India and

* For a teaching case on artemisinin production, see Kileken ole-MoiYoi and William Rodriguez “Investing in Global Health: Botanical Extracts Ltd.” HBS No.GHD-016 (Boston: Harvard Business Publishing, 2011).

† Bristol-Myers Squibb, GlaxoSmithKline, and Boehringer Ingelheim.

the remaining 15% come from South Africa⁴ (see **Exhibit 2** for detailed information on ARV use in Sub-Saharan Africa).

Characterization of the available sources of production leads to another segmentation of pharmaceuticals into three general categories: multisource products, limited-source products, and single-source products. Each of these categories has very different implications for quality assurance and price negotiations.

- ◆ **Multisource products** are pharmaceutically equivalent products that are available from multiple manufacturers. They tend to be off-patent and unrestricted by intellectual property agreements or exclusive market arrangements. Multisource products generally have published pharmacopoeial quality standards and reference standards for quality control testing.⁵
- ◆ **Limited-source products** are pharmaceutically equivalent products available from a limited number of manufacturers due to patents and exclusive market arrangements. Pharmacopoeial and reference standards for quality-control tests may not yet be publicly available.⁵ When a drug is produced by the patent-holding company in some countries and by a generic producer in countries where the drug is not patented, this drug is considered limited-source.
- ◆ **Single-source products** are generally under patent, available from only one manufacturer, and under no licensing arrangements that allow other companies to produce the drugs. In addition to patents and market exclusivity arrangements, a product may be single-source because it is technically difficult to manufacture or because there is no economic incentive for other firms to produce it. Pharmacopoeial and reference standards for quality-control tests may not yet be publicly available.⁵

Patents and Intellectual Property Law

As mentioned, one of the most effective ways to lower the cost of pharmaceuticals is by purchasing them in a generic form. Usually when a manufacturer holds a patent on a medical product, all other producers are prohibited from making or selling that product. For most pharmaceuticals, the period of patent protection is 20 years; after this time has elapsed, generic forms of the drug can enter the market. Patents are country-specific; therefore, a drug may be under patent protection in certain countries but not in others. This may be because the originator has not sought a patent in these countries or because the patent has expired. The only way to know if a product is under patent protection or close to coming off patent is to check with a country's patent office. One product may also be covered by a number of patents (product patents and process patents) in a country, so it can be difficult to determine if a product is covered by patents.

The trade of generic versions of patented drugs is governed by the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). On an international scale, the TRIPS agreement requires all World Trade Organization members to adhere to minimum standards of intellectual property protection.⁶ It establishes minimum international obligations for the protection of patented pharmaceutical products. In 2001 the members of the World Trade Organization adopted the Doha Declaration on the TRIPS Agreement and Public Health, which authorizes the governments of "least developed countries to forgo the enforcement of patents on all pharmaceutical products until January 1, 2016. If a government decides not to enforce a patent, it is important for the government to issue an official document to that effect. Otherwise the generic supplier might be reluctant to sell because of the risk of liability⁵ (see **Exhibit 3** for the World Bank's flowchart of procurement for least developed countries).

Developing countries that are not in the category of “least developed” have the option of issuing a “compulsory license,” which allows a producer to override existing patents. A national government can issue such a license to itself (called a “government use license”) or to a third party. Article 31 of the TRIPS Agreement allows every government to grant compulsory licenses. The government can grant a compulsory license for in-country production or can request a foreign government to grant a compulsory license for export.⁵

When a compulsory license is issued, the government issuing the license and the originator agree on a royalty to be paid to the originator; this amount is often only a small percentage of the purchase price.⁵ In addition, because originator companies are aware of the World Trade Organization regulations that allow their patents to be bypassed, these companies sometimes offer voluntary licenses for the manufacture or import of their products to least developed and developing countries. Alternatively, some originators have developed access programs that sell ARVs at prices that are lower than the prices of generics (i.e., equity pricing initiatives, as described in Pricing section).⁵

Another way of acquiring patented medicines at a low price is through the process of parallel importing. Parallel importing involves finding the lowest price for the patented drugs in any country and buying in the country with the lowest price. The drugs can then be imported without the consent of the in-country patent holder—the originator having already been compensated by the first sale of the drugs. It is, however, unlawful to re-export products that were imported directly from the originator as part of an access program.⁵

Quality

Proving that drugs are safe and effective can be essential for getting drug purchases approved for funding and getting drugs registered so that they can be legally imported. Hence, quality assurance is an important aspect of the manufacturing process. Auditors must be able to verify a manufacturer’s compliance with quality specifications as well as good manufacturing and distribution practices.

Various institutions, including the World Health Organization (WHO), have set definitions of good manufacturing and distribution practices. Substandard products can be common, especially among generic medications produced specifically for export. Counterfeit products that contain the wrong ingredients, too little of the active ingredient, or no active ingredient are also found. The process of quality assurance involves evaluating individual products’ dossiers and running independent laboratory tests to monitor quality. It is important to create ongoing systems for assuring drug quality, as producers may not remain reliable over time.⁵

In order to be imported, pharmaceuticals must be registered with the country’s national regulatory authority (that is, of course, if the country has a functioning national regulatory authority). Registration is a country’s way of ensuring that the drugs are safe and effective, but many countries’ regulatory authorities do not have the facilities or the resources to conduct their own tests. It is possible to get drugs registered without any in-country testing, but the process can be difficult and drawn out. A significant amount of data must be provided in a registration dossier, including the active ingredients, indications, dosing, stability, and bio-equivalency results (for generics). In addition, the manufacturer must provide a certificate of good manufacturing practices (GMP) and a certificate of pharmaceutical product (CPP). The packaging, labeling, and marketing of the product are also subject to review by national regulatory authorities. In the case of HIV drugs, however, some governments have declared health emergencies because of high rates of HIV infection. Where this has occurred, it is sometimes possible to import unregistered drugs.⁷

If a drug is not registered, it is possible to secure preregistered status through a “fast-track” process. Unlike a regular registration process, a fast-track process does not require the supplier to submit clinical and toxicological data to prove safety and efficacy. Rather, the national regulatory authority relies on previously published literature and registration documents from the country of origin. Countries often engage in a fast-track process when procuring well-established generics and urgently needed drugs.⁵

The WHO Prequalification Program was created in 2001 to facilitate the approval of high-quality medicine for HIV/AIDS, malaria, and tuberculosis. The program evaluates manufacturers for compliance with WHO standards for generics and good manufacturing practices. Prequalification can make it easier to secure funding for drug purchases, since funding organizations can be assured the drugs are coming from a prequalified program.

