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Processes and Issues for Improving Access to Medicines

The evidence base for domestic production and greater access to medicines

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The DFID Health Systems Resource Centre (HSRC) provides technical assistance and information to the British Government's Department for International Development (DFID) and its partners in support of pro-poor health policies, financing and services. The HSRC is based at the Institute for Health Sector Development's (IHSD) London offices and is managed by an international consortium of seven organisations: Aga Khan Health Services Community Health Department, Kenya; CREDES-International, France; Curatio International Foundation, Georgia; IDS (Institute of Development Studies, University of Sussex, UK); IHSD Limited, UK; IHSG (International Health Systems Group, Harvard School of Public Health, USA); and the Institute of Policy Studies, Sri Lanka.

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List of acronyms

ACT	Artemesinin-based Combination Therapy
API	Active Pharmaceutical Ingredient
ARV	Anti-retroviral drug
ECOWAS	Economic Community of West African States
EMCCA	Economic and Monetary Community of Central Africa
FDC	Fixed-Dose Combination (of drugs)
GDP	Gross Domestic Product
GMP	Good Manufacturing Practices
ICH	International Conference on Harmonization (for drug development and approval – includes the US, Europe, and Japan)
NPV	Net Present Value
OHADA	Organization pour l'harmonisation du Droit des Affaires en Afrique (Organization for Business Law in Africa)
OTC	Over The Counter (self medication drug)
PICS	Pharmaceutical Inspection Cooperation Scheme
SS+	Smear-positive tuberculosis case
SSA	Sub-Saharan Africa
TB	Tuberculosis
TRIPs	Trade-Related Aspects of Intellectual Property Rights
UNICEF	United Nations Children's Fund
UNIDO	United Nations Industrial Development Organization
WAEMU	West African Economic and Monetary Union
WHO	World Health Organization

1 Foreword

MSH EUROPE has been commissioned by the UK Department for International Development to examine “whether and how, in what circumstances and time-frames, the domestic production of quality medicines can improve their availability and affordability for the poor in developing countries”, with a focus on sub-Saharan Africa (SSA).

This study was carried out by a team of consultants using data available through interviews with experts and through field visits to Ghana and Côte d’Ivoire in April and May of 2004 (Annex 1).

For the purposes of the study, South Africa was not included because its industrial capacity places it in a category apart from the other 47 countries generally included in the definition of SSA, where industrial capacity is much less developed.

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2 Executive Summary

The issue of domestic production of drugs in developing countries has provoked lively discussion since the end of the 1970s. During this time period, several international organizations, including the United Nations Industrial Development Organization (UNIDO), supported efforts to establish pharmaceutical industries in these countries in order to reduce dependence on imported drugs, create employment, and earn foreign exchange as well as improve access to drugs. However, few of these efforts were successful, and international interest in supporting drug production in these countries waned.

The concept of access to drugs has continued to evolve, and is often defined in terms of four dimensions relative to access to quality drugs, i.e. those that are manufactured in plants that meet Good Manufacturing Practice (GMP) standards, are properly registered, and that reach the end-user through distribution systems that include quality assurance systems. These four dimensions include: geographical accessibility, physical availability, acceptability, and affordability. Of these, the first two are largely dependent on functioning distribution systems rather than the location of drug manufacturing and the third is often dependent on marketing, as end-users in developing countries may need to be persuaded to choose domestically produced drugs over imports. This leaves affordability as the primary opportunity for domestic production to have an impact on access to drugs.

The recent focus on ensuring access to the drugs used to treat HIV/AIDS, tuberculosis (TB), and malaria, diseases which disproportionately affect the populations of SSA, and to ensure their quality, has raised the question of whether the production of these drugs in the region can improve affordability while meeting quality standards. As of June 2004, no enterprise within SSA had been prequalified by the World Health Organization (WHO) for drugs related to these diseases. However, within the past year, several initiatives to start up production, especially of anti-retrovirals (ARVs), have been launched in SSA in order to increase their affordability.

This study seeks to contribute to the discussion of domestic production by analyzing, from a business context, whether or not such production of drugs in SSA is sufficiently profitable to enable an enterprise that produces drugs to be a going concern[1] while at the same time enabling increased access to drugs by providing them at prices lower than those available from international sources.

When the factors that affect the operations of a going concern in SSA are examined, including those related to the country environment, government strategy and policy, and potential market size, a few countries appear to offer a moderately favourable climate

for pharmaceutical production in terms of political risk and human resource availability, but throughout the region drug manufacturers face obstacles in terms of access to financial capital, technical know-how, purchasing and maintaining equipment, and obtaining spare parts. Furthermore, domestic producers face several challenges in the market place. First, institutions and governments will be major buyers of the currently recommended drugs to treat HIV/AIDS, TB, and malaria and will be obliged to respect the procurement guidelines of major donors. For domestic producers, this means that the drugs they manufacture for these buyers have to meet international quality standards, such as those of WHO prequalification, as well as be competitive in price with drugs that are produced on a large scale by international competitors. Second, most national markets in SSA are too small alone to absorb the production of drugs to treat these three diseases. This requires domestic manufacturers to develop an export strategy, which will require registering their products in each of the countries they export to as well as negotiating and obtaining licences, where necessary, for the right to export drugs still under patent to countries that are signatories to the Trade-Related Aspects of Intellectual Property Rights (TRIPs) agreement.

To examine the potential for a going concern that manufactures drugs to operate under these conditions, this study uses a model to simulate the cost structure of an imaginary enterprise manufacturing quality drugs, based in West Africa and serving a market covering 236 million people (i.e. 35% of the entire population of SSA) in 12 countries. This region was chosen because the proximity of countries belonging to different economic trading blocs and different language zones presents opportunities as well as constraints.

Three scenarios were tested: (1) a baseline public health-oriented scenario for the production of 13 drugs to treat HIV/AIDS, TB, and malaria; (2) the production of these same drugs along with the production of eight ethical drugs used to treat diabetes, hypertension, and gastrointestinal ailments, which are currently less of a focus for public health programmes in SSA; and (3) the production of the baseline drugs along with two over the counter (OTC) drugs which do not contribute to public health priorities. For each scenario, two cases were developed: a “greenfield” case simulating the establishment of a new pharmaceutical production plant and an “extension” case simulating the addition of these drugs to the output of an existing enterprise.

The results of the simulation indicate that for all three scenarios, and for both the greenfield and extension cases, the imaginary enterprise can be profitable by the third year of production or earlier. As expected, the extension case is always more profitable than the greenfield case for two reasons: first, less capital investment is required and second, production is at full capacity in the first year. By product type, the ethical drugs are the most profitable, the ARVs and one of the anti-malarial drugs are intermediately profitable while drugs for TB, the antibiotics, and a second commonly-used anti-malarial drug are unprofitable.

The presentation of net present value (NPV) and financing needs demonstrates that all of the scenarios have a positive NPV except the scenario 1 greenfield case. As could be expected, the greenfield cases have much higher requirements (>$10 million) for external financing. This indicates that investment in domestic pharmaceutical production under the conditions outlined in the study can pay off as long as investors choose either to invest in the extension of an existing pharmaceutical plant or in a new enterprise which produces drugs to treat other diseases and conditions as well as HIV/AIDS, TB, and malaria. A minimum of $4 million to $6.2 million, or roughly half of that required for the greenfield case, will still be needed for investing in the extension of an existing pharmaceutical plant, but it may be easier to meet GMP standards with a plant that is built from scratch.

If the available free cash flow generated by the enterprise is used to reduce ex works prices, it appears that the potential for reducing prices from the baseline ranges from 11% to 26%. However, a sensitivity analysis shows that the ability of the enterprise to provide these price reductions is dependent on stable prices for active pharmaceutical ingredient (API) and on achieving sufficient market share.

In conclusion, it appears that under certain conditions (i.e. at prices that are competitive with those of imported drugs, with significant market share, a stable political context, and the production of drugs to treat both priority diseases and conditions of lesser public health importance etc.) domestic production in SSA has the potential to be financially viable as well as to offer the possibility of a modest reduction in the ex works prices of quality drugs. However, there is no guarantee that all of the drugs produced will necessarily meet widely accepted international quality standards, because the WHO prequalification only covers a limited set of drugs. The financial viability of the enterprise appears fragile because it depends on two significant factors which it cannot totally control: the price of API and market share. The inability to obtain favourable prices for API from suppliers, or failure to obtain needed market share would threaten the ability of the enterprise to continue as a going concern. In addition, the enterprise will: (i) have to ensure that the products which it will sell through international and national tendering procedures are prequalified by the WHO (or registered in a country that is a member of either the International Conference on Harmonization, ICH, or the Pharmaceutical Inspection Cooperation Scheme, PICS); (ii) successfully register all of its products in each country it exports to; and (iii) obtain compulsory licences and voluntary licences as needed to produce patented drugs for both domestic consumption and export requirements. Lastly, the logistics for supplying API, equipment, spare parts, and ensuring maintenance will have to be assured in order to avoid costly delays and interruption of production.

Further research is needed in several areas, particularly those related to manufacturing and quality, distribution, and intellectual property.

- To reinforce manufacturing quality, operational research could help better define

the human resource needs and additional costs that current manufacturers would incur in order to consistently meet GMP standards and to prepare comprehensive dossiers for their products.

- Exploring the possibility of subsidizing API. Just as the prices of products which are considered vital are subsidized in many countries, this intervention could help make essential drugs more affordable, whether or not they are made domestically.

- Drug regulatory authorities and quality assurance systems need to be reinforced to ensure that only quality drugs reach the end-user through distribution systems.

- Distribution needs to be made efficient, so that the large mark-ups that are commonly added in both public and private distribution systems do not outweigh or even negate the impact of lower ex works prices for manufactured drugs.

- Lastly, research is needed to further explore how the compulsory licensing provisions provided for in TRIPs might affect the potential for domestic manufacturing to provide increased access to existing drugs patented before 2005 as well as the new drugs which will be patented after 2005.

3 Introduction

3.1. What is access to medicines?

The concept of access to medicines must be defined in terms of access to **quality** medicines. The notion of quality encompasses issues related to production, such as proper registration and manufacturing according to GMP, the systems that assure and control quality within the distribution system, and national regulatory systems that are able to control and monitor quality.

According to the literature, access can be defined using various frameworks, such as that below which was developed at a recent conference[2]:

- **Geographical accessibility**, which includes the concept of the distance between the end-user and a drug outlet which has the needed items.
- **Physical availability**, which can be measured in terms that include indicators related to the stock levels of needed items as well as the availability of drug information for both providers and consumers.
- **Acceptability**, which concerns the relationship between products and services provided and end-user satisfaction with these products and services.
- **Affordability**, which can be understood by relating the price of drugs to the capacity of populations to pay for them. This refers to the price of drugs at the point of distribution where they are paid for by the end-user.

This study does not question the indisputable benefit of better access to medicines for improving health and enabling social and economic development. It addresses the question of whether access to medicines can be improved in SSA by producing them locally. For this production to be sustainable, it must be both economically viable while meeting quality standards, and result in the improvement of access along one or more of the dimensions outlined above.

For the purposes of this study, quality drugs are defined as those that meet internationally recognized standards. These include those of the WHO Prequalification Project[3] or those of countries participating in either the Pharmaceutical Inspection Cooperation Scheme and/or the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use[4]. Currently few, if any, domestically produced drugs within SSA meet these standards. For example, a recent study[5] showed that a significant percentage of commonly-used anti-

malarials (those not covered by the WHO Prequalification Project) distributed in several SSA countries failed to meet test standards for content and dissolution. No drug produced by an enterprise within SSA[6] had met the requirements of the WHO Prequalification Project covering drugs for HIV/AIDS, TB, and malaria as of June 2004.

Therefore, it was not feasible to gather data on domestically produced drugs to evaluate their effect on access, and the decision was made to use a simulation that covers different production scenarios to test if the production of high quality drugs in SSA can result in an improvement in access.

3.2. Promotion of domestic production in the 1970s and 1980s

As the topic of domestic production of drugs in developing countries has been debated and discussed for many years, and continues to be a subject of ongoing discussion[7], it is worthwhile to review other perspectives on domestic production before analyzing the current impact of domestic production on access, and developing the simulation. It should also be noted here that this study does not consider in-depth the impact of domestic production on industrial development. However, pharmaceutical production is capital intensive, and employs relatively few people. This consideration, along with the fact that almost all of the inputs for pharmaceutical production, including raw materials and equipment, have to be imported, suggests that the impact of domestic production on industrial development in SSA is likely to be minimal.

During the 1970s and 1980s the creation of domestic capacity for producing drugs was strongly promoted by certain international organizations and governments. UNIDO provided help to many countries in an effort to create pharmaceutical industries[8]. The assumptions underlying these initiatives were reviewed and analyzed by Foster in 1986[9] and 1999[10]. These assumptions included several principal arguments to justify support to the pharmaceutical industry:

- The country will become self-sufficient in drug supply, thereby reducing the importation of drugs and the subsequent loss of foreign exchange;
- Drug quality will be improved;
- Domestically manufactured drugs will earn foreign exchange through exports;
- Domestic production will create new jobs;
- National prestige will be enhanced both internally and internationally (through discovery of new drugs), and among other developing countries (potential customers).

Foster's papers included reviews of the status of worldwide pharmaceutical production and discussions of the impact of macroeconomic changes over time, changes in the trade environment, the developing country environment, and the priorities of partners such as UNIDO and the World Bank. One key development that she highlights in her second paper is the increase in the market for generic drugs. The increased purchase of generics combined with increased price competition, in turn, led to significant decreases in the prices of many essential drugs. This market shift started in the 1980s as information on drug prices from suppliers around the world became more available, through efforts such as that of the UNICEF Supply Division, which began publishing a list of indicative prices. While this increase was favourable for consumers, Foster notes that it worked against domestic manufacturers who were unable to produce drugs at prices that were competitive with those of large-scale international drug producers. Her conclusions about the difficulties of establishing viable domestic production of pharmaceuticals were borne out by the disappointing results from several initiatives to establish pharmaceutical production in developing countries. By the mid to late 1980s UNIDO had reconsidered its policy on pharmaceutical production, and had shifted to concentrating on quality control and procurement issues.

Two other recent papers have also examined the potential role of domestic production[11,12]:

- Kaplan's study analyzes domestic production from a global viewpoint, using indicators based on macroeconomic indices such as gross domestic product (GDP), balance of trade figures, and industrial competitiveness. The case studies that are included appear to be mostly market reviews of the pharmaceutical sector in several countries but do not include either a detailed review of the activities of specific enterprises or a grounds-up business analysis of the costs, opportunities and constraints that would face a drug manufacturer who is establishing an operation in a developing country. According to Kaplan's indicators, only a few developing countries have the potential to become global suppliers of pharmaceuticals because the majoritydo not meet the criteria in terms of GDP, population size, educational status, industrial competitiveness and positive balance of trade in pharmaceuticals.

- Webber's paper also takes a global perspective, looking more directly at the processes of manufacture and supply, including capacity issues. His paper concludes that the most efficient way to ensure the supply of quality drugs for the entire world would be via their large-scale production in a limited number of plants, located where there is a sufficient industrial infrastructure and available human resources to support them. However, it does not address the crucial question of whether the cost efficiencies realized by such large-scale production would be passed on to the consumer and result in lower prices for drugs.

Both of these papers are unfavourable for domestic production, particularly so when

considering the status of SSA countries relative to their conclusions.

However, despite this pessimism, and the current lack of support for domestic pharmaceutical production in SSA by international institutions, there are today several examples of successful pharmaceutical enterprises operating in SSA[13] (Annex 2). Although none of them have been prequalified by the WHO for the production of drugs to treat HIV/AIDS, TB, and malaria, the WHO is currently analyzing dossiers which have been submitted by a number of these firms.

3.3. Revisiting the issues of domestic production

HIV/AIDS, TB, and malaria have emerged as three priority diseases of public health importance over the past few years. Therefore, this study pays particular attention to the potential for domestic production of drugs to treat these diseases and the simulation includes them in all of the scenarios for the following reasons.

First, there is increased momentum in the international community to combat these diseases, which disproportionately affect the populations of SSA. This has resulted in the creation of high-profile global partnerships such as the WHO "3 x 5" initiative[14], Stop TB[15], and Roll Back Malaria[16], and the establishment of funding mechanisms such as The Global Fund[17], the Multi-Country HIV/AIDS Programme of the World Bank[18], and other scaled-up efforts by bilateral and multilateral institutions as well as governments. As a result, significant public funding is available to buy drugs on behalf of the people who need them for these three diseases.

Second, countries such as India and China, which have been supplying the bulk of generic forms of these drugs, will be required to respect the patent protections outlined in the TRIPs agreement as of 2005[19]. While the 2001 Doha Declaration[20] and subsequent Decision of 30 August 2003[21] have some provisions to allow the continued export of these drugs from India and China to the least developed countries, these have yet to be tested. A more clearly established route would be the use of the compulsory licensing options, authorized in the original TRIPs agreement, by SSA countries to enable domestic manufacturing of the drugs needed for treating HIV/AIDS, TB, and malaria.

Third, there is a rapidly increasing number of initiatives to begin domestic production, particularly of ARVs, but also of artemesinin-based combination therapies (ACTs), in sub-Saharan Africa.[22,23,24]

Taking into consideration the new focus in public health priorities, the changes in intellectual property regimes, and the increasingly widespread use of generics, all of which have occurred since the earlier discussions of domestic production, it is possible to reassess the relationship of domestic production in SSA to quality and access.

- **Quality.** Domestic production does not guarantee better quality because:

  - Both imported and domestically produced drugs to treat HIV/AIDS, TB, and malaria will be required to meet internationally recognized quality standards under donor-funded initiatives.

  - National regulatory systems should control the quality of all drugs sold and distributed in the country, whether they are imported or made domestically.

- **Geographical accessibility.** This is not linked with where drugs are manufactured, but depends on the existence of distribution networks and points of distribution in the public and private sectors where drugs are sold.

- **Physical Availability.** Contrary to what is commonly thought, domestic manufacturing does not improve availability because it depends on a fully functioning distribution network which can be supplied by either imported drugs or domestically produced drugs. Domestic production could ensure physical availability if there is a breakdown in the supply chain for imported drugs *but only if the missing drugs correspond to those that are produced locally.* However, proper forecasting of drug needs and logistical management should avoid disruptions in supply.

- **Acceptability.** In some cases, domestically produced drugs may improve acceptability because packaging conforms with local tastes and because labelling may be in the local language, but in other cases, end-users often perceive drugs imported from developed countries to be of better quality than those made locally and will prefer to buy them if given a choice. Therefore, it is not clear that domestic production will lead to improvement in this dimension of access.

- **Affordability.** Both domestically produced and imported drugs have to pass through either a public or private distribution system before they reach the end-user. The use of subsidies that will be required for drugs such as ARVs and ACTs means that both the downstream perspective of the end-user who obtains the drug at the end of the distribution system and the upstream perspective of the government or other institution that is purchasing the drug in bulk need to be considered:

  - For the end-user, the price of a drug can increase dramatically as it passes through multiple layers within the distribution system (Annex 15) and mark-ups are added. It is not uncommon to see the total of mark-ups add 50-100% to the ex works price of a drug by the time it reaches the end-user, or consumer (Annex 3). Domestic production can improve affordability for the end-user only if drugs can be both produced domestically at lower cost and if these savings are passed on to the end-user through the systems of distribution, whether via

private retail distribution channels or via subsidized and/or regulated distribution mechanisms.