Procurement

The first stage in procurement is selecting which drugs are needed for a health project’s target population. The WHO has established a model list of essential medicines. It is organized by type of disorder and lists the most important treatments to keep stocked for each category. It has been updated every two years since 1977, and includes medicines that address most global health priorities, including malaria, HIV/AIDS, tuberculosis, reproductive health, and, increasingly, chronic diseases such as cancer and diabetes. In addition, most countries develop and publish their own essential medicines lists, adapted to address local medical conditions. Some also have provincial or state lists.⁷

For certain infectious diseases, such as HIV and tuberculosis, product selection is complicated because of the danger of drug resistance. Multiple drug combinations (multitherapy) are used to avoid creating drug-resistant strains, and patients who develop drug resistance or unbearable side effects need to be moved to less commonly used drugs called “second-line” drugs. Drugs are classified as second line when they are less effective, have potentially worse side effects, or because they are more expensive to produce.

Forecasting

After determining which diagnostics and drugs will be stocked, a health care organization must determine its short- and long-term needs. Due to the presence of numerous regulations, multiple parties with vested interests, and a high level of expertise required to make these decisions, the ultimate purchasing decision is not in the hands of one party. In this case, the end consumer of the product, namely the patient, has a limited say in the decision-making process. Forecasting is used to estimate the quantities of each product that a program will dispense to users for a specific period of time in the future. Forecasters must be able to project longer-term trends in usage and procure appropriately. At the program level, the procurement process can be lengthy (often more than a year) and inflexible (because it is usually contract-based), making it necessary to estimate long-term trends in consumption. An adequate forecasting process must consider the following:

- ◆ **Historical data:** The decision maker must consider the past use of commodities and how that use pattern has changed over time. This can be done simply by graphing the data. Forecast accuracy generally improves with the use of more sophisticated forecasting tools that incorporate statistical measures and time series methodologies.
- ◆ **Future program plans:** The decision maker must know the future plans for the program and have some way of realistically estimating the effect of those plans on the demand for commodities.

- ◆ **Underlying patterns:** The decision maker can base assumptions on knowledge of typical demand variance patterns over time, new products entering the market, length of new drug approval, clinical utilization rates, changes in disease burden, and population demographics.

In global health, forecasting is usually done on an annual or semiannual basis to align with the purchasing process, where transactions are spaced over longer periods to enable bulk quantity orders. The delivery of drugs, however, can be made in installments so that shipments do not spoil and do not overload storage facilities.

Forecasting is aligned with the ordering process, since the party making the order is the one responsible for anticipating demand. A simple way to characterize the ordering process is according to the push/pull boundary in the supply chain flow. “Pull processes” are initiated by customers based on actual consumption. “Push processes” are performed in anticipation of orders from customers.

In global health, the push/pull distinction has led to a characterization of the entire system. In a pull system, individual health facilities do their own forecasting and assemble a requisition that details what drugs they need and in what quantities. This requisition is sent to higher-level authorities and eventually to the organization that will buy the drugs (usually the Central Medical Stores (CMS) in a national system or the procurement manager of a nongovernmental organization). In theory, these higher authorities do not do any forecasting; they simply buy the drugs that the health facilities include in the requisition. The advantage of a pull system is that it gives individual health facilities more ownership of the procurement process and allows them to base forecasts on the nuances of local conditions. A disadvantage in systems where resources are limited is that health facilities often ask for more than they need because they are accustomed to receiving only a fraction of what they order.

In a push system, the health facilities do not do their own forecasting. Instead, they draft a “requisition” that is simply a report of the stock on hand, consumption from the past procurement period, losses, and adjustments. This report is sent to higher-level authorities, who then do the forecasting and purchase the amount of drugs that they believe the facilities need.

Forecasting requires an understanding of the timing for new product introductions, product life cycle management (i.e., patent to off-patent), drug-recall management, and identifying and eliminating counterfeits from the clinical inventory. The challenge of drug forecasting illustrates how providers and managers must understand their own systems and the supply chain of new and old commodities.

Purchasing

Governments in some countries have established organizations to procure medicines and health-related commodities. Health projects working in those countries, including non-governmental organizations, usually have the option to purchase drugs through the national government’s organization. Purchases can also be made directly from manufacturers, although manufacturers rarely have the lowest prices. The best prices are often those offered by nonprofit procurement agents that buy in bulk and specialize in supplying high-quality, low-cost medicines for developing countries.⁷

Pricing

There is no single price for a given pharmaceutical product. Prices vary among manufacturers, and prices also vary as the product passes through different stages of the supply chain. The manufacturer’s selling price (i.e., the price of the drug when it leaves the factory) reflects raw material and production costs combined with fixed overhead and markup. In-country wholesale prices include the price of transportation,

insurance, and import taxes in addition to the manufacturer's price, plus the wholesaler's markup. Retailers in turn add their own markup.⁵

Perhaps the most complex and least predictable aspect of pricing is the way in which suppliers adjust the price of a given product according to the country where it is being sold. Depending on the reason for these adjustments, this practice is called either "differential pricing" or "equity pricing."

- ◆ **Differential pricing** is the practice by patent-holding companies of adjusting prices in different countries and different regions according to demand characteristics (e.g., overall market demand, buyer's purchasing power). The purpose of differential pricing is to increase sales in markets that otherwise could not afford the product.
- ◆ **Equity pricing** aims to make drugs affordable to patients of all income levels. This method of pricing is not always in conflict with profit-oriented strategies; but even when it does not maximize profit, its philanthropic purpose is often economically beneficial because investors look on it favorably.

Producers may be reluctant to implement either of these pricing schemes because of the possibility that drugs purchased at low prices might be illegally exported and sold in markets where they fetch higher prices. If this is the case, governments can press for differential or equity prices by stressing their ability to prevent the purchased drugs from going into illegal markets.⁵ To help prevent sale in illegal markets, manufacturers often label and package drugs differently for different markets. Drugs sold to the developing world or produced for sale at concessional or differential pricing may be a different color, and the packaging may also look different from the regularly priced, developed-world product. This visual difference makes it easy to identify when donated or low-cost drugs end up for sale in other markets. In addition, producers can limit parallel trading by inserting clauses in their sales contracts that prohibit reselling of differentially priced drugs. Countries can also limit parallel trading by making rules of "intellectual property exhaustion," which outlaw parallel importing.

Purchasing Methods

For many commodities, the way to assure the lowest prices is through open international bidding where a buyer advertises its needs, multiple suppliers make offers to meet those needs, and the supplier that makes the lowest offer is chosen. Open international bidding, however, rarely makes sense for pharmaceutical products because there are usually very few producers for a given product, and when there are multiple producers, it is more likely that some products will be of dubious quality. The following methods are usually more appropriate ways to find the best price:

- ◆ **Limited international bidding** is used when there are very few quality-assured suppliers that are capable of manufacturing the needed product. Quality-assured suppliers are invited to participate in bidding, which is not openly advertised.⁵
- ◆ **Single-source (direct) contracting without competition** is used when there is only one producer whose products can be legally imported. Reasonable prices to be used as a basis for direct contracting negotiations can be found in the drug-pricing bulletins regularly published by UNICEF, Management Sciences for Health, and Médecins Sans Frontières (Doctors Without Borders). A country can often get lower prices by purchasing in bulk with neighboring countries.⁵
- ◆ Shopping means comparing prices from local and international suppliers for readily available, off-the-shelf goods.⁵

However, once the actual contracting is arranged, it is always cheaper to buy in bulk by pooling the purchases of several organizations. Pooled procurement can refer to pooling the purchases of local health systems in a single national purchase or even pooling the purchases of several nations.

National pooled procurement is usually carried out by a country's Central Medical Stores, which is a nonprofit, parastatal (i.e., having some political authority and serving the state indirectly) agency. The CMS is the arm of the Ministry of Health that is responsible for buying, storing, and distributing drugs on a national scale. The CMS provides drugs for government programs and sells drugs to other health projects. The CMS often lacks infrastructure, personnel, or expertise (see Delivery Logistics section), but it has advantages over non-state procurement agencies. In particular, because it has some political power, it is in a better position to handle international patents and negotiations surrounding drug regulation.⁵

When the CMS cannot procure the necessary products in sufficient quantities, health projects often go directly to an international procurement agency. Because procurement agencies buy in bulk, conduct their own quality-assurance tests, and organize shipping, they tend to be a reliable source for low-price, quality-assured drugs. Nonprofits themselves, procurement agencies usually charge a small, fixed percentage over the cost of the purchase and shipping to cover overhead. The drawback of buying from a procurement agency is that most are based in Western Europe, where many drugs are under patent protection, which might pose difficulties for importing and conducting tests of low-cost generics. It is possible, however, for governments such as those in Western Europe to establish a "regulatory review exception" for procurement agencies providing services to the developing world.⁵ The CMS of low-income countries, as well as non-profits, often purchase their drugs through procurement agencies.

Another way to secure bulk prices is to create a long-term, indefinite-quantity contract, also called a "framework contract." A framework contract is an agreement to place orders with a given supplier over several ordering cycles. The actual amount of the future orders is unspecified, but certain minimum quantities are usually agreed on. Framework contracts are effective ways to lower prices, but they require the health project to have an assured source of funding, and they also limit the health projects' options if a better or cheaper producer were to come on the scene.

Distribution

Once drugs are imported, they need to be stored and delivered to health facilities. While these stages may seem straightforward, there is significant debate over how the in-country supply chain should be organized.⁸

Historically, global health initiatives have preferred to establish independent, disease-specific systems that function in parallel with other disease-specific programs and the national essential drugs system.† When a country starts a new disease program (e.g., an antiretroviral therapy program), it will often create a parallel system to manage the commodities for the new program. This means employing separate, additional staff and using separate transportation equipment, storage facilities, and monitoring systems. While a vertical parallel system is often the simplest and most reliable option, it can also be inefficient. As a program grows, it starts to require more staff and equipment, and it may enter into competition with other programs for these resources.

† The term "essential drugs" can have different meanings depending on the context in which it is used. In the context of the WHO's list of essential drugs, the term includes drugs for tuberculosis and HIV. In the case of "national essential drugs system," it refers to the drugs needed for a primary care facility, excluding the drugs that are delivered through disease-specific programs.

Because of the problems that arise from parallel systems, many advocate for a system in which storage and delivery for all drugs is integrated. The advantage of an integrated system is that resources are often used more efficiently. The disadvantage is that as a program grows and becomes more complex, it may develop its own needs that put strain on a system that was designed for a different purpose. For instance, ARVs require security measures to protect against theft because they are valuable commodities on the black market. Condoms are not. For this reason, it may not make sense to include both in the same supply chain.

As a program develops, the challenge is to create a balance between these two extremes. In some cases, supply chains are integrated for those services that have similar needs and function on a similar scale while the supply chain is kept separate for services with different needs.⁸

International

Transport makes up a substantial part of the cost of delivering care in the developing world because most products are not produced locally. There are several options for international transport, with wide variations in speed and price. For bulky supplies, shipping by sea is the cheapest option, but it is also the slowest. Air transport costs considerably more, but it is much faster. For example, sending a 20-foot container to Rwanda from the United States by ship in early 2008 cost about USD 7,000 and took 10 to 12 weeks; sending the same amount by air cost around USD 20,000 but took only a few days.⁷

Many unpredictable factors can affect the shipping time of a container. Changes in port security procedures can cause delays, even if the container is passing through en route to another country. Customs clearance can be held up by new paperwork or inspection requirements. Local unrest in the destination country or neighboring countries can result in shipments being rerouted, delayed, or lost.⁷ Customs clearance requirements vary from country to country and can be the most challenging part of international transport. Customs ensures that drugs were legally purchased and are registered for use or sale in-country. Bureaucracy and corruption in the customs office can complicate this process.⁹ The process is somewhat simplified, however, by the fact that most non-governmental organizations are tax-exempt and can import medicines and medical supplies free of duties or taxes. Many health projects simplify the international transport process by using freight forwarders, which are independent third parties that assume all responsibility for the transportation of the shipment from origin to destination, including preparing and executing the necessary documentation.⁷

In-Country

Once commodities arrive in-country, they typically are distributed through a multitiered system to reach patients. The typical tiers in the public sector are the CMS, regional and/or district medical stores, and service delivery points (e.g., clinics and hospitals). The key decisions in managing the distribution system include locating and managing facilities, allocating inventory across facilities, and transporting commodities between the facilities.

Facilities

Often a country's SCM system is insufficient to store and transport the quantity of drugs required for a large-scale treatment program. Many national warehouses do not have enough space to organize large volumes of medicines and protect them from common threats such as extreme weather conditions, insects, rodents, and thieves.⁷ It is common at the beginning of a major treatment scale-up for shipments to pile up, unorganized and unprotected, outside of the CMS. Because the effects of an inefficient CMS can be catastrophic, an external agency (e.g., Crown Agents or UPS) will sometimes be hired to manage the CMS.