- For bulk purchasers, if domestic production reduces the cost of drugs, these savings could allow the purchase of increased quantities of drugs for the same expenditures, thus enabling public health programmes to expand their coverage. On the other hand, cost-recovery mechanisms and subsidies will still have to be designed in a way to ensure that drugs are affordable to the end-user.

Of these elements related to access, it appears that domestic production could most impact affordability, and for this reason, this study focuses on whether it is possible to lower drug prices through domestic pharmaceutical production in SSA.

3.4. What is the current level of affordability of drugs in SSA?

Generic versions of many essential drugs are currently available in most SSA countries, yet one recent study[25] has shown that paying the full out of pocket price for a complete treatment for a disease episode is out of the reach of as much as 40-70% of the population once this price is over $1.

Although prices of the drugs to treat HIV/AIDS[26] have dropped over the past few years, and the availability of component drugs for ACTs in generic form could enable lower prices for anti-malarials, large segments of the population will be unable to afford these drugs without a distribution system which includes a financing mechanism, such as a subsidy, to absorb most of the cost. In the case of ACTs, no country in SSA has adopted them as first-line treatment without first having secured external funding – funding that will be channelled into large-scale procurements. In TB programmes, anti-TB drugs are typically distributed for free through vertically managed programmes. With HIV/AIDS, funding and procurement are managed at country level. These factors mean that institutions or governments are likely to be bulk purchasers of the majority of the drugs that will be used to treat these three diseases, thus creating a large demand that is different from the type of demand which exists for drugs which are sold through private distribution channels.

3.5. How will the criteria of bulk purchasers of drugs differ from that of an individual who buys in the private sector?

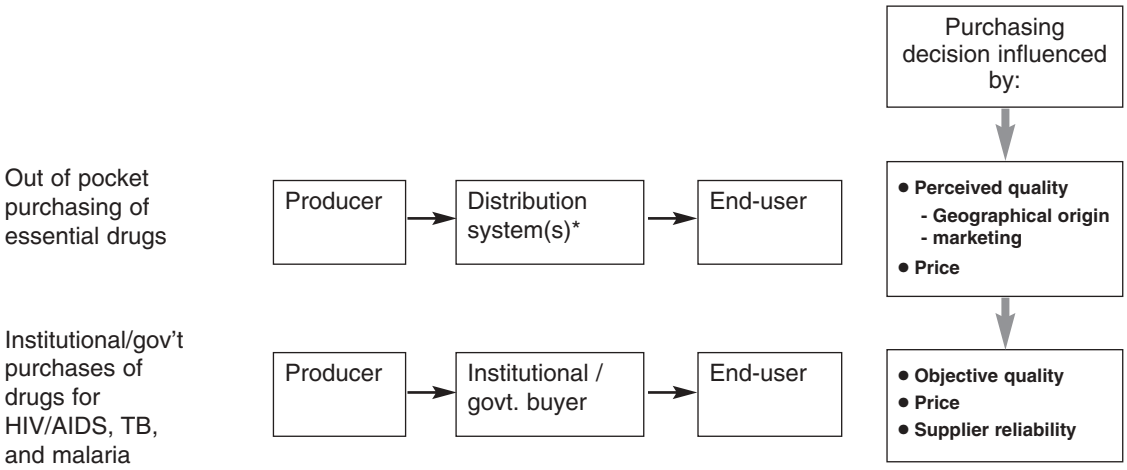
End-users who purchase essential drugs in the private sector pay the full retail price, but in return often have the choice between multiple brands of the same drug at different prices. This choice can be influenced by advertising and promotional activities on the part of the drug manufacturer, and these efforts will often enable a drug manufacturer to

earn a higher profit per unit on the drugs they sell in the private sector.

On the other hand, given the public health urgency of making treatment available on a large scale for HIV/AIDS, TB, and malaria, and the high cost of the currently recommended treatment regimens, institutional and government buyers will be the major purchasers of drugs to treat these priority diseases and will be buying them in large volumes following the procurement guidelines required either by the donors who fund these purchases or by national law. These guidelines[27,28] typically require that the drugs purchased meet international quality standards and that the lowest cost drug be selected for purchase. Profit margins per unit sold will be lower but sales volumes will be large and payment more certain for drug manufacturers.

The contrast between these purchasing criteria and those of individuals buying drugs through the private sector is shown below (Figure 1) although the risk that decisions involving the purchase of large quantities of drugs could be subject to "undue influences" must be acknowledged.

Figure 1: Relationship of end-user to drug manufacturer



In conclusion, domestic manufacturers who wish to enter the growing market for drugs to treat HIV/AIDS, TB, and malaria must produce quality drugs which respect internationally recognized quality standards at competitive prices. As of 2005, The Global Fund will only allow procurement of drugs at the lowest possible prices[29] that have either been prequalified by the WHO or registered in a PICS or ICH country. Manufacturers who wish to succeed in this market will have to focus on quality and production efficiency rather than in advertising and promotion. In addition, because of the wide publicity given to procurement prices in several countries, they will have to consider these prices as a ceiling for their production.

4 Analyzing the potential impact of domestic production on access

First, a discussion is presented of the factors that affect the operating and business environment of a pharmaceutical enterprise based in SSA, second, the current activities of a few firms that were visited in West Africa are presented, and lastly, the simulation is developed.

4.1. What factors affect the operations of a going concern in SSA?

An enterprise that is producing pharmaceuticals in SSA is affected by country environment, government policy and strategy, and the market (Annex 6). These are summarized below.

Country Environment

Factors that need to be considered here include:

- Political and business risk: only Botswana, Namibia, Mauritius, and Swaziland out of the 47 SSA countries have established a sufficient track record to be rated within the "A" classification by the Coface Group[30,31] while the rest are rated "B" or lower. While a rating less than "A" does not rule out investment opportunities (for example, Brazil has a "B" rating) it is an element that potential investors are likely to take into consideration and which will have an impact on interest rates.

- Availability of trained personnel: in some countries the presence of universities and training institutions assures an adequate supply of human resources for the pharmaceutical industry, while in others it is difficult to find trained personnel.

- Access to financial capital, which is often difficult, because of high interest rates[32] and short payback periods of commercial bank loans. Private funds in Europe and the US and foreign direct investment are potential other sources of funds but may be difficult to access.

- Technical know-how, such as that needed to meet GMP standards or to manufacture fixed-dose combinations (FDCs), which has to be imported or licensed from elsewhere.

- Lack of local availability of the raw materials, equipment, and spare parts, which have to be mostly imported from countries with established pharmaceutical industries.

Government strategy and policy

Many SSA governments have adopted fiscal policies in order to favour local industrial development and investment, and several trading blocs have been created with the goal of harmonizing tariffs. Progress in this area is variable: some blocs have already engaged in implementing a common drug registration process[33], common tariffs and common currency, and for others these achievements are several years off (Annex 7).

Pharmaceutical-related policies have made some progress in facilitating domestic production but harmonized standard treatment guidelines, which could inform drug manufacturers on which drugs and dosage forms should be widely used, have not been fully implemented. Therefore drug manufacturers still have to produce many different dosage forms for each drug.

Lastly, labour regulations, environmental protection requirements, and the presence of organized labour generally do not pose obstacles to the establishment of pharmaceutical plants, with the exception of a very small number of selected drugs such as steroids which are not included in the simulation.

Market

Apart from large countries like Nigeria, the national market of SSA countries is too small to absorb all of the production of a domestic enterprise. A drug manufacturer producing drugs for HIV/AIDS, TB, and malaria will therefore be impelled to look beyond national borders in order to sell its products. This requires building a sales and distribution network if the private retail sector is targeted, in addition to participating in international tenders where there will be many competitors.

For patented drugs, compulsory licences need to be obtained both in the producing country for domestic consumption and in countries where the drugs will be exported. Alternatively, a voluntary licence from the patent holder must be obtained.

Conclusion

Although a few countries currently offer a moderately favourable climate for pharmaceutical production in terms of political risk and human resource availability, generally drug manufacturers still face obstacles throughout SSA in terms of access to financial capital, technical know-how, and equipment and spare parts, and have to develop an export strategy in order to sell drugs to treat the three priority diseases, including obtaining both compulsory licences and authorization of the patent holders.

Some of the factors discussed above, such as the lack of availability of raw materials and equipment, are beyond the control of SSA countries, but there are others, such as the availability of trained personnel, or procedures for the regional registration of drugs, where government policies could have a positive impact. Training programmes in industrial pharmacy could be established or reinforced, which could serve the needs of both the local pharmaceutical industry and the regulatory authorities who have to enforce these standards. Regional registration procedures could make new drug products more widely available while at the same time enabling countries to pool resources for more thorough evaluation of new product dossiers and more comprehensive plant inspections than is possible through the resources of the national regulatory authority in any one country.

4.2. What firms are doing now

Within the limitations of the study, it was only possible to visit three different pharmaceutical enterprises, all located in West Africa. Further research should be considered to evaluate the situation in East Africa. However, these visits, which covered firms located within two different economic zones, are illustrative of the different ways in which such enterprises can be structured.

Firm A is an owner-operated firm that grew from a four-man operation to an enterprise that now employs over 300 people with production lines for tablets, liquids, capsules, syrups and powders. Private sector sales comprise the large majority of its business, but the firm also sells to the public sector. The firm does not export at this time, but has developed a large sales and distribution network that covers the entire country. Financing for expansion came from internally generated profits, supplemented by loans from commercial banks. As the company already has significant domestic market share, it is looking for new markets and new products, including drugs to treat HIV/AIDS and malaria, in order to keep growing. Its status as an owner-operated and controlled firm has probably helped with keeping overhead costs low, but if the owners seek to maintain full control, this could deter the recruitment of talented individuals from outside the firm whose expertise may be needed to help the firm make the transition into an international player.

Firm B is majority-owned by large European multinational pharmaceutical companies and produces products under licence agreements with them and other international partners. Its structure enables the enterprise to benefit from both the financial support and technical expertise of well-established companies. However, procurement of API may not be cost-effective because the majority of API is bought through these parent companies at high transfer prices, rather than through open international procurement. In turn, this makes it difficult for the firm's drug products to be price competitive with imports from Asia. The firm does not intend to produce ARVs, TB drugs, or ACTs.

Firm C is privately owned but run by professional expatriate managers who were

brought in by the principal investors. These investors are based outside of the country. The benefits to this company include facilitated access to international financing and management expertise. The international outlook of the firm is reflected in its current efforts to reach export markets throughout West Africa. The disadvantages faced by this structure include the added costs of an expatriate management team. Plans are underway for the production of an ACT.

Each of these firms has different advantages and disadvantages with respect to the production of pharmaceuticals in SSA. However, firms A and C are better positioned to choose which generic drugs they will produce, although meeting WHO prequalification requirements is likely to be challenging for both firms.

4.3. Use of a simulation tool

To measure the impact of domestic production on access, a simulation tool is used to evaluate whether an imaginary enterprise based in SSA could produce drugs at prices which are competitive with imports while permitting it to function as a going concern. The purpose of the simulation is to be able to answer the following question:

Is the domestic production of essential medicines in SSA in a plant which meets GMP standards compatible with the operation of a going concern and with getting these medicines to a suitable market at prices which are competitive with or lower than the same medicines which are imported?

4.4. Simulation methodology

Choice of scenarios and cases

The simulation covers three different scenarios corresponding to three different market strategies:

- **Scenario 1.** An enterprise that is exclusively oriented towards HIV/AIDS, TB, and malaria and only sells to institutions and governments;

- **Scenario 2.** An enterprise that manufactures the same drugs and in addition provides drugs to treat diseases such as hypertension, gastrointestinal ailments, and diabetes, which are currently less of a public health priority in SSA and for which there is a limited market in the private and public sectors;

- **Scenario 3.** An enterprise that manufactures the same drugs and in addition provides OTC drugs such as vitamins and analgesics which are not of public health importance and which are sold only in the private sector.

The distinction between the three scenarios makes it possible to separately calculate the

effect of choosing strategies with differing degrees of orientation towards public health priorities.

For each of these scenarios two cases are considered:

- "Greenfield", which corresponds to the creation of the new plant from scratch.
- "Extension", corresponding to the addition of new products to drug production by an existing enterprise.

It was decided not to develop a scenario including the production of other widely used essential generic drugs because these drugs, such as paracetamol[34], are readily available from many suppliers and profit margins are very low, making it difficult to justify investment in the domestic production of these drugs in SSA when worldwide supply is already adequate.

Assumptions included in simulation

The simulation models the operation of an imaginary pharmaceutical enterprise operating under the constraints of SSA. It allows the adjustment of inputs such as the price of raw materials and sales volumes to evaluate if the domestic production of quality drugs can be done at a lower cost. The simulation is based on several assumptions -

- Intellectual property considerations will not pose a barrier to the production and export of drugs for the following reasons:
  - The basic patents for all of the drugs used to treat HIV/AIDS in the simulation were issued before 1995, the start date for the TRIPs obligations[35] (Annex 4).
  - The API for these drugs is available from multiple sources as of 2004[36].
  - If needed, a compulsory licence will be issued both in the country where the drugs are produced and in the countries that comprise the export market to allow trade. The possibility of a voluntary licence being offered to a firm which meets GMP standards would offer another alternative to obtaining the necessary know-how.
  - A fee of 5% of sales is added to the FDC formulations to cover the costs of licensing and technology transfer.
- It is limited to SSA, excluding North Africa as well as South Africa, where the issues facing pharmaceutical production differ.
- It focuses on secondary manufacturing, that is, the formulation and packaging of

the API into a packaged product (Annex 5), ready for shipping and distribution. These steps represent approximately half of the ex works price and one-fourth of the retail price paid by end-users (Annex 3).

- Re-packaging of bulk finished product is not considered, as the value added by packaging alone is very low, and cost-savings in this step of the drug manufacturing process would not contribute significantly to improving drug affordability.

- The production plant conforms to GMP, and that appropriate studies of safety and bioequivalence are carried out for those drugs which are covered by the WHO prequalification project[37, 38].

- The imaginary pharmaceutical production enterprise is a "going concern".

- It takes into account the factors that determine the ability of a pharmaceutical plant to continue as a going concern, including sales volumes, ex works prices for the finished products, and the cost of raw materials.

Product selection

Priority diseases

13 products, including monotherapies and FDCs, were selected: six ARVs (zidovudine, didanosine, lamivudine, nevirapine, stavudine, and the FDC of lamivudine + zidovudine), two antibiotics (ciprofloxacin and doxycycline) needed for treating sexually transmitted illnesses, three anti-TB drugs (pyrazinamide, ethambutol, and isoniazid + rifampicin), and two anti-malarial drugs (artesunate and amodiaquine) (Annex 8).

This selection is justified as these drugs are included in the recommendations of the WHO, and are likely to be among the most commonly used as public health interventions scale up for the three diseases[39,40,41].

Although the use of FDCs is recommended by the WHO for the priority diseases because it promotes better adherence and can potentially limit the emergence of drug resistance, there are many different combinations possible, particularly for ARVs[42]. Furthermore, the lack of harmonization among different treatment guidelines compounds the difficulty of estimating potential sales with any degree of confidence. Therefore, only two FDCs are used in the simulation: for ARVs, a generic FDC which is already in use in an SSA country, and for TB, an FDC which is likely to be widely used according to the WHO treatment guidelines.

Ethical Drugs

Eight drugs were chosen in three different therapeutic classes to treat chronic diseases:

three anti-hypertension drugs (amlodipine, captopril, and hydrochlorothiazide), two anti-ulcer drugs (ranitidine and omeprazole), and three drugs to treat diabetes (metformin, gliclazide, and glibenclamide). These drugs were chosen because their sales are among the highest (by value) within their respective therapeutic classes (Annex 8).

Over The Counter Drugs

Two OTC drugs were selected (ascorbic acid in effervescent form, and aspirin combined with codeine): one very commonly used vitamin and one painkiller. These were also chosen because they correspond to the highest sales levels in their therapeutic class (Annex 8).

Determination of sales revenues

Country selection

12 countries have been selected across three trading or economic blocs located in West Africa: 10 within the Economic Community of West African States (ECOWAS), seven within the West African Economic and Monetary Union (WAEMU), and two within the Economic and Monetary Community of Central Africa (EMCCA), (Annex 7). This selection was chosen for several reasons:

- Easy access is possible to the majority of the populations of these countries via ports and coastal roads, such as the Abidjan-Lagos corridor.
- Three different economic zones are covered, two francophone (WAEMU and EMCCA), and one which has both francophone and anglophone countries (ECOWAS). This diversity creates opportunities as well as obstacles, as the WAEMU and EMCCA share a common currency and a common tariff schedule. On the other hand, the ECOWAS states that are not part of either WAEMU or EMCCA have made less progress towards economic integration, although there is discussion of establishing a free trade and customs union and a common currency with a central bank located in Accra by 2007[43].
- This region covers a significant proportion (35% of the entire population) of SSA, with an estimated population of close to 235 million.
- 10 of the 13 countries are members of the Organization for Business Law in Africa (OHADA), which is a non-institutional organization that aims to harmonize business regulation in Africa.

Market share and sales volume

Within the defined market, sales volumes for the drugs (scenarios 1-3) to treat the three priority diseases were determined in four steps (Annex 9).

- The need for drugs to treat the three diseases is derived from epidemiological information available from WHO and UNICEF, and population size information was taken from the UN Population Division[44].

- Public health goals[45] are taken into consideration for estimating the demand for anti-TB and anti-malarial drugs: 100% of smear-positive (SS+) TB patients will be treated and 60% of malaria episodes. For calculating ARV and antibiotic sales, a combination of the 3 x 5 treatment targets and actual purchases by a central medical store were used to project required quantities for the population of the 12 selected countries.

- The enterprise's market share of all these drugs is semi-empirically chosen to be 10%. It is obvious that market conditions vary from one product to another, and that the market share will not be the same across all products in reality, but the use of one figure avoids adding undue complexity to the model.

- Full production capacity (100%) is reached by year 3 for the greenfield case and starts at 100% in year 1 for the extension case – meaning the 10% market share is achieved in these years. Once full production capacity is reached, sales increases are set at 10 points per year thereafter and capital investment in plant and equipment is adjusted accordingly.

Based on this market size estimate, which in turn is based on public health goals and an optimistic assumption of market share, the production of slightly more than 100 million tablets per year will satisfy expected sales of drugs to treat HIV/AIDS, TB, and malaria. For a modern enterprise producing pharmaceuticals on an industrial scale, this quantity corresponds to a single production line[46].

The aggregate sales for the chosen ethical drugs (scenario 2) total less than 18 million additional tablets and their production does not require an increase in production capacity or investment in equipment. However, production of these drugs complicates the manufacturing process, lowering the productivity of the production line because of the time needed to change equipment and for cleaning between manufacturing lots.

For the OTC drugs (scenario 3), expected sales volumes of an additional 58 million tablets and specific manufacturing requirements (Vitamin C will be produced in an effervescent form) do require an increase in production capacity (from one to two lines).

Sales unit prices

Sales unit price for each product is set at the lowest purchase price found between two sources: supplier prices in the 2003 edition of the MSH/WHO International Drug Price Indicator Guide[47] and the results of a procurement cycle in 2003 by a central medical store in an SSA country.

Capital expenditures and operating expenses

Costs of setting up production

For the greenfield cases, these include the costs needed to set up a new manufacturing enterprise, including the costs of plant, property and equipment, taxes and tariffs, royalties, and research and development, but for the extension cases, costs did not include those for buildings and land (Annex 10). Because GMP is not specific about items such as building materials or equipment but notes that "…premises must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out..." and that "…equipment must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out…[48]" costs for building and equipment were based on actual information from a confidential source and adjusted to take into account the estimated additional investment required to upgrade to meet GMP. In addition, the following adjustments were made for the three scenarios:

- Scenario 1, which is based on drugs for HIV/AIDS, TB, and malaria only, requires the establishment of one production line.
- Scenario 2, which includes ethical drugs to treat chronic diseases, requires more frequent line changes, cleaning cycles, and additional maintenance. This is accounted for by adding in $500,000 per year in additional indirect costs.
- Scenario 3, which includes OTC drugs, requires additional production capacity estimated at $2 million to set up an additional production line.
- The calculations take into account one year to set up the company, five years of operations for the greenfield case and immediate production for the extension case.

API costs

Costs of API were based on median values taken from publicly available reports[49].

Other costs

For the purposes of analysis, the rest of the unit cost of production is divided into direct and indirect costs. Direct costs include raw materials, direct labour, utilities, and quality control. Indirect costs include depreciation and amortization, indirect labour (such as sales and administration), and overhead expenses. The choice of how to allocate indirect costs is generally done for various internal accounting purposes such as determining the profitability of each product. In this simulation, indirect costs were calculated on a per tablet basis; alternative choices could include the allocation of these costs as a percentage of sales of each product, or by batch size. While the alternatives

will not affect the calculations of profit or loss for the company as a whole, they could affect other internally calculated results, such as the profitability of each product. However, information on batch size was unavailable and it was felt that allocating these costs by tablet would be the most accurate way to reflect the resources actually used in the production of each drug.

Capital Structure

There are a number of ways that a pharmaceutical enterprise could be financed, including the use of investor capital, commercial bank loans, other sources of loans (such as the International Finance Corporation), and grants. There are choices that have to be made about the relative proportions of equity and debt that are used for financing. It is not possible within the context of this study to explore all the possible options, and therefore a mix of financing was chosen, including investor equity, grants, commercial bank loans, and a loan from an organization such as the International Finance Corporation.[50]

The details of these assumptions, as well as an explanation of the other costs factored into the simulation, can be found in Annex 10**,** along with an explanation of how the discount rate was derived in order to calculate NPV.

5 Results and sensitivity analysis

This section is divided into two parts: first, a presentation of the main financial indicators, including a sensitivity analysis of how net income would be affected by changes in API prices and by changes in market share; and second, an examination of the possibility for the imaginary enterprise to contribute to improving access through a reduction in the ex works prices, also using a sensitivity analysis of how this potential reduction would be affected by the changes in API prices and market share. The sensitivity analysis is only performed on the greenfield cases because of the difficulty of applying this analysis in the extension cases when the size of the existing production is unknown. The rationale and methodology of the sensitivity analysis is detailed in Annex 16.

5.1. Financial Indicators

Sales and Income

In each of the six cases, the enterprise appears profitable, with a positive net income by the end of the third year (Figure 2). Two other results stand out: first, the extension cases are more profitable than the greenfield cases for all the scenarios; second, among the three scenarios, scenario 1, the baseline scenario which focuses on drugs for HIV/AIDS, TB, and malaria only, is always the least profitable, whether as a greenfield or extension case. In other words, adding production capacity to an existing facility is more profitable than building a new one. Also, manufacturing a wider range of products is more profitable, as the profit margins for priority disease drugs are relatively low because of their specific procurement requirements. These requirements lead to market conditions that are characterized by intense price competition among many internationally-based drug manufacturers who are trying to win large orders.

A breakdown of profitability by drug product[51] (Annex 12, 13) shows that:

- the ethical drugs are the most profitable;
- ARVs and anti-malarial drugs are intermediately profitable;
- drugs for TB, antibiotics, OTC drugs and a second commonly used anti-malarial drug can only be produced by the imaginary enterprise at a loss.

While these conclusions are partly dependent on the fact that indirect costs were allocated on a per tablet basis, they would not significantly change even if indirect costs

were allocated differently, i.e. by batch size or as a percentage of sales. This conclusion can best be understood by comparing net income per product (the calculation of which depends on an internal accounting decision of how to allocate indirect costs) with the proportion of the cost of API in each product (an external cost which is independent of internal accounting decisions), (Annex 13). There is an inverse correlation between the proportion of API represented in the ex works selling price and the profitability of each product. In particular, for the ethical drugs the cost of API is less than 5% of the selling price. Therefore, it appears that even if indirect costs were allocated differently, this category of drugs would still be highly profitable when compared to the other two categories of drugs.

Furthermore, this analysis suggests that prices for ethical drugs are relatively high when compared to the prices of either the drugs to treat the priority diseases or OTC drugs, especially considering the much smaller sales volumes of the ethical drugs.

Figure 2: Comparison of financial results

	Scenario 1	Scenario 2	Scenario 3
	HIV/AIDS TB Malaria **Q = 108 million**	HIV/AIDS TB Malaria **Q = 108 million**	HIV/AIDS TB Malaria **Q = 108 million**
	+	+	+
	None	**Ethical drugs** 3 Anti-hypertensive 2 Anti-ulcer 3 Anti-diabetic **Q = 18 million**	**OTC** 1 Analgesic 1Vitamin **Q = 58 million**
Greenfield			
Sales (millions $)	**10,5**	**14,0**	**13,2**
Net income (million $)	**1,2**	**6,2**	**4,1**
Net income (% of sales)	**11,6**	**44,4**	**30,9**
Extension			
Sales (millions $)	**12,2**	**16,4**	**15,4**
Net income (million $)	**4,3**	**7,7**	**5,5**
Net income (% of sales)	**35,3**	**47,0**	**35,9**

Results at the end of year 3

Notes: Sales figures differ between the greenfield and extension cases for each scenario because it is assumed that in the case of the extension, production is at 100% capacity in year 1 and grows by 10% per year, while in the greenfield case, production ramps up during years 1 and 2, reaching 100% only by year 3.

Q represents the number of tablets per year produced for each category.

Return on investment and financing needs

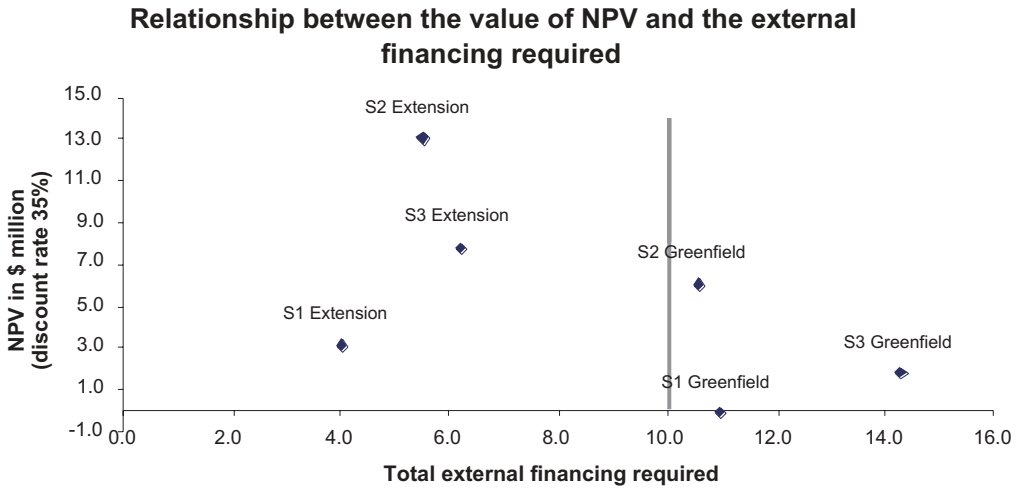
To understand the simulation from the perspective of a potential investor, NPV, external financing needs, and profitability index were calculated (Figure 3, Annex 11g). These calculations show that the different scenarios can be categorized in two different ways:

- those cases which have a positive NPV – all except for one greenfield case;
- those cases which have high external financing needs (>$10 million) – all of the greenfield cases.

Nevertheless, external financing needs are considerable across all scenarios and for both cases. This favours investment in the extension of an existing pharmaceutical plant with the production of either ethical drugs or OTC drugs, along with drugs to treat the priority diseases. A minimum of $4 million to $6.2 million of external financing will still be required, that is to say roughly half of that required for the greenfield cases.

Figure 3: Comparison of NPV and financing needs

	NPV	Rank	External financing	Rank	Equity investment (capital + grants)	Rank	Profitability index	Rank
S2 Extension	13.03	1	5.5	2	3.0	2	4.3	1
S1 Extension	3.16	4	4.0	1	2.0	1	1.6	3
S3 Extension	7.77	2	6.2	3	3.7	3	2.1	2
S2 Greenfield	6.04	3	10.5	4	4.0	4	1.5	4
S3 Greenfield	1.77	5	14.3	6	5.5	6	0.3	5
S1 Greenfield	-0.07	6	11.0	5	5.0	5	0.0	6

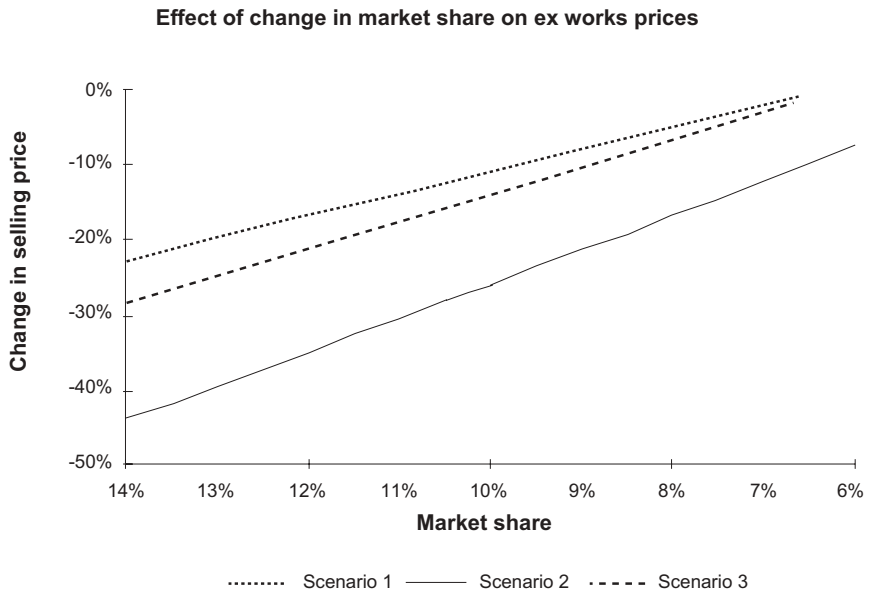


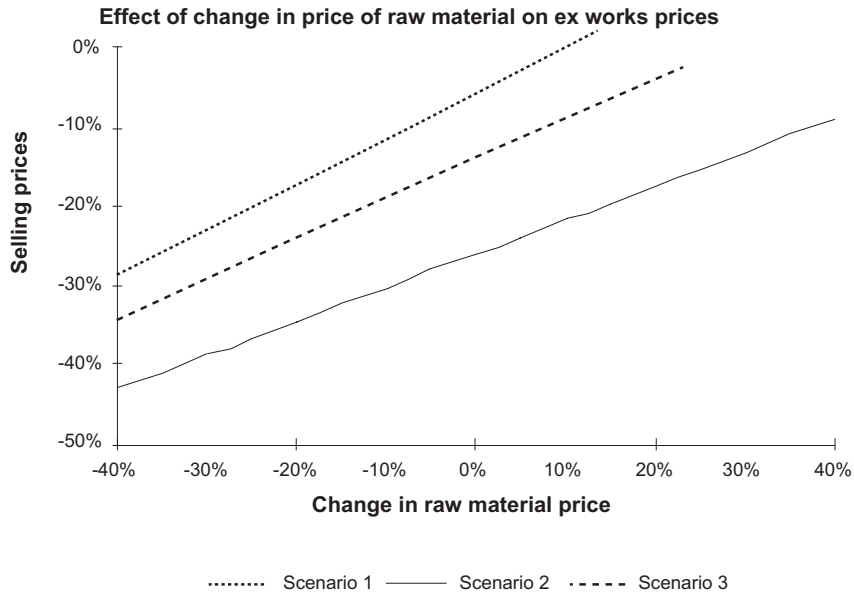
In summary, domestic production appears to be potentially profitable across all three scenarios for both the greenfield and extension cases. However, the latter case is cheaper for investors in all three scenarios, but still requires significant funding.

5.2. Potential to reduce ex works selling prices

If the enterprise decides to use available free cash to enable a reduction in ex works prices (see sensitivity analysis methodology in Annex 16), it appears that the potential for price reductions ranges from 11%-14% (scenarios 1 and 3) to 26% (scenario 2). This difference is due to the much higher profitability of the ethical drugs included in scenario 2.

Figure 4: Effect of change in API price and market share on ex works selling prices





However, an increase in API prices or a loss of (or failure to reach) market share could easily make these price reductions unfeasible. This is quite possible, as typically API prices vary, depending not only on general market demand, but also on the choice of supplier and the ability of an enterprise to negotiate favourable prices. For example, the highest quoted price for zidovudine API from a Brazilian supplier is 45% above the lowest quoted price from an Indian supplier (Annex 17).

As for market share, this depends on the ability of the enterprise to succeed in getting prequalified by the WHO for the drugs to treat HIV/AIDS, TB, and malaria. It must also complete registration of all of its drugs both nationally and within each country that it exports to and establish distribution networks, accompanied by marketing efforts, for those drugs which will be sold through the private sector.

In quantitative terms, an increase of 25% in the price of API would make it impossible to offer any price reductions in scenario 1, almost none in scenario 3, and only 17% (down from 26%) for scenario 2. Similarly, if the enterprise only reaches 6.5% of expected market share, it would be also impossible to offer any price reduction in scenarios 1 and 3, and only 8% in scenario 2.

In conclusion, the imaginary enterprise that is set up as a greenfield offers the potential for a modest reduction in the ex works selling prices of the drugs that are produced, but this reduction is vulnerable to factors that are beyond its direct control.

6 Contribution of domestic production to improving access

6.1. Conclusion

This study shows that under certain conditions (i.e. at prices that are competitive with those of imported drugs, with significant market share, a stable political context, and the production of drugs to treat the three priority diseases and other conditions), domestic production in SSA has the potential to be financially viable as well as offering the possibility of producing quality drugs that are cheaper than imported products.

Financial viability

The financial viability of an enterprise functioning in these conditions appears fragile because it depends primarily on two significant factors, which it cannot totally control: the price of API and market share. The inability to obtain favourable prices for API from suppliers, or failure to obtain the necessary market share, would threaten the ability of the enterprise to continue as a going concern.

An enterprise operating in SSA also has to contend with the other difficulties encountered in the business environment discussed earlier.

In addition, the potential for competitors, such as the large-scale generic producers located in China or India, to undercut prices has to be considered. This would be especially problematic if the prices for ethical drugs were to decrease, as much of the potential profitability of a domestic producer might depend on this category of products if it chose to produce drugs other than those used to treat HIV/AIDS, TB, and malaria[52].

Moreover, several other conditions need to be fulfilled. These conditions fall into two categories:

Technical and Administrative:

- Failure to obtain or significant delays in obtaining:
- WHO prequalification for the drugs to treat HIV/AIDS, TB, and malaria;
- drug registration for all of its products;

- the licensing and other conditions required under TRIPs both for the production of certain patented drugs and for their export to a regional market, which could require negotiations within each of these countries
  These delays would require continued external funding to the enterprise until it reached sufficient market share to be financially independent.

- Availability of sufficient numbers of qualified personnel

Financial:

- Investors have to be willing to forego the repayment of their equity for several years;

- Commercial credit is available;

- No tariffs and VAT are paid on raw materials, including API;

- Corporate income tax is set at zero for the life of the pharmaceutical enterprise;

- Other products with higher profit margins besides those used to treat HIV/AIDS, TB, and malaria must be produced if investors in a greenfield plant demand an adequate rate of return;

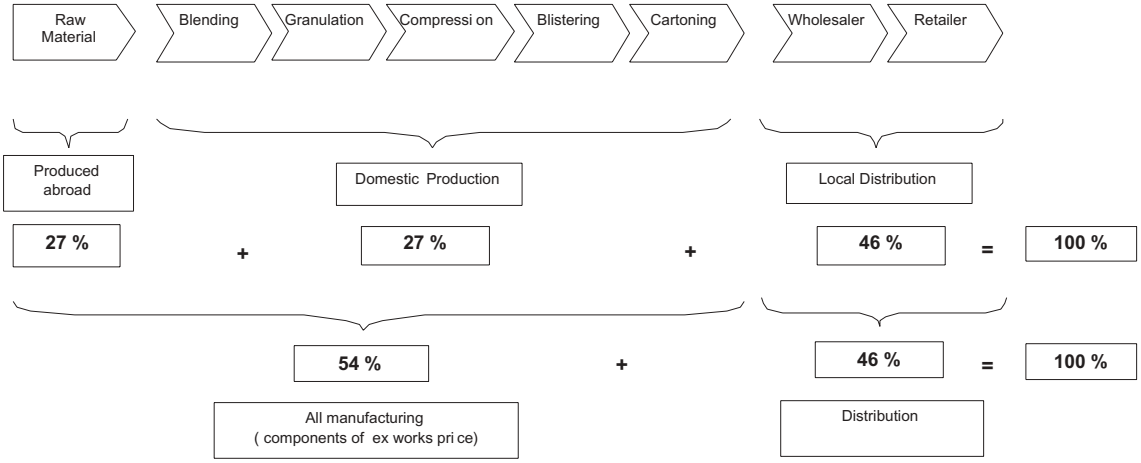
- International financing, especially from The Global Fund, for the purchase of drugs to treat the three priority diseases must be sustained.

The likelihood that these conditions could be fulfilled is difficult to predict. Some are within the control of governments, such as the levels of taxes and tariffs, while others are within the control of the company, such as the choice of drugs produced, but most of these are both external and critical, such as the possibility of sustained international financing to buy large volumes of drugs to treat priority diseases.

Reducing ex works prices

For drugs that are unsubsidized, the reduction in ex works prices will only lead to increased affordability of drugs if part of the savings are passed on to the end-user through the distribution system. While this study has focused on domestic production, these steps cover only roughly one-fourth of the overall cost of a drug to the consumer (Figure 5, Annex 3). The size of the mark-ups that are subsequently added during distribution in both the public and private sectors is likely to outweigh the reduction in ex works prices in a large proportion of SSA countries. This could diminish the primary contribution of domestic production to access if the distribution system does not pass on the savings. This may be less of a risk in the case when drugs bought by the government are distributed by the public networks, but nevertheless mark-ups added in the public sector still add significantly to drug prices.

Figure 5: Value Chain Flowchart of pharmaceutical production



Notes: Based on a drug in which API represents 50% of the ex works price. For the drugs used in this study, with the exception of the ethical drugs, the median and mean costs of API in the ex works price are 47% and 51%, respectively.