Ideally these agencies make an effort to hire from among the people who are already working with the national distribution system, and their presence is temporary until a local organization can take over their work.⁵

Beyond the CMS, regional and/or district stores are typically established to position stock closer to the service delivery points to enable more rapid response to needs. Deciding whether to use regional stores, district stores, or both involves trade-offs. Establishing district stores closer to service delivery points increases the service but requires more inventory. Regional stores provide risk-pooling benefits, since inventory is held at a higher level to respond to demand rather than being committed to districts where consumption may not match forecasts; however, the travel time to service delivery points is increased. Establishing stores at both regional and district levels could further improve service, but a very effective inventory management approach is required to manage the high number of stocking points.

Inventory

An inventory control system is designed to keep track of when to order a product, how much to order, and how to maintain ideal stock levels to prevent stock-outs while avoiding unnecessary surpluses of products. Maximum-minimum inventory control systems maintain stock levels within a determined range and are very common. If applied effectively, stock levels should never exceed the maximum level or fall below the minimum level under normal circumstances. The minimum level is the point at which stocks should be replenished. In many global health systems, both the maximum and minimum stock levels are expressed in months of supply as opposed to set quantities of stock. The maximum stock level (in months) remains fixed while actual quantities of medicines and supplies needed from month to month may vary.¹⁰

Several important factors must be considered when setting minimum levels to avert stock-outs. A safety stock level acts as a buffer or stock reserve that can prove useful in instances of unexpected events such as spike in demand or delayed deliveries. A lead-time stock level is the level of stock needed between the moment when a new order is placed and when it will arrive and be available. Both safety stock and lead-time stock should be incorporated into the minimum stock level that triggers an order. Finally, an emergency order point is a level below the minimum at which an emergency order is placed.

When setting the maximum levels, different factors must be considered to avoid unnecessary surpluses and effectively use scarce resources. Products with short shelf life should not be overstocked, since they may expire. Large products such as bednets can consume limited facility space. Overstocking expensive commodities squanders limited financial resources that could have been used to stock different commodities.

Finally, the inventory control system must determine the intervals of time used to assess stock levels and decide if orders should be placed:

- ◆ In a **forced ordering (or periodic review) system**, stock is always ordered at the end of a review period, making the minimum irrelevant. However, an emergency order point must exist to trigger an order should stock levels drop dangerously low between review periods.
- ◆ In a **continuous review system**, rather than having a review period at set intervals, stock levels are reviewed each time a product is issued, and if the stock level is at or below the minimum, enough is ordered to bring the level to the maximum. An emergency order point is not necessary, since the stock is reviewed every time stock levels decrease. In a system with many items to review, continuous review of stock levels may be overwhelming.

Transportation

Transportation can be arranged by the facility providing the product or by the facility receiving the product. In many commercial supply chains, the facility providing the product will often arrange for transportation once an order is received and include the cost in the price of the product. This enables the provider to pool orders for several facilities and deliver them together, lowering the cost. In global health supply chains, service delivery points and regional/district stores often arrange for transportation to pick up supplies when needed. This is due in part to the limited information flow of orders upstream in the supply chain. Communication of orders is necessary for the supplying facility to plan for transportation.

Sometimes product characteristics can determine the transportation requirements. Certain pharmaceuticals must be stored at cooler temperatures and require transportation in refrigerated vehicles. Large items such as bednets must be transported with heavy-duty trucks.

Donations

Not all medicines enter a country through the purchasing mechanisms described above. Sometimes medicines and medical supplies can enter a country in the form of donations. While donations can be helpful and free up monetary resources, sometimes nonprofits are given low-quality, dysfunctional, or unnecessary medicines and equipment.⁷

There are a large number of medical supply recovery organizations operating in the United States and Europe. These organizations collect used medical equipment, repair it as necessary, and either sell the equipment at deeply discounted prices or donate it outright. Medical supply recovery organizations should be evaluated for the quality and range of their products, service and shipping fees, and other services offered (e.g., installation, training, etc.). They can be valuable partners for non-governmental organizations with limited resources and help non-governmental organizations use their procurement dollars more effectively.

Financing

In most health projects, the majority of funding goes toward the purchase and transportation of pharmaceuticals. Because it constitutes such a large part of the budget, all of the major funding organizations have their own requirements for how SCM should be carried out. The policies of the Global Fund and PEPFAR are described below as examples of two very different ways in which major funding organizations have become involved in the SCM process.

Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund)

As of 2009, the Global Fund did not play an active role in SCM. Recipients of Global Fund money, however, must abide by a set of minimum standards for effective procurement.¹¹

- ◆ When applying for a Global Fund grant, the principal recipient submits a report detailing what products will be purchased, how they will be delivered, and how the process will develop over the course of two years. Then the Global Fund's local fund agent (i.e., a public or private consulting agency) evaluates the SCM plan and either approves it or makes suggestions for improvement.
- ◆ Procurement of multisource pharmaceuticals with Global Fund money is fairly easy. The Global Fund defines multisource pharmaceuticals as off-patent products with publicly available quality

assurance standards. Any multisource product that has the approval of the in-country national drug regulatory authority can be procured with Global Fund money. The Global Fund will pay for national laboratories to conduct tests to assure that the product being delivered is manufactured to the specifications found in the pharmacopoeia.

- ◆ Procurement of single-source and limited-source pharmaceuticals is more difficult. Global Fund defines single- and limited-source pharmaceuticals as products for which there is no monograph for the finished dose form of the drug published in the International Pharmacopoeia, the British Pharmacopoeia, or the United States Pharmacopoeia. For single- or limited-source pharmaceuticals to be purchased with Global Fund money, the products must either (1) have approval under the WHO Prequalification Program or (2) have been authorized for approval by a stringent regulatory authority.[§]
- ◆ All medications purchased for the treatment of multi-drug-resistant tuberculosis must be conducted through the Green Light Committee of the Stop TB Initiative.
- ◆ In the interest of transparency and to aid other procurement projects, all prices paid for drugs purchased with Global Fund money must be submitted for publication on the Global Fund's website for the Price Reporting Mechanism**.
- ◆ While some Global Fund projects have benefited from the relative lack of involvement of the fund in SCM, many Global Fund projects have had serious problems with maintaining the necessary drug supply. In response, the fund has begun to organize its own SCM mechanism to support Global Fund-sponsored projects. It is called the Voluntary Pooled Procurement Mechanism, and it is expected to function similarly to PEPFAR's Supply Chain Management System (described below).

The United States President's Emergency Plan for AIDS Relief (PEPFAR)

PEPFAR plays a relatively large and direct role in SCM. In addition to strengthening existing, in-country distribution systems, PEPFAR operates its own mechanisms for procurement and regional drug distribution on a super-national level.¹² PEPFAR's Supply Chain Management System Project (SCMS) is contracted out to the Partnership for Supply Chain Management—a partnership of 16 public- and private-sector organizations.^{††} The partnership, managed by John Snow Inc., operates PEPFAR's own regional distribution centers and provides technical support and medical products for national government supply chains.