For subsidized drugs, the reduction in ex works prices could enable either expanded coverage or reduction in the cost of subsidies.

Drug quality

Access to drugs is defined in terms of access to quality drugs. For domestic production in SSA under the conditions of the simulation, it is assumed that the plant will be built or modified and operated in accordance with GMP. However, there is no internationally accepted standard mechanism for evaluating **all** of the drugs produced in terms of quality, safety, and efficacy. This is because the WHO Prequalification Project only covers drugs to treat HIV/AIDS, TB, and malaria. For the other drugs (i.e. the ethical and the OTC drugs), this kind of stringent evaluation would require registration of the drugs in a country that is either a member of PICS or ICH. The administrative burden imposed by this, particularly for an application in an ICH country, might be difficult to justify for a small production volume of these medicines, and is likely to require technical and administrative know-how that would be hard to find in SSA. Therefore, alternative processes for evaluation may have to be developed to ensure that the other drugs also meet acceptable standards for quality, safety, and efficacy.

On the other hand, the domestic production of quality drugs at reasonable prices could help reduce the amount of substandard and counterfeit drugs in circulation, particularly if accompanied by a campaign to educate the public about the dangers of substandard and counterfeit drugs.

Intellectual Property Issues

The domestic production of patented drugs, in particular ARVs, is likely to be affected after 2005 when all non-least developed country member states of the World Trade Organization will be required to grant product patent protection. This will affect the supply of drugs patented after 2005, and possibly some drugs patented before that date, to importing developing countries. TRIPs does provide some mechanisms, such as compulsory licensing, which could permit the domestic production of patented drugs in SSA. However, there can be many legal, political, practical and economic constraints in using these mechanisms[53,54], in which case the developing country will be dependent on branded versions, and will have little leverage over prices. In selected circumstances, the capacity for local production in least developed countries could help overcome the practical difficulties in using TRIPs flexibilities, and the following possibilities emerge:

- A compulsory licence may be issued for production of a patented drug for domestic use only. While this would enable domestic producers to manufacture these drugs, the small size of the national market may make it difficult for a domestic producer to justify the investment in bioequivalence studies and validation of production processes that would be necessary to ensure the highest quality of the drug produced. Furthermore, if the API is also under patent protection, then this could require a compulsory licence to be issued by the country where the API is manufactured in order to allow export. Although a possible route around this would be to import the intermediates (which are not patent protected), and then produce the API and finished product domestically, this was not considered in this study and would require a careful evaluation of technological capacity and the availability of the expertise in pharmaceutical chemistry that would be required.

- A compulsory licence may be issued for the domestic production and consumption of a patented drug and corresponding steps taken to enable its export to non-producing countries. This could require separate negotiations with each of these countries and completing the necessary procedures is likely to be time-consuming. The possibility of being able to reach an export market may justify this investment in time and costs for a domestic producer and it was assumed that this occurred in the simulation.

- A voluntary licence may be issued for the domestic producer, contingent on meeting GMP standards. This is likely to require an independent assessment and inspection of the plant, either by the WHO, or by the grantor of the licence, if it was felt that the national drug regulatory authority was not fully competent to do a comprehensive inspection. This option could offer the opportunity both to meet domestic needs and to export the drug product. The main drawback of this option is that separate licences would have to be obtained for each branded drug, and that the effort involved to obtain a voluntary licence for just one product may not

justify the time and cost involved. For example, drawing on the results of the simulation, the number of tablets of any single ARV needed to serve 10% of the West African market is less than two million; this represents less than two days worth of output for a single tabletting machine, which would not represent the efficient use of equipment, especially when the added downtime for cleaning and changeover is factored in.

As the TRIPs mechanisms have yet to be tested, it is likely that other options will emerge over the next few years. At this point, it is highly speculative to predict how this will affect the business decisions of domestic producers. In the simulation, selling prices were set using international reference prices to test the financial viability of the imaginary enterprise. If the supply of generic versions of patented drugs is restricted once the TRIPs obligations are applied, this could dramatically alter the market potential if there is no established reference price for patented drugs.

It is difficult to predict how the manufacturers of innovator products will respond to the public health needs of developing countries. Several years ago, a year's treatment with an ARV cost thousands of dollars; few people would have predicted that this cost would fall to the current level of a few hundred dollars a year. While the availability of generic forms of ARVs from countries such as India and Brazil contributed to the pressure that eventually led to lower prices, political and humanitarian concerns also played a role. Lastly, it should be noted that the production in SSA of the relatively older ARVs used in the simulation, along with the vast majority of essential drugs, is not likely to be affected by the application of TRIPs although the possibilities of exporting them have to be evaluated. Certainly, given the dire need to scale up access to existing ARVs in SSA, the decision of whether or not to invest in the domestic production of the current generation of ARVs that are recommended within the WHO guidelines should not hinge on untested considerations of what might happen with respect to newer drugs. Rather, this decision should take into account the other elements of the analysis above, such as country environment, potential market, price trends, and the availability of the trained personnel and technical know-how that will be required to get WHO prequalification etc.

Local Production vs. Drug Donation

Without engaging in a full discussion of the pros and cons of drug donation, which has been offered on a large-scale[55,56] as a solution to access to medicines, there are sound reasons why exploring the feasibility of domestic production is preferable to promoting drug donation as a solution to the problem of access to medicines. These include the notions of sustainability and reliability which are included in the WHO framework for equitable access[57].

It is evident that a pharmaceutical enterprise is vulnerable to business and financial risk. However, from any one country's standpoint, there is more opportunity to play an active role with respect to a domestic enterprise than there is with a large multinational

company located in another continent, for whom a drug donation programme is likely to be of low priority.

Conclusion

Given the overall need to improve access to drugs, which includes many issues related to drug management and rational use, stakeholders may have to consider whether resources should be focused on supporting the domestic production of drugs, or used to support other areas, such as improving distribution systems, strengthening drug regulatory systems, or subsidizing API prices to reduce upstream costs of production. This study shows that domestic production could have a modest impact on drug affordability. It is not clear whether domestic production could improve the other dimensions of access - geographical accessibility, physical availability, and acceptability.

6.2. Directions for further research

This study of the issues involved in the domestic production of drugs in SSA reveals a number of areas where further research and/or technical assistance could help improve access to medicines.

- **Meeting GMP standards and WHO Prequalification.** A number of enterprises producing drugs for their national market exist already in SSA, mostly run by private entrepreneurs. Many of them have expressed interest in contributing to the fight against HIV/AIDS, TB, and malaria, but they do not have production plants that meet GMP and they find the documentation requirements of the WHO Prequalification Project difficult to meet. Operational research in understanding how much it costs to reach GMP requirements and the human resource needs in terms of training could help address this gap.

- **Finding ways to verify the quality, safety, and efficacy of drugs.** Other than the WHO Prequalification Project, which covers only a few categories of drugs, there is no internationally accepted way to verify drug quality other than the registration processes of individual countries within PICS or ICH. Exploring ways to either expand the coverage of the WHO Prequalification Project or to develop an alternative pathway to verify drug quality, safety, and efficacy could help cover this gap.

- **Reducing the quantity of substandard and counterfeit drugs.** If, in the near future, a domestic pharmaceutical enterprise in SSA does become prequalified by the WHO for any of the drugs to treat HIV/AIDS, TB, or malaria, follow-up research should be done to find out if this reduces the circulation of substandard and counterfeit drugs. Perhaps well-designed public education campaigns for “buying domestic” could persuade end-users to buy high-quality domestically made products and dissuade them from buying bad drugs.

- **Reinforcing quality.** This study has alluded to quality issues; strengthening drug regulatory authorities and the associated systems in SSA countries could ensure quality throughout the drug distribution system and would be a valuable use of resources, as access to drugs can only have meaning in terms of access to quality drugs.

- **Exploring the current status of manufacturing capacity in other countries within SSA.** Within the limitations of this study, it was only possible to visit West Africa. However, there is active pharmaceutical production within East Africa, and the prevalence of HIV/AIDS is higher. This could translate into a greater demand for drugs as well as offer the opportunity of partnership with an established enterprise for expanding production. Confirmation would require visits to drug manufacturers in the region and an analysis of the elements (tariffs, patent status) that could affect the market.

- **Role of public-private partnerships (PPPs).** At a global level, PPPs such as Medicines for Malaria Venture and The Global Alliance for TB Drug Development have been successful in mobilizing funding for drug development. The possibility of mobilizing money at regional or local levels to enable the financing of drug production at favourable interest rates should be explored.

- **Improving the efficiency of drug distribution.** Better knowledge of the flow of drugs through distribution systems in both the public and private sectors could help find ways to lower the cost of mark-ups – which can comprise up to 50% more of the price paid by the end-user – and improve geographic availability.

- **Establishing a mechanism to stabilize or subsidize raw material (API).** As noted above, the price of API can be as high as 27% of the end-user price of a drug, but these prices are subject to considerable variability, which in turn will have an impact not only on the sustainability of a pharmaceutical enterprise, but on the prices ultimately paid by the end-user. Just as the prices of vital products are subsidized in many countries, it could be worthwhile to explore whether the same could be done for API in order to make essential drugs more affordable, whether or not they are produced domestically, given their importance to public health.

- **Establishing regional drug registration.** Work on regional registration procedures is already underway in at least one trading bloc. Success in this endeavour would enable countries to pool their resources together to enable the thorough examination of the registration dossier, testing of drug samples, and full inspections of pharmaceutical production plants. External technical assistance could support this work.

- **Examining how the application of TRIPs provisions could affect the role of domestic production.** The ability of an enterprise to obtain a voluntary licence

from the patent holder or to use compulsory licences, first within the country to produce for the domestic market, and secondly, within exporting countries in order to sell internationally, could determine both the size of its market as well as the prices of competing products (if these are only branded drugs). Further research could be undertaken to determine the patent status of the different drugs in SSA countries as well as exploring the conditions under which patent holders would be willing to issue voluntary licences.

Annex 1

List of persons encountered

Dr. Clive Ondari, Technical Officer, Policy and Rational Use team, Essential Drugs and Medicines Policy, WHO

Dr. David Webber, Director, World Self Medication Industry

Dr. Denis Broun, Director, MSH Europe

Dr. Lembit Rago, Team Coordinator, Quality Assurance & Safety: Medicines team (QSM), Essential Drugs and Medicines Policy, WHO

Dr. Louis Teulières, Director of International Affairs, National Pharmaceutical Industry Association – France

Dr. Patrick Choay, President of Choay Laboratories, France

Dr. Paul Lalvani, Procurement Officer, The Global Fund

Dr. Philippe Baetz, Senior Vice President, Corporate Affairs, "Access to Medicines" Mission, Sanofi-Synthelabo

Mr. Bill Haddad, CEO, Biogenerics

Mr. Francis Adiasani, Senior consultant, tax and legal services, and Lydia Pwadura, assistant consultant, tax services, Price Waterhouse Coopers, Accra, Ghana

Mr. Kofi Nsiah-Poku, Managing Director, Kinapharma, Accra, Ghana

Mr. Lee Yerkes, Senior Technical Officer, IMPACT Project, FHI Institute for HIV/AIDS

Mr. Malcolm Clark, Principal Program Associate, MSH

Mr. Michael Van Vleck, CEO; Mr. Mitchell Fenster, CFO; Mr. Bruce Brown, COO Herbal Division, Phyto-Ryker Pharmaceuticals Ltd., Accra, Ghana

Mr. Tom Moore and Mr. Hugo Vrakking, Stop TB department, WHO

Ms. Kristen Fenster and Mr. Samuel Dzotefe, Investment Officers, International Finance Corporation, Accra, Ghana

Dr. Pierre Guillet, Communicable Diseases Control, Prevention and Eradication, World Health Organization

Mr Alassane N'Diaye, Projects Officer, IFC, Abidjan, Cote d'Ivoire

Mr Assane Coulibaly, Directeur Industriel, Cipharm, Abidjan, Cote d'Ivoire

Mr Vincent Valabregue, Directeur Général, Cotecna, Abidjan, Cote d'Ivoire

Mr Guillaume Kokora, Directeur Commercial, Laborex, Abidjan, Cote d'Ivoire

Mr Jean Serge Adjepone, DDSP, Ministère de l'Industrie, Abidjan, Cote d'Ivoire

Confidential source #1, drug manufacturer, sub-Saharan Africa

Confidential source #2, drug manufacturer, sub-Saharan Africa

Annex 2

Summary of data on pharmaceuticals production in selected sub-Saharan African countries

(Based on information that is readily accessible. List not intended to be exhaustive.)

Country	Mfr, Contact Info	Market size	NRA/DRA Status	Products	APIs	Capacity	Ownership	Known quality problems
Angola	ANGOMEDICA UEE[58] Ruedo Sanitorio Barrio Palanca PO Box 2648 Luanda, Pres Coimbra Adao Manuel	13.1 M	No information	Chloroquine antibiotics	--	Only 20% in use	State	--
Cameroon	CENAME, Centre National d'Approvisionnement de Médicaments Essentiels[59] came into being in 1996 with support from IMF (Enhanced Structural Adjustment Facility),[60] now gets lowest available prices internationally on antiretrovirals (ARVs) of good quality[61] and tuberculosis (TB) drugs.[62] It is said that the private sector pharmaceutical manufacturers are no longer competitive.							
	Plantecam[63] (now closed)	Export	No information	Herbal bark for export	--	Closed	Private (French)	Problem with meeting CITES standards

Country	Mfr, Contact Info	Market size	NRA/DRA Status	Products	APIs	Capacity	Ownership	Known quality problems
	CINPHARM Dr Jules Ngandun, Production Manager, created in 1988 by Rhône-Poulenc and bought in 1995 by Eurapar	15.8 M		Tablets, capsules, oral liquids, and sterile powders under licence for Rhône Poulenc Rorer and Pfizer[64]		4 B FCFA in 2001	Private	--
	Unite Camerounaise Phamaceutique SA (UC-Pharm)[65]			Mainly imports pharmaceuticals at competitive cost	--	--	Private, IFC-supported	--
Chad	Societe Industrielle Pharmaceutique de Tchad, created May 1994	8.34 M	No information	Tablets, Parenteral solutions, and ORS[66]	--	140 M tablets per year, 140 M FCFA	Private	--
Côte d'Ivoire	Pharmivoire Nouvelle,[67] Zone Industrielle de Yopougon, BP 930, Cidex, Abidjan, tel 225 235 14285, founded 1991, closed and then reopened recently	16.5 M	Not fully functional, but GMP and GDP enforced	Parenteral solutions	--	26.50 staff	Private	--

Country	Mfr, Contact Info	Market size	NRA/DRA Status	Products	APIs	Capacity	Ownership	Known quality problems
	CIPHARM,[68] BP 06/226, Abidjan 01, tel 22430394, szy@africaonline.co.ci Director General M Didier Marin,[69] created in 1988[70]	16.5 M, some export[71]		Tablets, capsules, syrups, sterile powders, essential medicines, finishing – antibiotics, IV sacks, herbal products	Technology transfer planned	9% of local market, $8 M US – 1997-2002,[72] 3M tablets per year	Private	--
Ethiopia	Bethlehem Pharmaceuticals, Addis Ababa, Chief Executive Yordanos Tadese[73]	67.2 M	Drug Administration and Control Authority (DACA), gave Certificate of Competency of Drug Manufacturing Plant to Bethlehem	Antimalarials and antibiotics, with from DACA	Preparing to produce ARVs under licence, working with S African NGO, Initiative for Pharmaceutical Technology Transfer	400M tablets and 280 M capsules	Private	--
	Ethiopian Pharmaceuticals Manufacturing (EPHARM), Addis Ababa, Woreda 23, Jebele 15[74]			42 essential drugs in capsules, tablets, small and large volume injectables, ointments, syrup and lotions, powders	--	--	Public enterprise	--

Country	Mfr, Contact Info	Market size	NRA/DRA Status	Products	APIs	Capacity	Ownership	Known quality problems
Ghana	Kinapharma, D 360/3 Derby Ave, P0 Box 14368, Accra Central Tel: 666-118/662-796	20.3 M	Ghana Food and Drug Board	Glibenclamide, omeprazole,[75] chloroquine, sulfadoxine + pyrimethamine	--	?	Private?	3/6 chloroquine tablet samples and 0/2 sulfadoxine/pyrimethamine tablets failed testing[76]
	Dannex Ltd, PO Box 5258, Accra-North, 228341[77]	20.3M	Ghana Food and Drug Board	ORS, reserpine,52 sulfadoxine + pyrimethamine chloroquine	--	?	Private?	3/3 chloroquine tablet samples and 3/6 sulfadoxine/pyrimethamine tablet samples failed testing[19]
	Healthcare (PZ)			Chloroquine	--	?	?	0/1 chloroquine sample failed testing[19]
	Phyto-Riker, Mile 7, off Nsawam Road, PO Box AN 5266, Dome – Accra North, CEO Michael Van Vleck[78]	Registered in 25 countries, plus Ghanaian market		Essential medicines including antibiotics, antimalarials, 30 products; Bringing in technology for penicillin, 6 new products developed in-house	Phyto-Laria, antimalarial herbal medicine, also herbal anti-asthmatic	4B tablets per year in 2 shifts	Private	--
	Note: There are at least 13 Indian pharmaceutical companies doing business in Ghana,[79] that are not included here							

Country	Mfr, Contact Info	Market size	NRA/DRA Status	Products	APIs	Capacity	Ownership	Known quality problems
Kenya	Elys Chemical Industries, PO Box 40411, Nairobi, tel 540415, elys@net2000ke.com	31.3 M	Pharmacy and Poisons Board of Kenya, plus a National Drug Quality Control Laboratory[80]	Several products including antibiotics, antimalarials	--	?	Private	0/2 samples sulfadoxine/pyrimethamine tablets tested failed[19]
	Cosmos Ltd, PO Box 41433, Nairobi	31.3 M	Pharmacy and Poisons Board of Kenya	Several products including antibiotics, antimalarials Approved by Poisons Board for 3 of a total of 6 ARVs, not yet producing as awaiting government approval for compulsory licensing[81]		?	Private	0/1 sample of chloroquine syrup, 1 /2 samples of chloroquine tablets, and 0/2 samples of sulfadoxine/pyrimethamine tablets failed testing[19]
	Note: there are 37 local drug manufacturers registered with the Pharmacy and Poisons Board of Kenya.[82] Only two were selected. In the WHO study,[19] 0/12 samples of sulfadoxine/pyrimethamine tablets from these other manufacturers, 2/5 samples of chloroquine tablets, and 2/6 samples of chloroquine syrup tested failed							
Mali	UsineMalienne de Produits Pharmaceutiques, Route de Sotuba ZI, BP 2286, Bamako, 223-215161. Dir Gen M Chen Xueryi, D Gen Adjunct, M Bakary Nana Coulibaly	11.4 M	There is a national control laboratory, but inspection service is little developed[83]	Produce 5 formulations, 33 products, 28 on Essential Drugs List: chloroquine, paracetamol, aspirin, antibiotics	No ARVs, no technology 2001	8% of $US 40M market[84]	State, created in 1983, from a Sino-Malgache cooperation	0/2 samples of sulphadoxine/pyrimethamine tablets, 3/ 4 samples of chloroquine syrup, and 8/12 samples of chloroquine tablets failed in WHO testing[19]

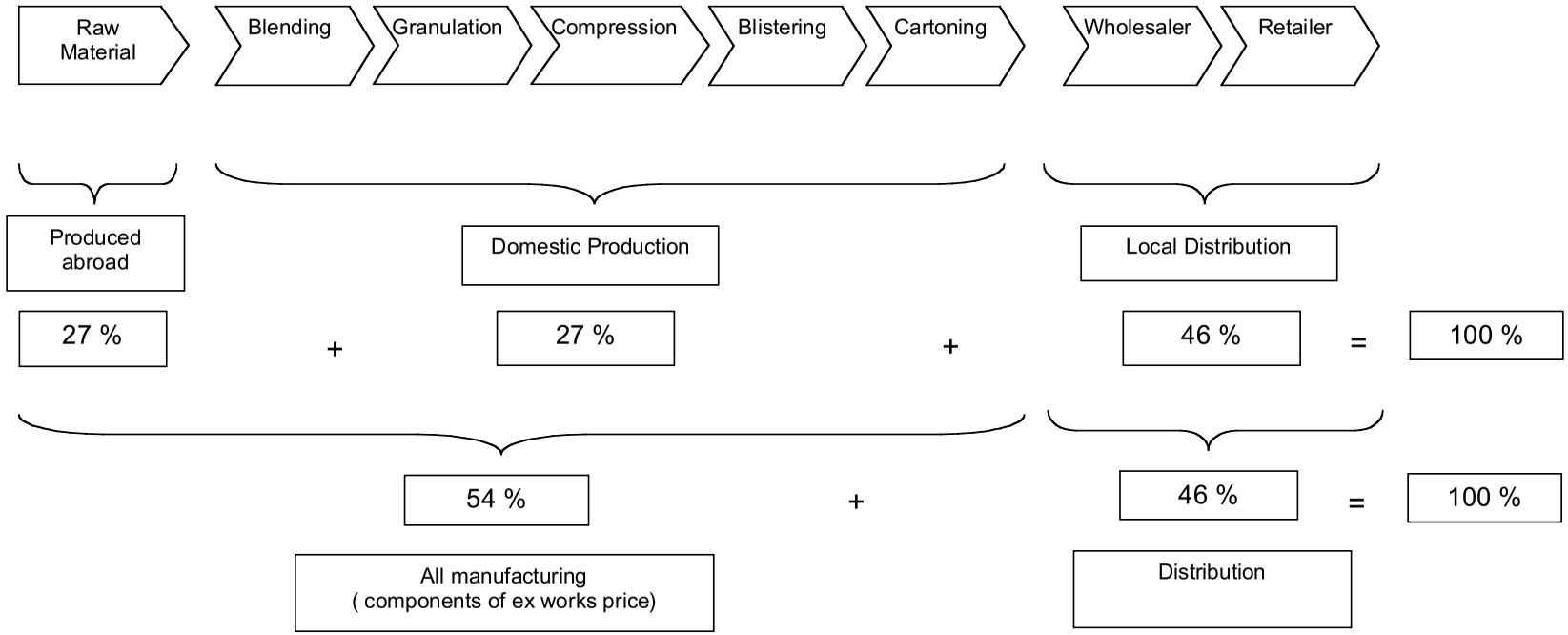
Country	Mfr, Contact Info	Market size	NRA/DRA Status	Products	APIs	Capacity	Ownership	Known quality problems
Nigeria	Nigerian-German Chemicals PLC[85]	132.9 M	NAFDAC, well developed regulatory authority, has recently threatened to withdraw licences of multinational drug manufacturers who fail to establish local drug production outfits after a minimum of 10 years of importation of drugs into the country[86]	Liquids and tablets of its own brand	International brands under licence. Some contract manufacturing	10M bottles liquid and 1 billion tablets per year	Private	--
Senegal[87 88]	SIPOA affiliated with Rhône Poulenc Rorer, now Aventis, Route de Rufisque, 8340163	West Africa	Functioning authority : Senegal has yellow fever vaccine production and its producer is prequalified for sale to UN agencies, a prerequisite of which is that the NRA is functional	About 90 generic products, including antimalarials, analgesics, antiTB drugs, vitamins	Makes under licence about 40 specialty pharmaceutical products	--	Private	0/1 samples of chloroquine syrup, and 1/ 2 samples of chloroquine tablets failed in WHO testing[19]
	Parke Davis			Generics in form of capsules, syrups, creams, and injections	Specialty products under licence	?	Private	--
	Valdafrique			External use	--	?	?	--

Country	Mfr, Contact Info	Market size	NRA/DRA Status	Products	APIs	Capacity	Ownership	Known quality problems
South Africa	Aspen Pharmacare, 2 plants, Durban and Port Elizabeth[89]	The largest manufacturer in Africa, it exports all over the world[90]	Medicines Control Council, fully functional NRA with control laboratories for both drugs and vaccines	Generics and products under licence, 1200 registered trademarks	Voluntary licensing of Stavudine from Bristol-Myers Squibb, and developing generic versions of other ARVs and triple therapy[91]	Several tons of product per day, set to double in 2004	Private	--
	South Africa has 148 companies registered to produce or distribute pharmaceutical products.[92]							
Tanzania	Keko Pharmaceuticals Industries, PO Box 40164, Dar es Salaam, +255-22-2866237, diocare@twiga.com[93]	35.2 M, no export	No information	Penicillin, infusions, injectibles	--	500M tablets and 8 M capsules per year; installed capacity is 1B; IPPN project to expand capacity[94]	Private (60% Diocare, 40% government)	--

Country	Mfr, Contact	Market size	NRA/DRA	Products	APIs	Capacity	Ownership	Known quality problems
Zambia	5 manufacturers in Zambia but only 1 contributes to local market[95]	10.2M	Pharmacy, Medicines, and Poison Board (PMPB), not well equipped and constructing a new testing facility[38]	?	Exploring JV with GPO Thailand to produce didanosine in new plant[96]	?	?	Suspected substandard drugs through lack of testing by PMPB[38]
Zimbabwe	Pharmanova (PVT) LTD, Highfield Road 93, Southerton, Harare	13M	Functional with well-functioning control laboratory	Antimalarials, etc	--	?	Private	1/20 samples of sulfadoxine/pyrimethamine tablets and 0/1 samples of chloroquine tablets failed WHO testing[19]
	CAPS, Harare				Received WHO GMP certificate from ITC[99]	?	?	1/13 samples of chloroquine syrup and 4/4 of chloroquine tablets failed WHO testing[19]
	Varichem				--	?	?	3/7 samples of chloroquine tablets failed WHO testing[19]

VALUE CHAIN FLOWCHART

(example for a drug in which API represent 50 % of the exworks price). Percentages equal value added in each of the corresponding steps to arrive at 100% which represents the final price paid by a consumer.



Annex 4

PATENT SITUATION OF ARV PRODUCED

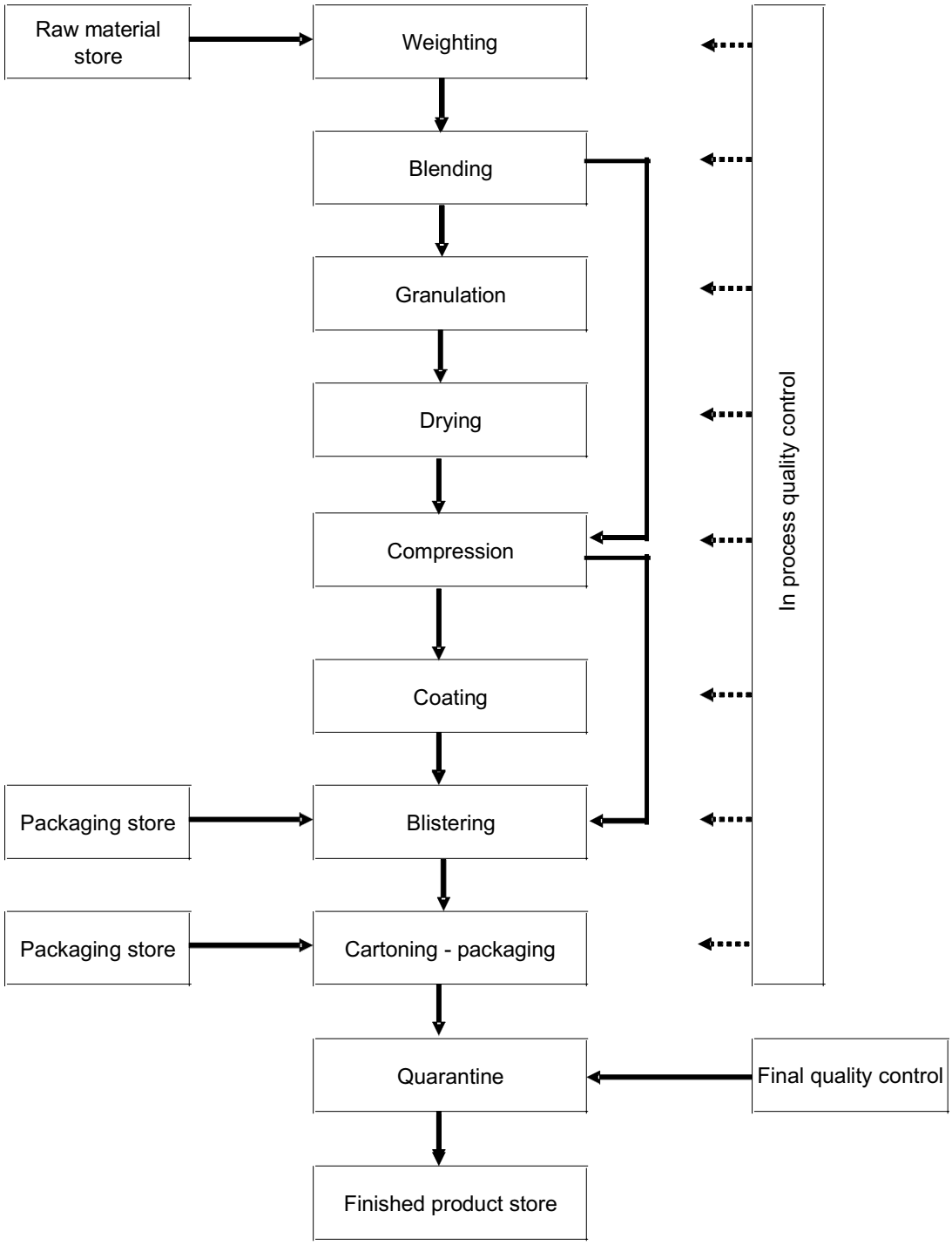
Information in this table is relevant to the filing dates for the basic patent of the ARVs used in the simulation. All of them are pre-1995. The reader is also referred to the discussion in: Boulet, P, Garrison, C and 't Hoen, E. 2003. "Drug patents under the spotlight: Sharing practical knowledge about pharmaceutical patents." Médecins Sans Frontières.

Drug (INN)	Patent owner	Basic Patent priority date (origin)	Max. 20 years patent protection	US patent expiry date	French or Europ. patent expiry date	Countries where similar patents have been filed or granted
didanosine	Wellcome Found	15 May 1985	15 May 2006		*EP* 14 May 2006	Australia, **Canada** , Denmark, **EP (AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE)** , Finland, Greece, Hungary, **Japan**, New Zealand, Portugal, **South Africa** , Spain, **US**
	US Gov.	26 Aug 1985	26 Aug 2006	29 Aug 2006 (17 years)	*EP* 21 Aug 2006 *Fr* ext. until 4 May 2009	Australia, **Canada** , Cyprus, **EP (AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE)**, Hong Kong, **Ireland** , Israel, **Japan**, Mexico, New Zealand, Singapore, **US**
lamivudine	IAF Biochem.	8 Feb 1989	8 Feb 2010	8 Feb 2009	*EP* 8 Feb 2010 *Fr* ext. until 7 Aug 2011 (15 years after MA)	**ARIPO**, Australia, Brazil, **Canada** , China, Croatia, Cyprus, **Czech Rep.**, **EP (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE)** , **Finland** , Hong Kong, **Hungary** , **Ireland** , Israel, **Japan** , **Korea** , Mexico, **Norway** , **New Zealand** , **OAPI** , Portugal, **Russia** , Singapore, **Slovakia** , Slovenia, **South Africa** , **US** , Yugoslavia
nevirapine	Boehringer	17 Nov 1989	17 Nov 2010	22 Nov 2011 (17 years)	*EP* 16 Nov 2010	Australia, **ARIPO**, **Canada** , **EP (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE)** , **Finland** , **Hungary,** Israel, **Ireland** , **Japan** , **Mexico** , **New Zealand** , **Norway** , OAPI, Portugal, **Russia** , Singapore, **US**, **South Africa**
stavudine	Yale University	17 Dec 1986	17 Dec 2007	25 Jun 2008 (ext. /MA)	*EP* 11 Dec 2007 *Fr* ext. until 8 May 2011 (15 years from MA)	Australia, **Canada** , Denmark, Egypt, **EP (AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE)** , Finland, Hong Kong, Ireland, Israel, **Japan** , **Korea** , New Zealand, **Philippines** , Portugal, **US** , South Africa
zidovudine	Glaxo	16 Mar 1985	16 Mar 2006	17 Sept 2005 (20 years)	*EP* 14 Mar 2006	**ARIPO**, Australia, **Canada** , Cyprus, Czechoslovakia, **Denmark** , **EP (AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE)** , **Finland** , Hong Kong, Hungary, **Ireland** , Israel, **Japan**, **Korea** , Latvia, Monaco, New Zealand, **Philippines** , Portugal, Singapore, **South Africa** , **US**

source: OMS/UNAIDS 2000 : Patent situation of HIV/AIDS-related drugs in 80 countries

Annex 5

FLOWCHART OF TABLET MANUFACTURING



Annex 6

BUSINESS ENVIRONMENT

Country Environment	
Political Risk	The risk of political instability must be considered. Only 40% of countries have a “B” risk rating or higher.
Human Resources	Quality and availability are variable among countries.
Access to financial capital	1. Difficult because commercial bank interest rates are high, with a short payback period. 2. Investment in pharmaceutical production is not a priority for international financial institutions for development. 3. Private funds exist in Europe and USA which can help with private sector projects but it may be difficult to access these funds.
Access to know-how (FDC)	Must be imported from countries where pharmaceutical industry is well-established
Availability of raw materials and spare parts	Lack of industrial infrastructure means that: 1. Raw materials and spare parts have to be imported 2. Possible delays in production 3. Higher maintenance costs
Government strategy and policy	
Economic and fiscal	Most governments have adopted fiscal policies in order to promote industrial development
Trade (tax and tariffs)	1. Harmonization of tariffs and a single currency facilitates trade within WAEMU and EMCCA. 2. Lack of harmonization and lack of a common currency within ECOWAS handicaps exchange of goods even though ECOWAS is planning to have a common currency by 2007 with a central bank based in Accra.

	3. Tariffs and customs duties vary among inputs needed for pharmaceutical manufacturing.
Pharmaceutical	1. Harmonization of standard treatment guidelines could lead to a reduction in the number of dosage forms being used but current practices require manufacturers to produce a large number of dosages and forms for the same drug. 2. WAEMU developing procedures for harmonizing registration procedures throughout the zone. 3. Regulatory authorities and quality assurance systems do not enforce internationally recognized GMP standards and may not recognize drugs registered in neighbouring countries. 4. Registration can be delayed because of a lack of capacity of the national regulatory authorities. 5. In some WAEMU countries the mark-ups in distribution are set to promote domestic production.
Health financing	Low purchasing power of populations means that external funding and the public sector will play an important role in purchasing these drugs. Purchase of these drugs by institutions and governments will mean internationally recognized quality standards, such as WHO prequalification, will be required, and prices will be competitive
Labour	Labour market is flexible and without difficulty hiring and firing in the majority of countries. Labour regulations and unions are not a problem
Environmental regulation	Environmental assessments required, but standard.
Trade guarantee	The absence of financial institutions which issue trade guarantees means that political risk is not covered for exporting countries in these zones.
Market	
Size	The small size of domestic markets necessitates that drug manufacturers export to regional market: 1. The West African market covers over 200 million people, which potentially represents a sufficient size for investment in pharmaceutical manufacturing.

	2. Choice of a regional market is justified by the regional scope of activities of multilateral and bilateral institutions such as the World Bank and USAID, and the existence of economic and trading blocks such as ECOWAS and WAEMU.
Acceptability to end-user	If the end-user can afford drugs which are imported from developed countries, these are often preferred over locally made products, when bought in the retail sector.
	Larger domestic drug producers realize that perception of quality can be improved if international GMP certified and/or WHO prequalified.
Competition	The type of products chosen will mostly be bought by institutional and government purchases. The solvency of these buyers and the large volumes purchased make this market attractive to drug manufacturers. There is intense competition on price and quality.