- ◆ SCMS supplies the following kinds of products: ARVs; rapid HIV test kits; laboratory equipment (e.g., EIA, CD4, NAT); drugs for opportunistic infections, sexually transmitted infections, home care and palliative care, and tuberculosis; and equipment (e.g., vehicles, computers).

[§] Stringent regulatory authorities under the Inspection Cooperation Scheme (PIC/S) include: Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Malaysia, the Netherlands, Norway, Portugal, Romania, Singapore, Slovak Republic, Spain, Sweden, Switzerland, and the United Kingdom. Stringent regulatory authorities under the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): EU member states, Japan, and the United States.

** www.theglobalfund.org/prm.

^{††} SCMS team member organizations include: Affordable Medicines for Africa; AMFA Foundation; Booz Allen Hamilton, Crown Agents Consultancy, Inc.; The Fuel Logistics Group; IDA Solutions; John Snow Inc. Research & Training Institute, Inc.; Management Sciences for Health; The Manoff Group; MAP International; North-West University; Northrop Grumman; PATH; UPS Supply Chain Solutions; Voxiva; and 3i Infotech.

- ◆ For all of the African countries supported by PEPFAR (all of PEPFAR's 15 focus countries are in Africa, with the exceptions of Haiti and Vietnam), supplies are delivered through three SCMS-operated regional distribution centers (see **Exhibit 4** for map of facilities). Maintaining large warehouses in these distribution centers allows for a streamlined supply chain and averts stock-outs by dramatically accelerating delivery of products.
- ◆ SCMS purchases drugs directly from manufacturers, using regional pooled procurement and long-term indefinite quantity contracts (framework contracts) to negotiate for lower prices. For a single order, countries save 23% on average by procuring generic ARVs through SCMS. Of the drugs procured by SCMS, 90% are generics. Although SCMS does not buy drugs through the International Dispensaries Association (IDA), IDA negotiates drug purchases for PEPFAR. While PEPFAR-sponsored projects are not required to purchase through SCMS, they are required to buy at the lowest prices available, and, according to PEPFAR, those prices are usually SCMS prices.
- ◆ SCMS provides technical support by contracting one of its partners to manage various aspects of the supply chain. For instance, SCMS might contract UPS (one of its partners) to handle transportation of drugs in country. In such a project, UPS uses an entirely local workforce—ideally including the workers who had a role in transportation activities before SCMS intervened.

Information Systems

Information systems make it possible to track drug supply, the rate of drug consumption, and the conditions being treated.⁷ This information is essential to forecasting and monitoring the efficacy of a supply chain.

The first step in information collection is tracking stock on hand—that is, recording what products enter and leave the warehouse. Toward this end, the WHO has developed a collection of drug stock management support tools, including stock cards for use at warehouses and dispensaries and forms for daily use records and annual inventories.⁷ Many programs have combined this system for recording stock information with their medical records system. This combination tends to be very effective because it allows forecasting to be informed by the actual medical condition of patients and their expected needs, not just the past drug usage. For example, it is possible to foresee how many HIV-positive patients not currently receiving ARVs will likely need them in the coming year by assessing national data on viral loads and CD4 counts.

Once data is recorded, it needs to be transferred to a central unit that is responsible for procurement. An information system is often the main channel for the communication of essential data between those who interact directly with patients and those who manage the supply chain. The medium for this communication depends on the availability of Internet and computers. If computers are not available at the level of the individual clinic, then data is initially recorded on paper and computerized at the district or regional level. If computers are available at the individual clinics, data can be computerized at the clinic and sent to a more central facility by Internet or with a messenger who transfers the data on portable memory (e.g., a jump drive). (See **Exhibits 5 and 6** for models of information system organization.)

Whichever system is employed, a key factor in success is minimizing the burden on those who collect and enter the data. This means refining a minimal data set to include only the most important information. The Clinton HIV/AIDS Initiative (CHAI) has put together a list of essential data, with a special subset

marked as essential data for HIV/AIDS procurement and supply chain purposes.† To further relieve the burden on health workers and to address a potential disconnect between health care workers and systems designers, it is often important to have a data management team that visits individual clinics, supervises the process, and takes care of some of tasks that would otherwise overburden health care workers.¹³

After data entry, the next step is to collect and organize the information. Even in developing countries, information is increasingly recorded in electronic medical records systems. This is partly an effect of lower prices for technology, but is also an effect of the major global health initiatives starting to give money for the improvement of information systems.

Human Resources

Managing health commodity supply chains requires cooperation between staff who specialize in SCM and others, such as nurses or community health workers, whose handling of medications and record keeping is essential to SCM, but for whom SCM is not a primary concern. It is also common to hire consultants and specialists to deal with specific parts of the process that require more expertise, such as international intellectual property law or supply chain logistics systems. The core procurement team usually consists of the following team members⁷:

- ◆ A **procurement and operations manager** who is responsible for managing budgets and placing orders. He or she also negotiates for better prices and works with organizations that provide donations and funding for drugs and other medical products.
- ◆ A **logistics supervisor** who ensures that products that arrive in country get to the clinic where they are needed. This task involves preparing all of the necessary documents for medical products to pass through customs and arranging for safe travel from the point of entry to the place of need.
- ◆ A **pharmacy supervisor** who is responsible for overseeing the flow of drugs from the point of entry into the warehouse, through the transfer to the pharmacy, and into the hands of patients.
- ◆ **Site pharmacists and pharmacy clerks** who also contribute to overseeing the flow of drugs and recording data on rate of use and stock on hand.
- ◆ A **data manager** who makes sure that there is an effective system in place for recording data and communicating relevant information between levels of organization—especially communicating information to the procurement and operations manager for use in planning future purchases.

Conclusion

Supply chain decisions are made with an objective to streamline three types of flows—product, information, and funds—within the supply chain. Supply chain management requires an alignment of stakeholders' objectives and timelines. Clinical providers and managers require a greater understanding of SCM as they continue to treat patients for chronic conditions requiring timely delivery of drugs and commodities.

† This subset includes: a unique patient ID number, a clinic ID number, date of death, referral information, ARV regimen, ARV dose dispensed, ARV regimen start/stop dates, other medication, other medication dose dispensed, other medication start/stop dates, and tests ordered.