Annex 7

MEMBERSHIP IN TRADING BLOCS AND RISK RATINGS

		Risk rating	CFA Franc Monetary Zone		ECOWAS	OHADA
			EMCCA	WAEMU		
Countries of the sample	Benin	B		X	X	X
	Burkina Faso	B		X	X	X
	Mali	B		X	X	X
	Senegal	B		X	X	X
	Niger	C		X	X	X
	Togo	C		X	X	X
	Côte d'Ivoire	D		X	X	X
	Ghana	C			X	
	Guinea	D			X	X
	Nigeria	D			X	
	Cameroon	B	X			X
	Chad	C	X			X
Other Countries	Guinea-Bissau	D		X	X	X
	Cape Verde	C			X	
	Gambia	D			X	
	Liberia	D			X	
	Sierra Leone	D			X	
	Gabon	C	X			X
	Equatorial Guinea	D	X			X
	Central African Republic	D	X			X
	Democratic Republic of Congo	D	X			X

Notes :
ECOWAS : Economic Community of West African States
EMCCA: Economic and Monetary Community of Central Africa
WAEMU: West Africa Economic and Monetary Union
OHADA: Organisation pour l'Harmonisation du Droit des Affaires en Afrique (Organization of business law in Africa)

Annex 8

LIST OF PRODUCTS CHOSEN QUANTITIES AND EX WORKS PRICE

International Non-Proprietary Name	Dosage form	(mg)	Quantity	Ex works price
Antimalarial				
Artesunate HCl	Tablet	100	43 000 000	0,1143
Amodiaquine HCl	Tablet	200	43 000 000	0,0114
Antibiotics				
Ciprofloxacin HCl	Tablet	500	1 600 000	0,0268
Doxycycline HCl	Tablet	100	1 900 000	0,0110
Antituberculosis				
Pyrazinamide	Tablet	400	1 800 000	0,0191
Ethambutol	Tablet	400	1 400 000	0,0153
Isoniazid + Rifampicin	Tablet	150/3002	800 000	0,0270
Antiretroviral				
Zidovudine	Tablet	100	177 634	0,2133
Didanosine	Tablet	100	1 603 340	0,2776
Lamivudine + Zidovudine	Tablet	300/150	4 302 836	0,4127
Lamivudine	Tablet	150	2 936 435	0,1222
Nevirapine	Tablet	200	1 325 787	0,2691
Stavudine	Tablet	30	1 808 518	0,0760
Anti-ulcer				
Ranitidine	Tablet	150	1 887 339	0,6352
Omeprazole	Tablet	20	98 834	1,8970
Antidiabetic				
Metformin	Tablet	850	1 254 057	0,0889
Gliclazide	Tablet	80	447 236	0,2432
Glibenclamide			1 156 369	0,1023
Antihypertensive				
Amlodipine	Tablet	5	941 546	0,5422
Captopril	Tablet	5	1 326 084	0,2817
Hydrochlorothiazide	Tablet	25	1 374 068	0,2688
OTC				
Acid ascorbic	Tablet	1000	7 155 520	0,1613
Aspirin + cafein	Tablet	500/50	21 802 215	0,0516

Annex 9

NUMBER OF CASES PER COUNTRY AND PER DISEASES AND QUANTITIES OF DRUGS PRODUCED IN THE THREE SCENARIOS

Countries	Total Population (1)	Malaria (2)		HIV (3)	Tuberculosis (4)
		Population under 5	Population more than 5		
Countries of the sample					
Ghana	19 593 000	5 593 288	4 907 465	52 697	7 732
Togo	4 562 000	1 533 144	1 128 12	021 957	1 203
Benin	6 222 000	2 210 587	1 545 232	17 566	2 415
Côte d'Ivoire	15 827 000	4 842 600	4 077 510	112 714	9 667
Burkina Faso	11 905 000	4 419 610	2 797 580	64 408	1 544
Mali	11 904 000	4 251 032	2 740 712	16 102	2 757
Niger	10 742 000	4 422 282	2 481 780	9 380	9 940
Cameroon	15 117 000	4 962 719	3 504 608	134 671	7 921
Chad	7 861 000	2 886 106	1 856 109	21 957	3 591
Other countries					
Nigeria	114 746 000	39 362 791	28 250 773	512 3352	1 936
Senegal	9 393 000	3 184 666	2 348 456	3 952	5 796
Guinea	8 117 000	2 895 758	2 011 916	20 020	4 300
Total	235 989 000	80 564 584	57 650 261	987 760	78 802
Number of tablets					
Artesunate HCl Tablet 100mg		43 000 000			
Amodiaquine HCl Tablet 200mg		43 000 000			
Zidovudine Tablet 100mg				177 634	
Didanosine Tablet 100mg				1 603 340	
Lamivudine Tablet 150mg				2 936 435	
Stavudine Tablet 30mg				1 808 518	
Nevirapine Tablet 200mg				1 325 787	
Zidovudine + lamivudine Tablet 300/150mg				4 302 836	
Ciprofloxacin HCl Tablet 500mg				1 600 000	
Doxycycline HCl Tablet 100mg				1 900 000	
Pyrazinamide Tablet 400mg					1 800 000
Ethambutol Tablet 400mg					1 400 000
Isoniazid + Rifampicin Tablet 150/300mg					2 800 000
Ranitidine Tablet150mg	1 887 339				
Omeprazole Tablet20mg	98 834				
Metformin Tablet850mg	1 254 057				
Gliclazide Tablet80mg	447 236				
Glibenclamide Tablet mg	1 156 369				
Amlodipine Tablet5mg	941 546				
Captopril Tablet5mg	1 326 084				
Hydrochlorothiazide Tablet25mg	1 374 068				
Acid ascorbic Tablet1000mg	7 155 520				
Aspirin + cafein Tablet '500/50mg	21 802 215				

Sources : (1) United Nations Population Division. "World Population Prospects: The 2002 Revision Population Database." (2003). http://esa.un.org/unpp/. (Accessed 5/30/2004) ; (2) Roll Back Malaria Project, World Health Organization. 2000. "The African Summit on Roll Back Malaria." The African Summit on Roll Back Malaria Abuja, Nigeria ; (3) Purchases by the CMS of the Cote dÕIvoire for 2003 projected for the population of the 12 selected countries

Annex 10

SIMULATION ASSUMPTIONS

Structure of the enterprise

The management and the board are private. Equity is divided among different shareholders but any public shareholder should not have the majority of votes and/or of equity. No dividends are distributed and all earnings will go back into the line: Retained Earnings.

1 - Scenario n° 1 (green field)

Capital expenditures

The total investment is set at $4,055,000, broken down as follows:

- Equipment: $2,000,000 (straight line depreciation over 4 years). It includes one complete production line for tablets, a complete laboratory for QA, storages with shelves, and furniture. The fifth year equipment is replaced. In order to have a valid figure to use for the CAPEX component of the NPV calculation, a quarter of its value is taken into account.

- Building: $1,500,000 (straight line depreciation over 20 years). The surface is based on a 1000 meter square base.

- Land: $100,000 (straight line depreciation over 50 years). The building is calculated on a 5000 meter square base.

- Research & development: $455,000 corresponding to $35,000 for each of the 13 drugs produced.

- Increase in production capacity: based on the annual increase in production, every 7 years investment is required in a new production line. The NPV calculation is adjusted accordingly.

Working Capital

- Supplier: payment at 30 days (this can vary according to the relationship with the raw material supplier: the more that there is confidence in the relationship the more the time of delay payment will be long). For the first year suppliers are paid cash.

- Buffer stock: finished goods: 30 days; raw materials: 45 days;
- Client: payment at 90 days. This takes into account the fact that institutions or governments will be buying the largest portion of the production while individual clients who pay cash directly will be buying only a small portion of the production.
- Total working capital at the end of the year 5: $3,729,000

Financing

The financing is split between capital, grant and loans as follows: (i) the amount of the capital stock is set at $3,000,000, (ii) the grant ($2,000,000) is defined as a bilateral organization grant or a grant from a foundation, (iii) the loan is split between a commercial bank loan ($2,100,000; 3 years; 18 %) and an IFC loan ($2,600,000; 3 years; 15 %); IFC in this exercise will not take any equity.

Production

An average of 108 million tablets per year will be produced at Year 3. This correspond (i) to a market share of 10 % and (ii) to one unit of production line and one shift of production (the first year's production is set at 30% of capacity, thereafter Year 2, 70% and Year 3, 100%).

Ex works prices

Reference price for ex-works is based on the cheapest price found between the supplier prices in the International Drug Price Indicator guide, 2003 edition, MSH and the CMS from Cote d'Ivoire 2003.

Raw materials

- Reference prices for raw materials are based on the international Trade Centre UNCTAD/WTO April 2004.
- FOB to DDP: 15%, including WAEMU intra-community taxes (see Annex 15)
- All RM have a drug master file.
- Production waste is estimated to 2%.

Income tax

In accordance with national regulations, a start-up company is exempted on income tax for a minimum of 5 years with possible extension to 8 years.

2 - Scenario n° 1 (expansion plant)

Capital expenditures

The total investment is set at $1,455,000, broken down as follows:

- Equipment: $1,000,000 (straight line depreciation over 4 years). It includes one complete production line for tablets, a complete laboratory for QA, storages with shelves, and furniture.

- Research & development: $455,000 corresponding to $35,000 for each of the 13 drugs produced.

Working Capital

- Supplier: payment at 30 days (this can vary according to the relationship with the raw material supplier: the more that there is confidence in the relationship the more the time of delay payment will be long). For the first year suppliers are paid cash.

- Buffer stock: finished goods: 30 days; raw materials: 45 days;

- Client: payment at 90 days. This takes into account the fact that institutions or governments will be buying the largest portion of the production while individual clients who pay cash directly will be buying only a small portion of the production.

- Total working capital at the end of the year 5: $4,371,000

- Increase in production capacity: based on the annual increase in production, every 7 years investment is required in a new production line. The NPV calculation is adjusted accordingly.

Financing

The financing is split between capital, grant and loans as follows: (i) the amount of the capital stock is set at $2,000,000, (ii) the loan is split between a commercial bank loan ($500,000; 3 years; 18 %) and an IFC loan ($1,500,000; 3 years; 15 %); IFC in this exercise will not take any equity.

Production

An average of 108 million tablets per year will be produced at Year 3. This correspond (i) to a market share of 10 % and (ii) to one unit of production line and one shift of production (the first year's production is set at 100% of capacity, thereafter Year 2, 110% and Year 3, 120%).

Ex works prices

Unchanged

Raw materials

Unchanged

Income tax

Unchanged

3 - Scenario n° 2 (green field)

Capital expenditures

The total investment is set at $4,300,000, broken down as follows:

- Equipment: $2,000,000 (straight line depreciation over 4 years). It includes one complete production line for tablets, a complete laboratory for QA, storages with shelves, and furniture. The fifth year equipment is replaced. In order to have a valid figure to use for the CAPEX component of the NPV calculation, a quarter of its value is taken into account.

- Building: $1,500,000 (straight line depreciation over 20 years). The surface is based on a 1000 meter square base.

- Land: $100,000 (straight line depreciation over 50 years). The building is calculated on a 5000 meter square base.

- Research & development: $700,000 corresponding to $35,000 for each of the 20 drugs produced.

- Increase in production capacity: based on the annual increase in production, every 7 years investment is required in a new production line. The NPV calculation is adjusted accordingly.

Working Capital

- Supplier: payment at 30 days (this can vary according to the relationship with the raw material supplier: the more that there is confidence in the relationship the more the time of delay payment will be long). For the first year suppliers are paid cash.

- Buffer stock: finished goods: 30 days; raw materials: 45 days;
- Client: payment at 90 days. This takes into account the fact that institutions or governments will be buying the largest portion of the production while individual clients who pay cash directly will be buying only a small portion of the production.
- Total working capital at the end of the year 5: $4,921,000

Financing

The financing is split between capital, grant and loans as follows: (i) the amount of the capital stock is set at $2,000,000, (ii) the grant ($2,000,000) is defined as a bilateral organization grant or a grant from a foundation, (iii) the loan is split between a commercial bank loan ($2,000,000; 3 years; 18 %) and an IFC loan ($3,000,000; 3 years; 15 %); IFC in this exercise will not take any equity.

Production

An average of 126 million tablets per year will be produced at Year 3 (108 million + 18 million). This correspond (i) to a market share of 10 % and (ii) to one unit of production line and one shift of production (the first year's production is set at 30% of capacity, thereafter Year 2, 70% and Year 3, 100%).

Ex works prices

Reference price for ex-works is based on the cheapest price found between the supplier prices in the International Drug Price Indicator guide, 2003 edition, MSH and the CMS from Cote d'Ivoire 2003.

Raw materials

- Reference prices for raw materials are based on the international Trade Centre UNCTAD/WTO April 2004.
- FOB to DDP: 15%, including WAEMU intra-community taxes (see Annex 15)
- All RM have a drug master file.
- Production waste is estimated to 2%.

Income tax

In accordance with national regulations, a start-up company is exempted on income tax for a minimum of 5 years with possible extension to 8 years.

4 - Scenario n° 2 (expansion plant)

Capital expenditures

The total investment is set at $1,700,000, broken down as follows:

- Equipment: $1,000,000 (straight line depreciation over 4 years). It includes one complete production line for tablets, a complete laboratory for QA, storages with shelves, and furniture. The fifth year equipment is replaced. In order to have a valid figure to use for the CAPEX component of the NPV calculation, a quarter of its value is taken into account.

- Research & development: $700,000 corresponding to $35,000 for each of the 20 drugs produced.

- Increase in production capacity: based on the annual increase in production, every 7 years investment is required in a new production line. The NPV calculation is adjusted accordingly.

Working Capital

- Supplier: payment at 30 days (this can vary according to the relationship with the raw material supplier: the more that there is confidence in the relationship the more the time of delay payment will be long). For the first year suppliers are paid cash.

- Buffer stock: finished goods: 30 days; raw materials: 45 days;

- Client: payment at 90 days. This takes into account the fact that institutions or governments will be buying the largest portion of the production while individual clients who pay cash directly will be buying only a small portion of the production.

- Total working capital at the end of the year 5: $5,759,000

Financing

The financing is split between capital, grant and loans as follows: (i) the amount of the capital stock is set at $1,000,000, (ii) the grant ($1,000,000) is defined as a bilateral organization grant or a grant from a foundation, (iii) the loan is split between a commercial bank loan ($1,000,000; 3 years; 18 %) and an IFC loan ($1,500,000; 3 years; 15 %); IFC in this exercise will not take any equity.

Production

An average of 126 million tablets per year will be produced at Year 3 (108 million + 18 million). This correspond (i) to a market share of 10 % and (ii) to one unit of production line and one shift of production (the first year's production is set at 100% of capacity, thereafter Year 2, 110% and Year 3, 120%).

Ex works prices

Unchanged

Raw materials

Unchanged

Income tax

Unchanged

5 - Scenario n° 3 (green field)

Capital expenditures

The total investment is set at $6,125,000, broken down as follows:

- Equipment: $2,000,000 (straight line depreciation over 4 years). It includes one complete production line for tablets, a complete laboratory for QA, storages with shelves, and furniture. The fifth year equipment is replaced. In order to have a valid figure to use for the CAPEX component of the NPV calculation, a quarter of its value is taken into account.

- Building: $1,500,000 (straight line depreciation over 20 years). The surface is based on a 1000 meter square base.

- Land: $100,000 (straight line depreciation over 50 years). The building is calculated on a 5000 meter square base.

- Research & development: $525,000 corresponding to $35,000 for each of the 15 drugs produced.

- Increase in production capacity: based on the annual increase in production, every 7 years investment is required in a new production line. The NPV calculation is adjusted accordingly.

Working Capital

- Supplier: payment at 30 days (this can vary according to the relationship with the raw material supplier: the more that there is confidence in the relationship the more the time of delay payment will be long). For the first year suppliers are paid cash.
- Buffer stock: finished goods: 30 days; raw materials: 45 days;
- Client: payment at 90 days. This takes into account the fact that institutions or governments will be buying the largest portion of the production while individual clients who pay cash directly will be buying only a small portion of the production.
- Total working capital at the end of the year 5: $4,667,000

Financing

The financing is split between capital, grant and loans as follows: (i) the amount of the capital stock is set at $3,500,000, (ii) the grant ($2,000,000) is defined as a bilateral organization grant or a grant from a foundation, (iii) the loan is split between a commercial bank loan ($2,500,000; 3 years; 18 %) and an IFC loan ($2,800,000; 3 years; 15 %); IFC in this exercise will not take any equity.

Production

An average of 166 million tablets per year will be produced at Year 3 (108 million + 58 million). This correspond (i) to a market share of 10 % and (ii) to one unit of production line and one shift of production (the first year's production is set at 30% of capacity, thereafter Year 2, 70% and Year 3, 100%).

Ex works prices

Reference price for ex-works is based on the cheapest price found between the supplier prices in the International Drug Price Indicator guide, 2003 edition, MSH and the CMS from Cote d'Ivoire 2003.

Raw materials

- Reference prices for raw materials are based on the international Trade Centre UNCTAD/WTO April 2004.
- FOB to DDP: 15%, including WAEMU intra-community taxes (see Annex 15)
- All RM have a drug master file.

- Production waste is estimated to 2%.

Income tax

In accordance with national regulations, a start-up company is exempted on income tax for a minimum of 5 years with possible extension to 8 years.

6 - Scenario n° 3 (expansion plant)

Capital expenditures

The total investment is set at $2,525,000, broken down as follows:

- Equipment: $2,000,000 (straight line depreciation over 5 years). It includes one complete production line for tablets, a complete laboratory for QA, storages with shelves, and furniture. The fifth year equipment is replaced. In order to have a valid figure to use for the CAPEX component of the NPV calculation, a quarter of its value is taken into account.

- Research & development: $525,000 corresponding to $35,000 for each of the 15 drugs produced.

- Increase in production capacity: based on the annual increase in production, every 7 years investment is required in a new production line. The NPV calculation is adjusted accordingly.

Working Capital

- Supplier: payment at 30 days (this can vary according to the relationship with the raw material supplier: the more that there is confidence in the relationship the more the time of delay payment will be long). For the first year suppliers are paid cash.

- Buffer stock: finished goods: 30 days; raw materials: 45 days;

- Client: payment at 90 days. This takes into account the fact that institutions or governments will be buying the largest portion of the production while individual clients who pay cash directly will be buying only a small portion of the production.

- Total working capital at the end of the year 5: $5,445,000

Financing

The financing is split between capital, grant and loans as follows: (i) the amount of the

capital stock is set at $2,700,000, (ii) the grant ($1,000,000) is defined as a bilateral organization grant or a grant from a foundation, (iii) the loan is split between a commercial bank loan ($1,000,000; 3 years; 18 %) and an IFC loan ($1,500,000; 3 years; 15 %); IFC in this exercise will not take any equity.

Production

An average of 166 million tablets per year will be produced at Year 3 (108 million + 58 million). This correspond (i) to a market share of 10 % and (ii) to one unit of production line and one shift of production (the first year's production is set at 100% of capacity, thereafter Year 2, 110% and Year 3, 120%).

Ex works prices

Unchanged

Raw materials

Unchanged

Income tax

Unchanged

7 - Discount Rate (Weighted Average Cost of Capital) used for calculating NPV

Generally, calculating NPV requires knowing the cost of capital to use for discounting the cash flows.

Calculation of the cost of capital, in turn, requires several intermediate steps:

- The cost of both equity and the cost of debt must be determined.
  - Cost of equity is typically calculated using the Capital Asset Pricing Model. This formula sets the cost of equity equal to the risk-free rate added to the calculated beta times the market risk premium. In SSA, this calculation is difficult because: (i) there is little or not data to guide the estimates for choosing a beta; and (ii) country risk premium must be factored in.
  - Cost of debt also has to take into account both the risk of company default as well as country spread.
- The capital structure of the hypothetical enterprise must be determined, based on

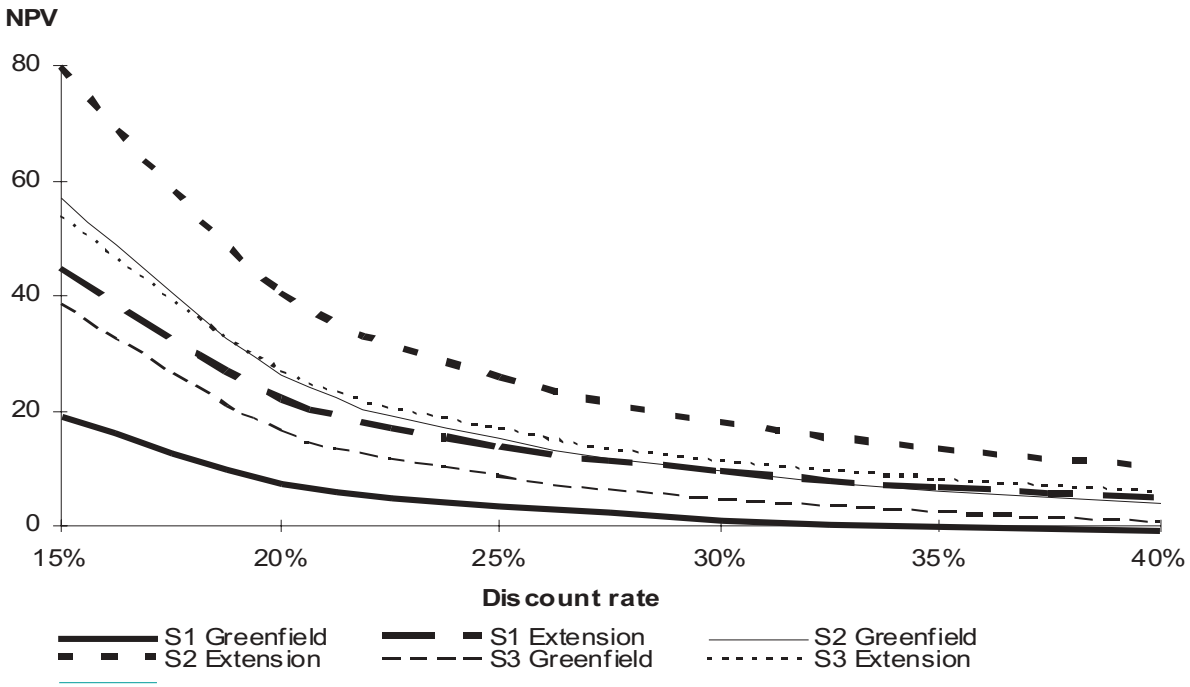
market values. While the starting capital structure is described above, it is difficult to subsequently determine the market valuation of the equity component without data from comparable enterprises.