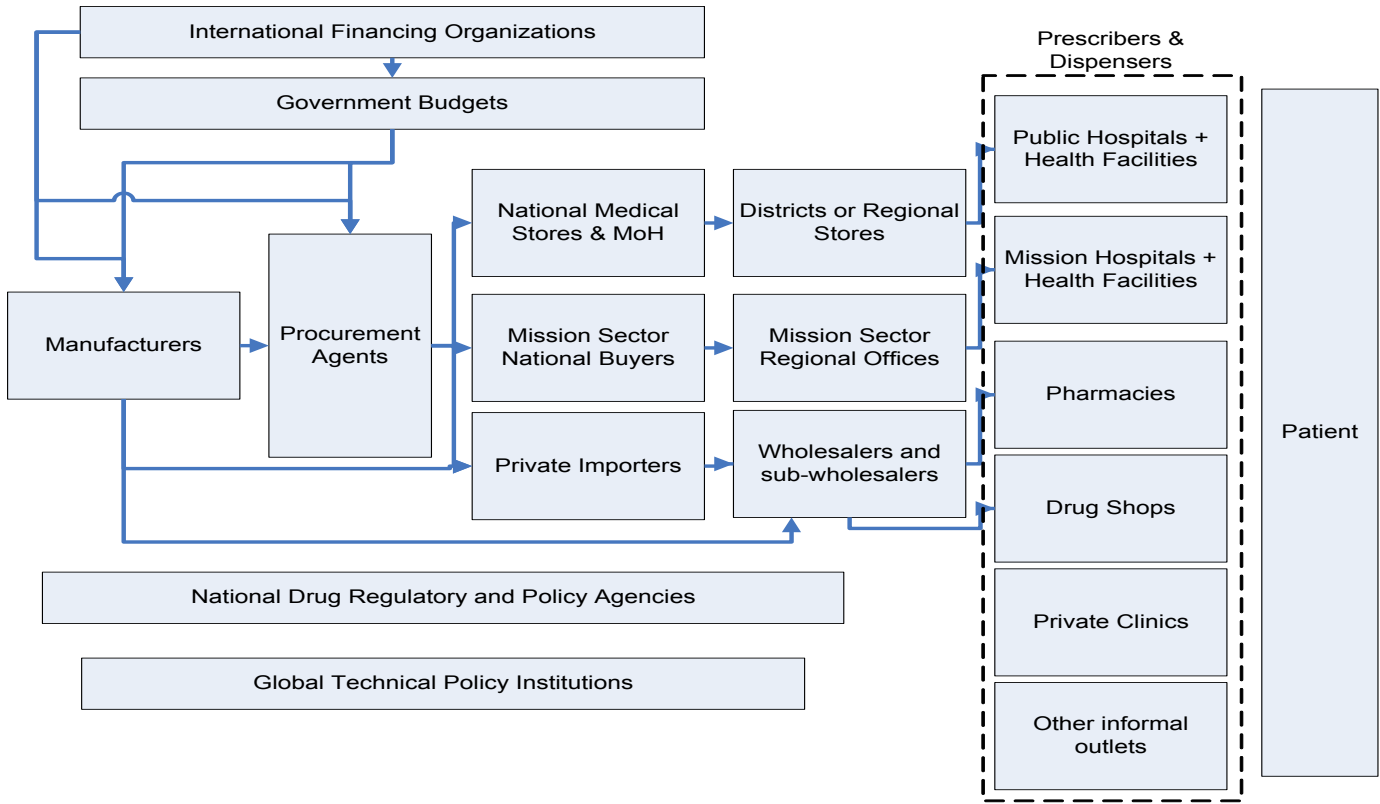
Any practitioner who prescribes drugs makes choices that affect where drugs can be purchased, which affects costs, quality assurance requirements, speed of shipment, and the logistics of delivery. Any patients who suffer because the local pharmacy is stocked out of their medicine feel the indirect effects of international patent laws, the inefficiencies of the national and international regulatory authorities, and the policies of funding organizations.

If the supply chain is treated as a role player, then supply chain–related decisions are determined by reacting to clinical demands. On the other hand, if the role of supply chain management is incorporated in the overall strategy, then it can be used to enhance the overall performance by improving the effectiveness of available assets and resources. An effective supply chain ensures high availability, reduces counterfeits, increases responsiveness, reduces waste, and plays a role in reducing medication errors in combination, driving greater value for all patients.

Abbreviations

ARV	Antiretroviral (drug)
CMS	Central Medical Stores
IDA	International Dispensary Association
PEPFAR	President's Emergency Plan for AIDS Relief
SCM	Supply chain management
SCMS	Supply Chain Management Systems (Project)
TRIPS	World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights
WHO	World Health Organization

Exhibit 1 *The Global Health Supply Chain*



Source: Prashant Yadav.

Exhibit 2 *HIV/AIDS Drugs for Sub-Saharan Africa: Brand vs. Generic Supply*

Table 1. First and Second Line Antiretroviral Drugs Procured for Sub-Saharan Africa

Drug Name	Volume (patient year equivalents)	% of Total Volume	Percentage Brand	Percentage Generic	Avg. Brand Price*	Avg. Generic Price*
First Line ARVs	522,517	96%	35%	65%	277	114
Second Line ARVs	18,984	4%	93%	7%	591	601
Total	541,501	100%	37%	63%	304	116

N = 2,162 orders
 Volumes calculated on the basis of WHO daily dosing guidelines to generate patient year equivalents
 *Average prices in \$/patient yr and calculated on the basis of total \$s paid for drugs/total drugs in category.
 doi:10.1371/journal.pone.0000278.t001

Table 2. First Line Fixed Dose Combination Antiretroviral Drugs

Fixed Dose Combinations	Volume (patient year equivalents)	% of Total Volume	Percentage Brand	Percentage Generic	Brand Maker of Individual Drugs in Combination*
Stavudine (d4T)+Lamivudine (3TC)+Nevirapine (NVP)	109,971	20%	0%	100%	BMS+GSK+BI
Zidovudine (AZT)+Lamivudine (3TC)	61,847	11%	50%	50%	GSK
Zidovudine (AZT)+Lamivudine (3TC)+Nevirapine (NVP)	8,006	1%	0%	100%	GSK+BMS
Stavudine (d4T)+Lamivudine (3TC)	7,537	1%	0%	100%	GSK+BMS
Total	187,361	34%	17%	83%	-

N = 501 Orders
 *BMS = Bristol Myers Squibb, GSK = GlaxoSmithKline, BI = Boehringer Ingelheim
 doi:10.1371/journal.pone.0000278.t002