- Weighting the costs of both equity and debt is done to determine the final weighted average cost of capital. Without a strong degree of confidence in the results of steps 1 and 2, this step is impossible to do.

Therefore, for the simulation tool, two elements were considered to estimate a discount rate: typical commercial bank rates[100] and expectations of international investment fund managers[101], resulting in the use of 35% for the discount rate in order to calculate NPV.

In the presentation of financial results, IRR was included to provide an alternative viewpoint.

NPV according to discount rates by scenario (million $)



Annex 11a

Financial results SCENARIO 1 (Greenfield)

Working capital

	Period / day	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Raw material	45		194 938	454 854	649 466	714 770	779 749
Finish Good	30		217 789	508 175	725 965	798 561	871 158
Clients	90		653 368	1 524 526	2 177 894	2 395 683	2 613 473
Supplier	30			-312 333	-445 966	-490 809	-535 428
Working capital			***1 066 095***	***2 175 222***	***3 107 358***	***3 418 206***	***3 728 951***
Change in Working Capital			**1 066 095**	**1 109 127**	**932 136**	**310 848**	**310 746**

Sources and Uses of cash

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Uses of cash						
Capital expenditures	3 600 000					785 714
Change in Working Capital	1 066 095	1 109 127	932 136	310 848	310 746	310 746
Bank Loan 18% Repayment			671 533	671 533	671 533	671 533
IFC Loan 15% Repayment		775 620	775 620	775 620	775 620	775 620
R&D	455 000					
Total	**5 121 095**	**1 884 747**	**2 379 290**	**1 758 002**	**1 757 900**	**2 543 614**
Sources of cash						
Bank Loan		2 100 000				
IFC Loan	2 600 000					
Equity	3 000 000					
Grant	2 000 000					
Advance account				256 785	236 399	756 156
Cash Flow		-500 828	430 527	1 256 649	1 521 501	1 787 458
Total	7 600 000	1 599 172	430 527	1 513 435	1 757 900	2 543 614
Changes in cash	**2 478 905**	**-285 575**	**-1 948 763**	**-244 567**		
Cumulative cash balance	***2 478 905***	***2 193 330***	***244 567***			

Net Present Value

		Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Earnings before Interest & Taxes (1)			-302 208	1 300 681	2 126 803	2 391 655	2 657 612
Taxes (2)							
Depreciation (3)			577 000	577 000	577 000	577 000	577 000
Capital expenditures (4)		4 055 000					785 714
Change in working capital (5)		1 066 095	1 109 127	932 136	310 848	310 746	310 746
Free cash flow (1 - 2 + 3 - 4 - 5)		**-5 121 095**	**-834 334**	**945 545**	**2 392 955**	**2 657 909**	**2 138 152**
Cumulative free cash flow		***-5 121 095***	***-5 955 429***	***111 211***	***3 338 501***	***5 050 864***	***4 796 061***
Internal rate of return	**9,2%**						
Pay back period	**4 years and 5 months**						
Discount rate	**35,0%**						
Net Present Value	**-68 256**						

(1) Including R&D

Profit & loss

	Year 1	Year 2	Year 3	Year 4	Year 5
Total Sales	2 613 473	6 098 103	8 711 575	9 582 733	10 453 890
% change		***133%***	***43%***	***10%***	***9%***
Cost of Good Sold	1 637 846	3 821 640	5 456 883	6 005 434	6 551 383
% sales	***63%***	***63%***	***63%***	***63%***	***63%***
Gross Margin	975 627	2 276 463	3 254 693	3 577 299	3 902 508
Contribution Margin	***37%***	***37%***	***37%***	***37%***	***37%***
Indirect cost	2 053 455	2 422 936	2 575 043	2 632 798	2 692 050
% sales	***79%***	***40%***	***30%***	***27%***	***26%***
Taxes					
Net Income	-1 077 828	-146 473	679 649	944 501	1 210 458
% sales	***-41%***	***-2%***	***8%***	***10%***	***12%***

Annex 11b

Financial results SCENARIO 1 (Extension)

Working capital

	Period / day	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Raw material	45		196 735	459 048	655 782	721 360	786 939
Finish Good	30		725 965	798 561	871 158	943 754	1 016 350
Clients	90		2 177 894	2 395 683	2 613 473	2 831 262	3 049 051
Supplier	30			-131 156	-306 032	-437 188	-480 907
Working capital			***3 100 593***	***3 522 135***	***3 834 381***	***4 059 188***	***4 371 434***
Change in Working Capital			**3 100 593**	**421 542**	**312 245**	**224 808**	**312 245**

Sources and Uses of cash

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Uses of cash						
Capital expenditures	1 000 000					392 857
Change in Working Capital	3 100 593	421 542	312 245	224 808	312 245	312 245
Bank Loan 18% Repayment		229 962	229 962	229 962		
IFC Loan 15% Repayment		656 965	656 965	656 965		
R&D	455 000					
Total	**4 555 593**	**1 308 470**	**1 199 173**	**1 111 735**	**312 245**	**705 102**
Sources of cash						
Bank Loan	500 000					
IFC Loan	1 500 000					
Equity	2 000 000					
Grant						
Advance account						
Cash Flow	765 647	2 463 640	3 332 504	3 765 400	4 219 993	4 559 403
Total	4 765 647	2 463 640	3 332 504	3 765 400	4 219 993	4 559 403
Changes in cash	**210 054**	**1 155 170**	**2 133 332**	**2 653 665**	**3 907 748**	**3 854 300**
Cumulative cash balance	***210 054***	***1 365 224***	***3 498 556***	***6 152 220***	***10 059 968***	***13 914 269***

Net Present Value

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Earnings before Interest & Taxes (1)						
Taxes (2)		2 528 637	3 307 514	3 636 167	3 969 993	4 309 402
Depreciation (3)						
Capital expenditures (4)		500 000	500 000	500 000	500 000	500 000
Change in working capital (5)	1 455 000					392 857
Free cash flow (1 - 2 + 3 - 4 - 5)	**3 100 593**	**421 542**	**312 245**	**224 808**	**312 245**	**312 245**
Cumulative free cash flow	***-4 555 593***	***2 607 095***	***3 495 269***	***3 911 360***	***4 157 747***	***4 104 300***

Internal rate of return	**66,2%**
Pay back period	**2 years and 5 months**
Discount rate	**35,0%**
Net Present Value	**3 155 223**

(1) Including R&D

Profit & loss

	Year 1	Year 2	Year 3	Year 4	Year 5
Total Sales	8 711 575	9 582 733	10 453 890	11 325 048	12 196 206
% change	***43%***	***10%***	***9%***	***8%***	***8%***
Cost of Good Sold	5 459 485	6 005 434	6 551 383	7 097 331	7 643 280
% sales	***63%***	***63%***	***63%***	***63%***	***63%***
Gross Margin	3 252 090	3 577 299	3 902 508	4 227 717	4 552 926
Contribution Margin	***37%***	***37%***	***37%***	***37%***	***37%***
Indirect cost	2 076 027	1 668 924	1 716 701	877 501	925 278
% sales	***24%***	***17%***	***16%***	***8%***	***8%***
Taxes					
Net Income	1 641 710	2 420 587	2 749 240	3 969 993	4 309 402
% sales	***19%***	***25%***	***26%***	***35%***	***35%***

Annex 11c

Financial results SCENARIO 2 (Greenfield)

Working capital

	Period / day	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Raw material	45		195 580	456 353	651 607	717 125	782 319
Finish Good	30		292 247	681 909	974 156	1 071 572	1 168 987
Clients	90		876 740	2 045 727	2 922 468	3 214 715	3 506 961
Supplier	30			-313 362	-447 437	-492 426	-537 192
Working capital			***1 364 567***	***2 870 627***	***4 100 794***	***4 510 985***	***4 921 075***
Change in Working Capital			**1 364 567**	**1 506 060**	**1 230 167**	**410 192**	**410 090**

Sources and Uses of cash

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Uses of cash						
Capital expenditures	3 600 000					785 714
Change in Working Capital	1 364 567	1 506 060	1 230 167	410 192	410 090	410 090
Bank Loan 18% Repayment			919 848	919 848	919 848	
IFC Loan 15% Repayment		1 313 931	1 313 931	1 313 931		
R&D	700 000					
Total	**5 664 567**	**2 819 991**	**3 463 945**	**2 643 970**	**1 329 937**	**1 195 804**
Sources of cash						
Bank Loan		2 000 000				
IFC Loan	3 000 000					
Equity	2 000 000					
Grant	2 000 000					
Advance account			1 541 187			
Cash Flow		-320 298	1 727 615	3 434 458	5 318 566	6 812 055
Total	7 000 000	1 679 702	3 268 801	3 434 458	5 318 566	6 812 055
Changes in cash	**1 335 433**	**-1 140 289**	**-195 144**	**790 488**	**3 988 629**	**5 616 251**
Cumulative cash balance	***1 335 433***	***195 144***		***790 488***	***4 779 117***	***10 395 368***

Net Present Value

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Earnings before Interest & Taxes (1)		416 633	3 384 393	5 091 237	5 661 414	6 235 055
Taxes (2)						
Depreciation (3)		577 000	577 000	577 000	577 000	577 000
Capital expenditures (4)	4 300 000					785 714
Change in working capital (5)	1 364 567	1 506 060	1 230 167	410 192	410 090	410 090
Free cash flow (1 - 2 + 3 - 4 - 5)	**-5 664 567**	**-512 428**	**2 731 226**	**5 258 045**	**5 828 325**	**5 616 251**
Cumulative free cash flow	***-5 664 567***	***-6 176 994***	***2 218 799***	***7 989 271***	***11 086 370***	***11 444 575***

Internal rate of return	**38,9%**
Pay back period	**3 years and 4 months**
Discount rate	**35,0%**
Net Present Value	**6 044 242**

(1) Including R&D

Profit & loss

	Year 1	Year 2	Year 3	Year 4	Year 5
Total Sales	3 506 961	8 182 910	11 689 871	12 858 858	14 027 845
% change		***133%***	***43%***	***10%***	***9%***
Cost of Good Sold	1 648 597	3 846 726	5 492 720	6 044 855	6 594 387
% sales	***47%***	***47%***	***47%***	***47%***	***47%***
Gross Margin	1 858 365	4 336 184	6 197 151	6 814 004	7 433 459
Contribution Margin	***53%***	***53%***	***53%***	***53%***	***53%***
Indirect cost	2 755 663	3 185 569	3 339 693	2 072 437	1 198 404
% sales	***79%***	***39%***	***29%***	***16%***	***9%***
Taxes					

Annex 11d

Financial results SCENARIO 2 (extension)

Working capital

	Period / day	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Raw material	45		651 932	717 125	781 928	847 512	912 705
Finish Good	30		974 156	1 071 572	1 168 987	1 266 403	1 363 818
Clients	90		2 922 468	3 214 715	3 506 961	3 799 208	4 091 455
Supplier	30			-478 084	-521 286	-565 008	-608 470
Working capital			***4 548 556***	***4 525 328***	***4 936 591***	***5 348 115***	***5 759 508***
Change in Working Capital			**4 548 556**	**-23 228**	**411 263**	**411 524**	**411 393**

Sources and Uses of cash

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Uses of cash						
Capital expenditures	1 000 000					392 857
Change in Working Capital	4 548 556	-23 228	411 263	411 524	411 393	411 393
Bank Loan 18% Repayment		459 924	459 924	459 924		
IFC Loan 15% Repayment		656 965	656 965	656 965		
R&D	700 000					
Total	**6 248 556**	**1 093 661**	**1 528 153**	**1 528 413**	**411 393**	**804 251**
Sources of cash						
Bank Loan	1 000 000					
IFC Loan	1 500 000					
Equity	2 000 000					
Grant	1 000 000					
Advance account						
Cash Flow	765 647	5 281 264	6 708 488	7 461 760	8 246 108	8 194 412
Total	6 265 647	5 281 264	6 708 488	7 461 760	8 246 108	8 194 412
Changes in cash	**17 091**	**4 187 603**	**5 180 335**	**5 933 347**	**7 834 714**	**7 390 161**
Cumulative cash balance	***17 091***	***4 204 694***	***9 385 029***	***15 318 376***	***23 153 090***	***30 543 251***

Net Present Value

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Earnings before Interest & Taxes (1)		5 186 258	6 498 301	7 117 602	7 746 106	7 694 410
Taxes (2)						
Depreciation (3)		250 000	250 000	250 000	250 000	250 000
Capital expenditures (4)	1 700 000					392 857
Change in working capital (5)	4 548 556	-23 228	411 263	411 524	411 393	411 393
Free cash flow (1 - 2 + 3 - 4 - 5)	**-6 248 556**	**5 459 486**	**6 337 037**	**6 956 078**	**7 584 712**	**7 140 159**
Cumulative free cash flow	***-6 248 556***	***-789 070***	***11 796 524***	***13 293 116***	***14 540 791***	***14 724 871***

Internal rate of return	**94,0%**
Pay back period	**2 years and 2 months**
Discount rate	**35,0%**
Net Present Value	**13 028 333**

(1) Including R&D

Profit & loss

	Year 1	Year 2	Year 3	Year 4	Year 5
Total Sales	11 689 871	12 858 858	14 027 845	15 196 833	16 365 820
% change	***43%***	***10%***	***9%***	***8%***	***8%***
Cost of Good Sold	5 495 322	6 044 855	6 591 264	7 143 919	7 693 451
% sales	***47%***	***47%***	***47%***	***47%***	***47%***
Gross Margin	6 197 151	6 814 004	7 433 459	8 052 913	8 672 368
Contribution Margin	***53%***	***53%***	***53%***	***53%***	***53%***
Indirect cost	2 593 429	1 944 804	1 996 179	926 584	977 959
% sales	***29%***	***16%***	***9%***	***6%***	***6%***
Taxes					

Annex 11e

Financial results SCENARIO 3 (Greenfield)

Working capital

	Period / day	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Raw material	45		216 295	504 687	720 656	793 080	865 178
Finish Good	30		274 777	641 145	915 922	1 007 514	1 099 106
Clients	90		824 330	1 923 436	2 747 765	3 022 542	3 297 318
Supplier	30			-346 552	-494 851	-544 582	-594 089
Working capital			***1 315 401***	***2 722 716***	***3 889 493***	***4 278 554***	***4 667 513***
Change in Working Capital			**1 315 401**	**1 407 315**	**1 166 776**	**389 061**	**388 959**

Sources and Uses of cash

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Uses of cash						
Capital expenditures	5 600 000					685 714
Change in Working Capital	1 315 401	1 407 315	1 166 776	389 061	388 959	388 959
Bank Loan 18% Repayment			1 149 810	1 149 810	1 149 810	
IFC Loan 15% Repayment		1 226 335	1 226 335	1 226 335		
R&D	525 000					
Total	**7 440 401**	**2 633 651**	**3 542 922**	**2 765 207**	**1 538 769**	**1 074 674**
Sources of cash						
Bank Loan		2 500 000				
IFC Loan	2 800 000					
Equity	3 500 000					
Grant	2 000 000					
Advance account			2 650 816	841 012		
Cash Flow		-464 474	630 631	1 924 195	3 578 282	5 158 445
Total	8 300 000	2 035 526	3 281 447	2 765 207	3 578 282	5 158 445
Changes in cash	**859 599**	**-598 125**	**-261 474**		**2 039 512**	**4 083 771**
Cumulative cash balance	***859 599***	***261 474***	***0***	***0***	***2 039 512***	***6 123 284***

Net Present Value

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Earnings before Interest & Taxes (1)		-315 139	1 929 776	3 223 340	3 651 091	4 081 445
Taxes (2)						
Depreciation (3)		1 077 000	1 077 000	1 077 000	1 077 000	1 077 000
Capital expenditures (4)	6 125 000					685 714
Change in working capital (5)	1 315 401	1 407 315	1 166 776	389 061	388 959	388 959
Free cash flow (1 - 2 + 3 - 4 - 5)	**-7 440 401**	**-645 454**	**1 840 000**	**3 911 279**	**4 339 132**	**4 083 771**
Cumulative free cash flow	***-7 440 401***	***-8 085 855***	***1 194 546***	***5 751 278***	***8 250 410***	***8 422 903***

Internal rate of return	**16,9%**
Pay back period	**4 years and 2 months**
Discount rate	**35,0%**
Net Present Value	**1 774 613**

(1) Including R&D

Profit & loss

	Year 1	Year 2	Year 3	Year 4	Year 5
Total Sales	3 297 318	7 693 743	10 991 061	12 090 167	13 189 273
% change		***133%***	***43%***	***10%***	***9%***
Cost of Good Sold	1 829 779	4 269 483	6 096 659	6 709 188	7 319 114
% sales	***55%***	***55%***	***55%***	***55%***	***55%***
Gross Margin	1 467 540	3 424 259	4 894 402	5 380 979	5 870 159
Contribution Margin	***45%***	***45%***	***45%***	***45%***	***45%***
Indirect cost	3 009 014	3 870 628	4 047 207	2 879 697	1 788 714
% sales	***91%***	***50%***	***37%***	***24%***	***14%***
Taxes					

Annex 11f

Financial results SCENARIO 3 (Extension)

Working capital

	Period / day	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Raw material	45		720 982	793 080	865 178	937 276	1 009 374
Finish Good	30		915 922	1 007 514	1 099 106	1 190 698	1 282 290
Clients	90		2 747 765	3 022 542	3 297 318	3 572 095	3 846 871
Supplier	30			-544 582	-594 089	-643 596	-693 104
Working capital			***4 384 669***	***4 278 554***	***4 667 513***	***5 056 473***	***5 445 432***
Change in Working Capital			**4 384 669**	**-106 115**	**388 959**	**388 959**	**388 959**

Sources and Uses of cash

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Uses of cash						
Capital expenditures	2 000 000					785 714
Change in Working Capital	4 384 669	-106 115	388 959	388 959	388 959	388 959
Bank Loan 18% Repayment		459 924	459 924	459 924		
IFC Loan 15% Repayment		656 965	656 965	656 965		
R&D	525 000					
Total	**6 909 669**	**1 010 775**	**1 505 849**	**1 505 849**	**388 959**	**1 174 674**
Sources of cash						
Bank Loan	1 000 000					
IFC Loan	1 500 000					
Equity	2 700 000					
Grant	1 000 000					
Advance account						
Cash Flow	765 647	4 334 990	5 449 487	6 065 032	6 707 676	6 518 154
Total	6 965 647	4 334 990	5 449 487	6 065 032	6 707 676	6 518 154
Changes in cash	**55 978**	**3 324 216**	**3 943 638**	**4 559 183**	**6 318 717**	**5 343 480**
Cumulative cash balance	***55 978***	***3 380 194***	***7 323 832***	***11 883 016***	***18 201 732***	***23 545 212***