Table 3. Sources of Generic Antiretroviral Drugs

Country of Manufacture	India	South Africa
Generic Volume (patient years)	288,439	51,947
% of Total Generics Volume	85%	15%
% of Total Volume	53%	10%

doi:10.1371/journal.pone.0000278.t003

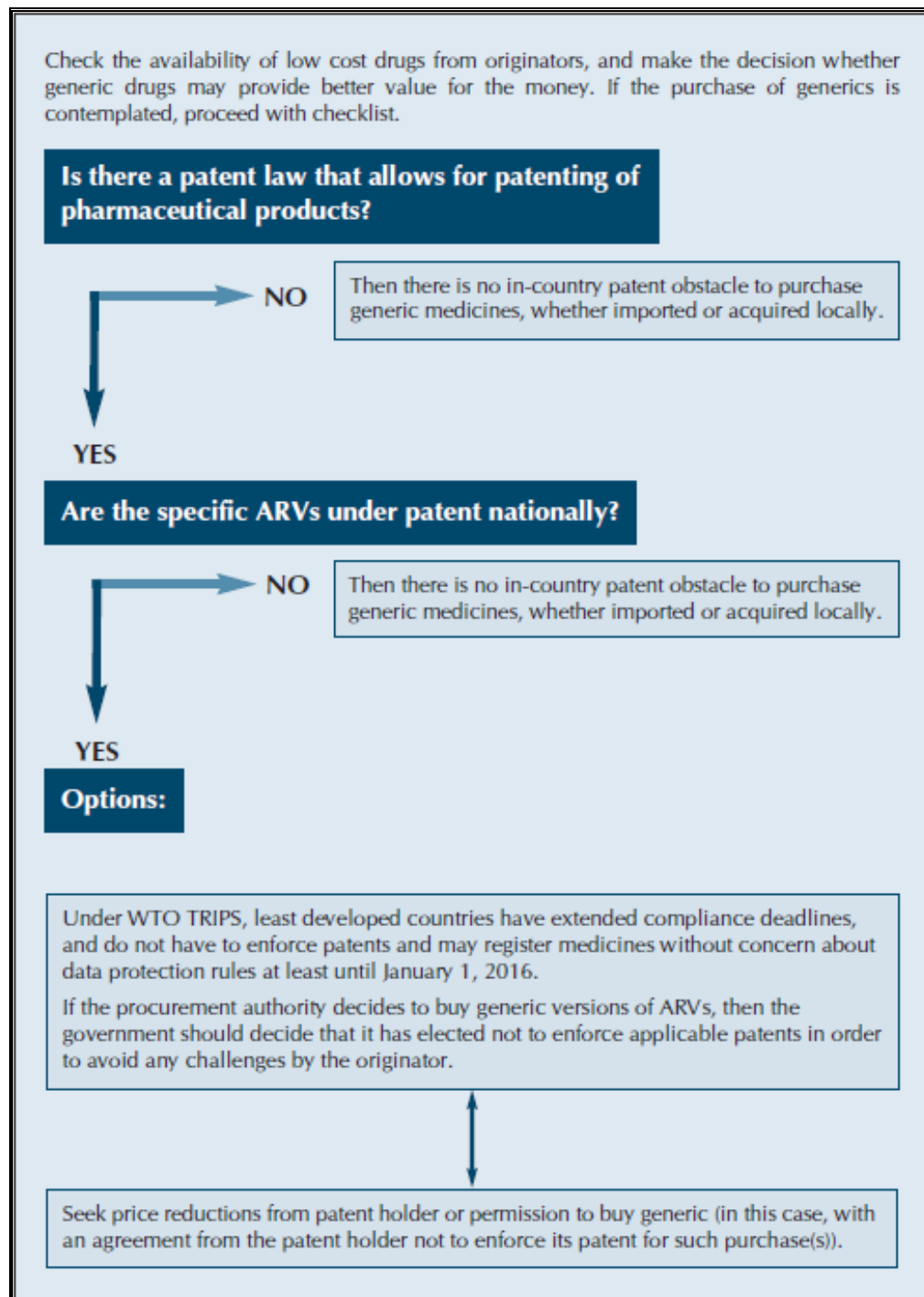
Table 4. Patent and Access Characteristics of First Line Antiretroviral Drugs in Sub-Saharan African Countries

Drug Name	Post-Jan 1, 1995 Priority Date? ^a	Number of Sub-Saharan African Countries in which drug patented ^b	Percentage of Total Countries ^c	Percentage of Order Volume from Generic Source	
				Countries in which drug patented ^d	Countries in which drug not patented ^d
Zidovudine (AZT)+Lamivudine (3TC)	Yes	32	84%	54%	46%
Lamivudine (3TC)	No	28	74%	62%	68%
Nevirapine (NVP)	No	25	66%	48%	59%
Zidovudine (AZT)	No	16 ^e	42%	79%	74%
Stavudine (d4T)	No	1	3%	0%	58%
Efavirenz (EFV)	No	1	3%	0%	16%

^aSource of data: [11,12]
^bSource of data: [14] The status of certain patents may have changed since publication, due to the failure to pay renewal fees, for instance. This would lend further support to the apparent brand company shift away from enforcement of patents in Sub-Saharan Africa.
^cTotal Countries = 38 countries in which transactions reported
^dCalculation performed on the basis of countries that had transactions in that drug category (n = 24-31 countries). Number of countries in which drug patented with 0% generic purchases = 5 (AZT+3TC), 2 (3TC), 2 (NVP), 2 (AZT), 1 (d4T), 1 (EFV).
^eThe expiry date of the US patent on AZT was September 2005 [11].
 doi:10.1371/journal.pone.0000278.t004

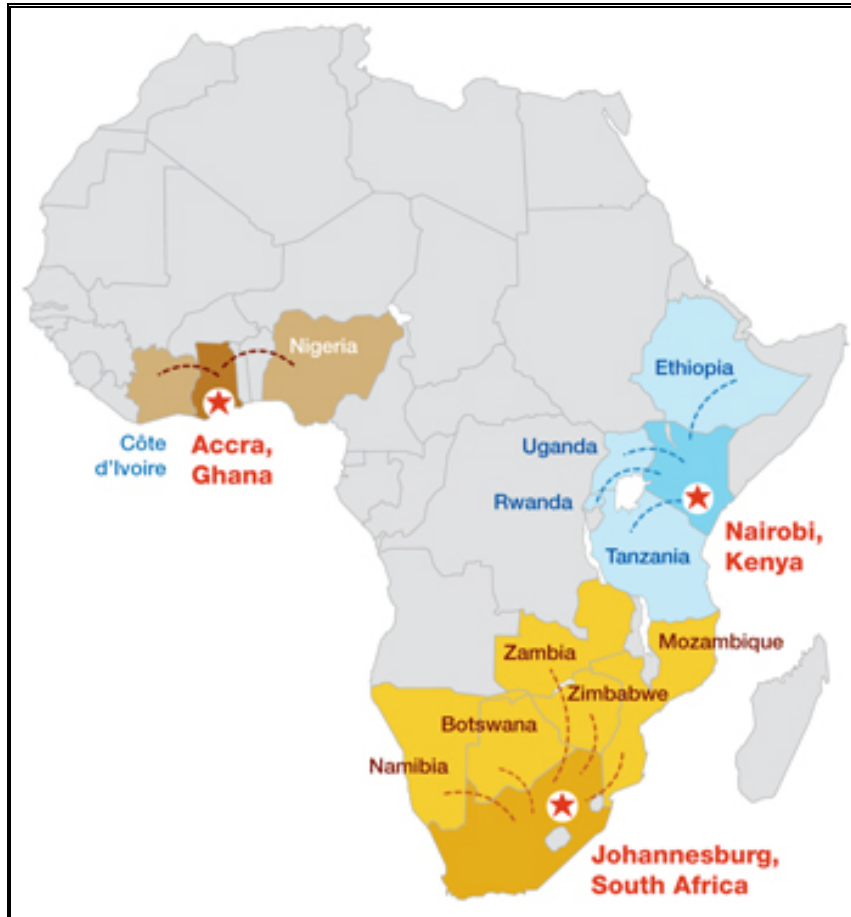
Source: Chien C. HIV/AIDS Drugs for Sub-Saharan Africa: How Do Brand and Generic Supply Compare? PLoS ONE. 2007;2(3).

Exhibit 3 *The World Bank Flowchart for Procuring Generic Drugs in Least Developed Countries*



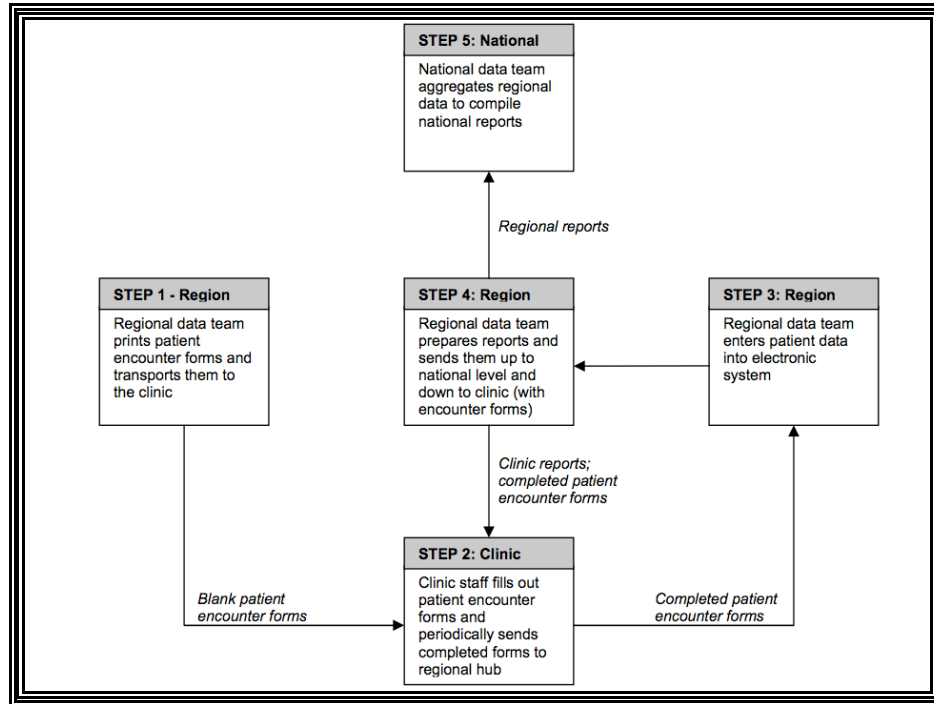
Source: World Bank, 2004.

Exhibit 4 *PEPFAR SCMS Regional Distribution Facilities*



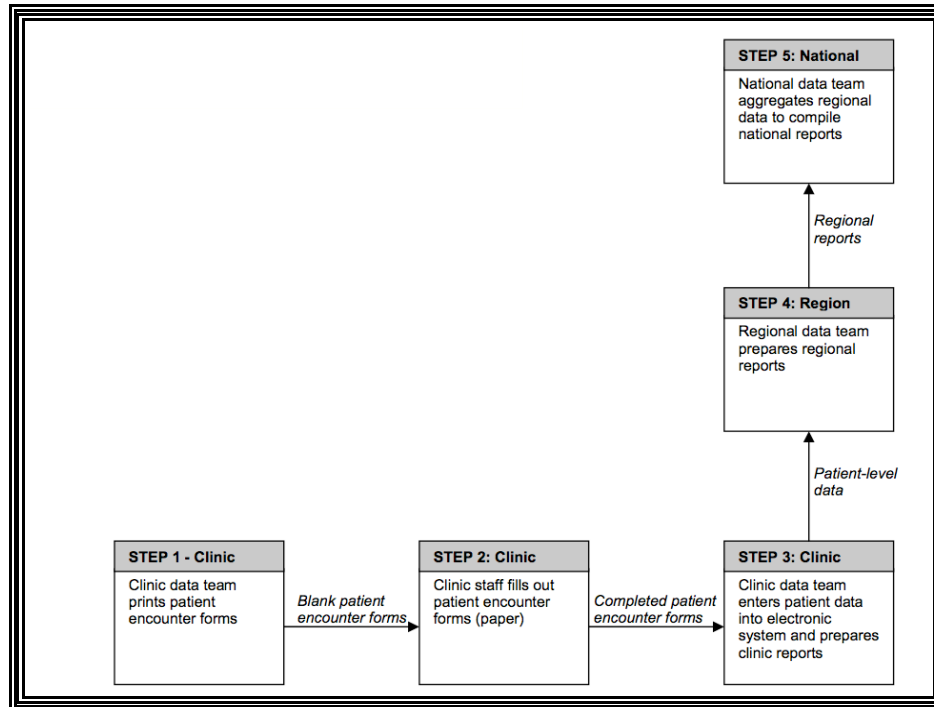
Source: The Supply Chain Management System (SCMS). Where We Work. Available at: www.scms.pfscm.org/scms/where.

Exhibit 5 *Clinton HIV/AIDS Initiative’s Model Information System 1: Paper-based at Clinics*



Source: Clinton HIV/AIDS Initiative, 2007.

Exhibit 6 *Clinton HIV/AIDS Initiative’s Model Information System 2: Computerized Clinics*



Source: Clinton HIV/AIDS Initiative, 2007.

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