Net Present Value

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Earnings before Interest & Taxes (1)		3 739 987	4 739 303	5 220 878	5 707 675	5 518 152
Taxes (2)						
Depreciation (3)		500 000	500 000	500 000	500 000	500 000
Capital expenditures (4)	2 525 000					785 714
Change in working capital (5)	4 384 669	-106 115	388 959	388 959	388 959	388 959
Free cash flow (1 - 2 + 3 - 4 - 5)	**-6 909 669**	**4 346 102**	**4 850 343**	**5 331 918**	**5 818 715**	**4 843 479**
Cumulative free cash flow	***-6 909 669***	***-2 563 567***	***9 196 445***	***10 182 262***	***11 150 634***	***10 662 194***

Internal rate of return	**63,6%**
Pay back period	**2 years and 5 months**
Discount rate	**35,0%**
Net Present Value	**7 770 910**

(1) Including R&D

Profit & loss

	Year 1	Year 2	Year 3	Year 4	Year 5
Total Sales	10 991 061	12 090 167	13 189 273	14 288 379	15 387 485
% change	***43%***	***10%***	***9%***	***8%***	***8%***
Cost of Good Sold	6 099 262	6 709 188	7 319 114	7 929 040	8 538 966
% sales	***55%***	***55%***	***55%***	***55%***	***55%***
Gross Margin	4 894 402	5 380 979	5 870 159	6 359 339	6 848 519
Contribution Margin	***45%***	***45%***	***45%***	***45%***	***45%***
Indirect cost	2 736 951	2 270 777	2 329 603	1 271 440	1 330 366
% sales	***25%***	***19%***	***18%***	***9%***	***9%***
Taxes					

Annex 11g

COMPARISON OF KEY FINANCIAL REQUIREMENTS AND RESULTS OF DIFFERENT SCENARIOS

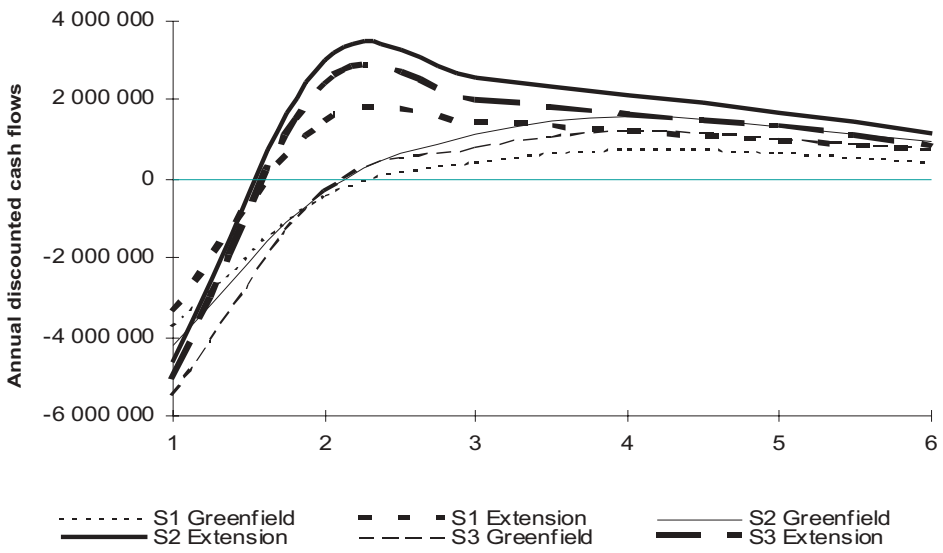
	Scenario 2 Public health includes Ethical drugs (Extension)	Scenario 3 Public health includes OTC (Extension)	Scenario 1 Public health (Extension)	Scenario 2 Public health includes Ethical drugs (Greenfield)	Scenario 3 Public health includes OTC (Greenfield)	Scenario 1 Public health (Greenfield)
Working capital	5 759 508	5 445 432	4 371 434	4 921 075	4 667 513	3 728 951
Loans	2 500 000	2 500 000	2 000 000	5 000 000	5 300 000	4 700 000
Equity and grants	3 000 000	3 700 000	2 000 000	4 000 000	5 500 000	5 000 000
Capital expenditures	1 700 000	2 525 000	1 455 000	4 300 000	6 125 000	4 055 000
Sales	16 365 820	15 387 485	12 196 206	14 027 845	13 189 273	10 453 890
Net income	7 694 410	5 518 152	4 309 402	6 235 055	4 081 445	1 210 458
Net Present Value at a 35 % discount rate	13 028 333	7 770 910	3 155 223	6 044 242	1 774 613	-68 256
Pofitability index	7,7	3,1	2,2	1,4	0,3	0,0
Payback period (in months)	26	29	29	40	50	53

All values for the end of the year 5

	Scenario 1 Public health (Greenfield)	Public health (Extension)	Scenario 2 Public health includes Ethical drugs (Greenfield)	Public health includes Ethical drugs (Extension)	Scenario 3 Public health includes OTC (Greenfield)	Public health includes OTC (Extension)
Working capital	3 728 951	4 371 434	4 921 075	5 759 508	4 667 513	5 445 432
Loans	4 700 000	2 000 000	5 000 000	2 500 000	5 300 000	2 500 000
Equity and grants	5 000 000	2 000 000	4 000 000	3 000 000	5 500 000	3 700 000
Capital expenditures	4 055 000	1 455 000	4 300 000	1 700 000	6 125 000	2 525 000
Sales	10 453 890	12 196 206	14 027 845	16 365 820	13 189 273	15 387 485
Net income	1 210 458	4 309 402	6 235 055	7 694 410	4 081 445	5 518 152
Net Present Value at a 35 % discount rate	-68 256	3 155 223	6 044 242	13 028 333	1 774 613	7 770 910
Pofitability index	0,0	2,2	1,4	7,7	0,3	3,1
Payback period (in months)	53	29	40	26	50	29

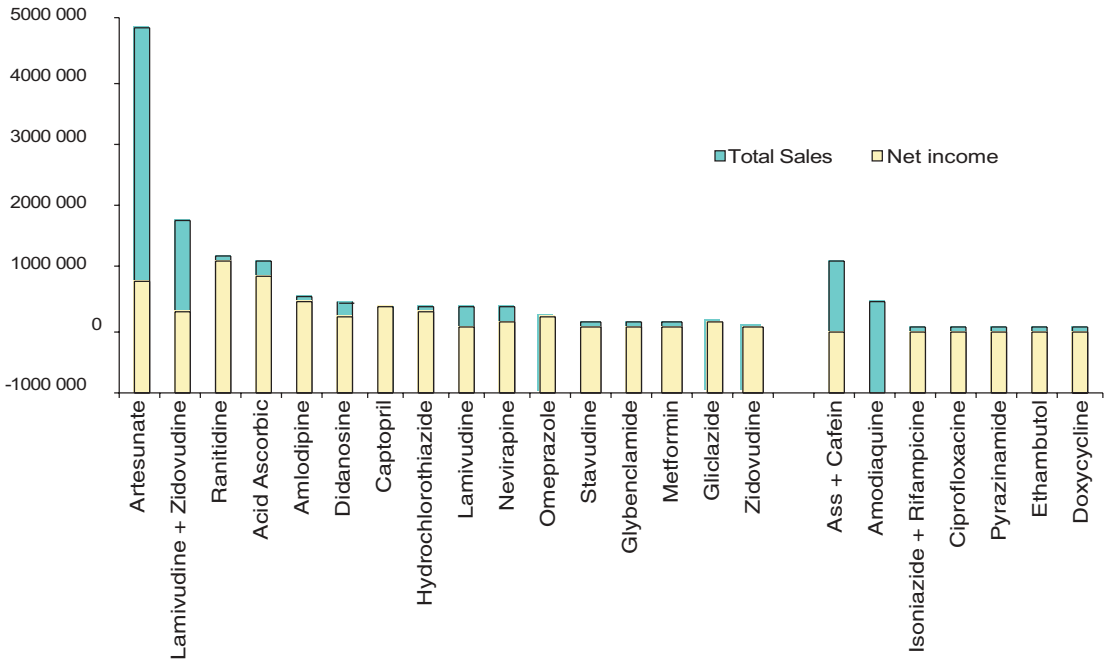
All values for the end of the year 5

Annual free cash flows by scenario



Annex 12

	Total Sales	COGS	% sales	Gross Margin	Contribution Margin	Indirect cost	% sales	Net income	% sales
Artesunate	4 914 900	2 989 427	61%	1 925 473	39%	1 167 718	24%	757 755	15%
Lamivudine + Zidovudine	1 775 780	1 283 090	72%	492 690	28%	184 749	10%	307 942	17%
Ranitidine	1 198 838	9 650	1%	1 189 188	99%	54 349	5%	1 134 839	95%
Acid Ascorbic	1 153 828	93 739	8%	1 060 088	92%	197 697	17%	862 391	75%
Amlodipine	510 533	2 591	1%	507 942	99%	26 990	5%	480 952	94%
Didanosine	445 103	149 645	34%	295 458	66%	43 541	10%	251 917	57%
Captopril	373 538	5 373	1%	368 165	99%	38 109	10%	330 056	88%
Hydrochlorothiazide	369 355	3 781	1%	365 574	99%	39 389	11%	326 185	88%
Lamivudine	358 964	246 598	69%	112 366	31%	79 742	22%	32 624	9%
Nevirapine	356 769	220 937	62%	135 832	38%	36 003	10%	99 829	28%
Omeprazole	187 489	371	0%	187 118	100%	2 839	2%	184 279	98%
Stavudine	137 447	55 301	40%	82 147	60%	49 113	36%	33 034	24%
Glybenclamide	118 339	2 974	3%	115 365	97%	33 137	28%	82 228	69%
Metformin	111 434	6 828	6%	104 606	94%	36 136	32%	68 470	61%
Gliclazide	108 771	4 270	4%	104 500	96%	12 988	12%	91 512	84%
Zidovudine	37 894	13 115	35%	24 779	65%	4 824	13%	19 955	53%
Ass + Cafein	1 125 658	546 037	49%	579 621	51%	602 365	54%	-22 744	-2%
Amodiaquine	489 555	389 302	80%	100 253	20%	1 167 718	239%	-1 067 465	-218%
Isoniazide + Rifampicine	75 600	32 682	43%	42 918	57%	80 037	106%	-37 120	-49%
Ciprofloxacine	42 880	22 631	53%	20 249	47%	43 450	101%	-23 201	-54%
Pyrazinamide	34 362	21 258	62%	13 104	38%	48 881	142%	-35 777	-104%
Ethambutol	21 420	20 475	96%	945	4%	38 019	177%	-37 074	-173%
Doxycycline	20 900	12 421	59%	8 479	41%	51 597	247%	-43 118	-206%

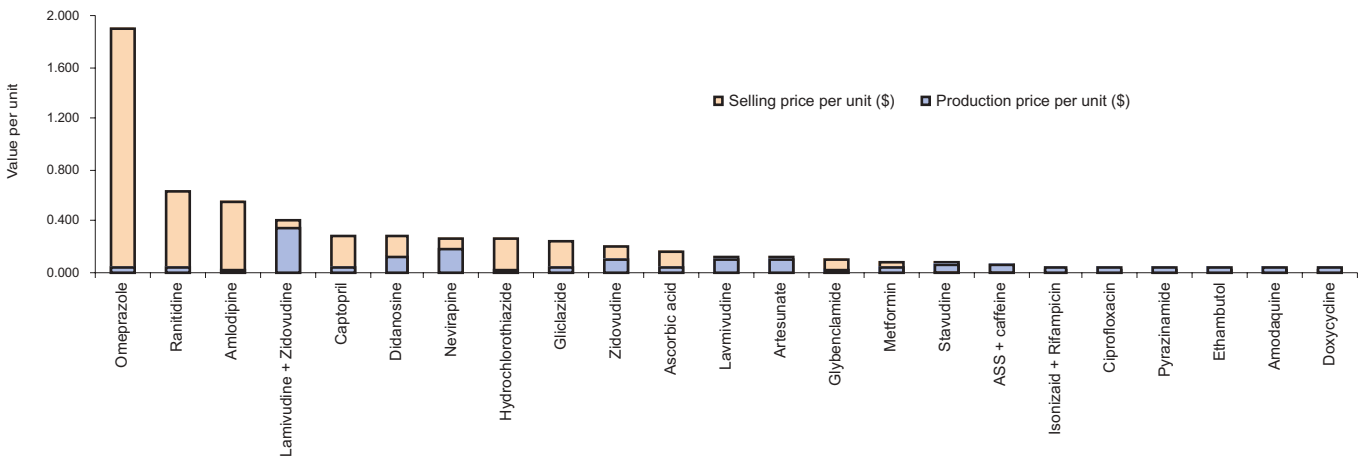


Annex 13

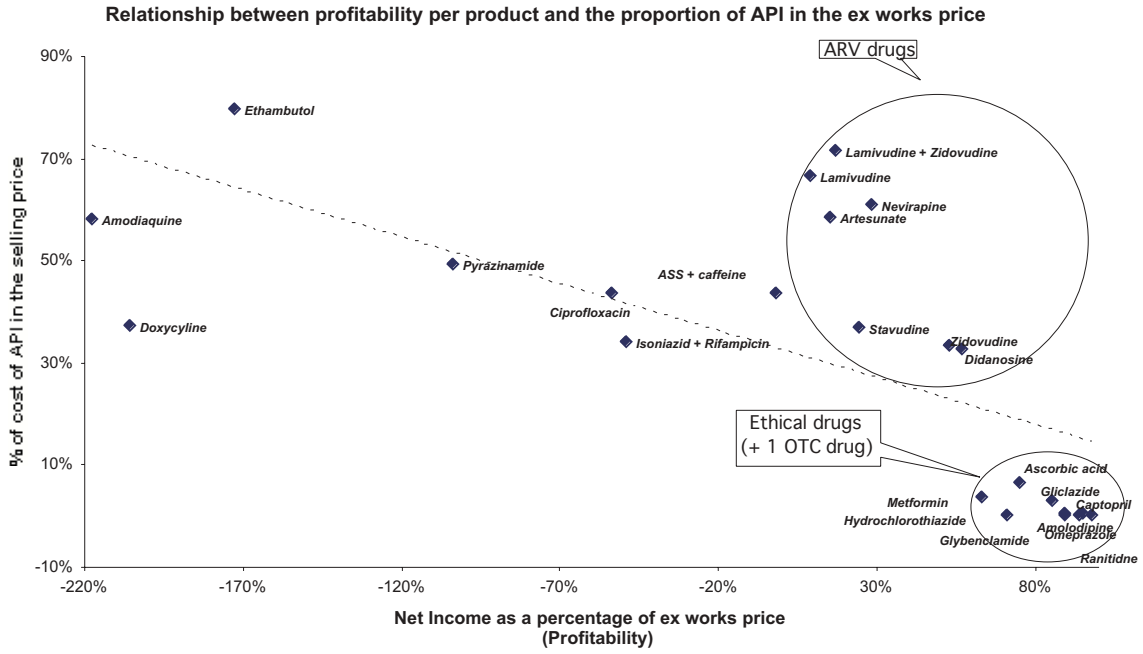
VARIATION OF THE PROPORTION OF THE API IN THE SELLING PRICE

International Non-Proprietary Name	Dosage form	Size (mg.)	API per unit ($)	Rate of net income	% API in the ex works price	Production price per unit ($)	Ex Works Price per unit ($)
Omeprazole		20	0.0015	98%	0.1%	0.0311	1.8970
Ranitidine		150	0.0030	95%	0.5%	0.0325	0.6352
Amlodipine		5	0.0005	94%	0.1%	0.0301	0.5422
Lamivudine + Zidovudine		300/150	0.2958	17%	71.7%	0.3411	0.4127
Captopril		25	0.0018	89%	0.7%	0.0314	0.2817
Didanosine		100	0.0909	57%	32.7%	0.1205	0.2776
Nevirapine		200	0.1642	28%	61.0%	0.1938	0.2691
Hydrochlorothiazide		50	0.0005	89%	0.2%	0.0301	0.2688
Gliclazide		80	0.0076	85%	3.1%	0.0372	0.2432
Zidovudine		100	0.0714	53%	33.5%	0.1010	0.2133
Ascorbic acid		1000	0.0107	75%	6.6%	0.0407	0.1613
Lavmivudine		150	0.0816	9%	66.7%	0.1111	0.1222
Artesunate		100	0.0671	15%	58.7%	0.0967	0.1143
Glybenclamide		5	0.0003	71%	0.3%	0.0299	0.1023
Metformin		500	0.0033	63%	3.7%	0.0329	0.0889
Stavudine		30	0.0282	24%	37.0%	0.0577	0.0760
ASS + caffeine		500/50	0.0226	-2%	43.8%	0.0527	0.0516
Isonizaid + Rifampicin		150/300	0.0092	-49%	34.2%	0.0403	0.0270
Ciprofloxacin		500	0.0117	-54%	43.7%	0.0413	0.0268
Pyrazinamide		400	0.0094	-104%	49.2%	0.0390	0.0191
Ethambutol		400	0.0122	-173%	79.7%	0.0418	0.0153
Amodaquine		200	0.0066	-218%	58.2%	0.0362	0.0114
Doxycycline		100	0.0041	-206%	37.4%	0.0337	0.0110

Proportion of the production cost in the ex works price



PROFIT & LOSS PER PRODUCT



Annex 14

INCOTERMS[102]

EXW Ex Works (named place). EXW applies to goods available only at the seller's premises. Buyer is responsible for loading the goods on truck or container at the seller's premises, and for the subsequent costs and risks. The risk is transferred when the seller places the goods at the disposal of the buyer as provided in the contract. (Any means of transport).

FCA Free Carrier (named place). The delivery of goods on truck, rail car or container at the specified point (depot) of departure, which is usually the seller's premises, or a named railroad station or a named cargo terminal or into the custody of the carrier, at seller's expense. The point (depot) at origin may or may not be a customs clearance centre. Buyer is responsible for the main carriage/freight, cargo insurance and other costs and risks. The risk is transferred when the seller delivers the goods into the custody of the carrier named by the buyer at the named place. (Any means of transport).

FAS Free Alongside Ship (named port of shipment). Goods are placed in the dock shed or at the side of the ship, on the dock or lighter, within reach of its loading equipment so that they can be loaded aboard the ship, at seller's expense. Buyer is responsible for the loading fee, main carriage/freight, cargo insurance, and other costs and risks. The risk is transferred when the seller delivers the goods alongside the vessel at the loading berth named by the buyer at the named port of shipment. (Ship).

FOB Free On Board (named port of shipment). The delivery of goods on board the vessel at the named port of origin (loading), at seller's expense. Buyer is responsible for the main carriage/freight, cargo insurance and other costs and risks. The risk is transferred when the goods have effectively passed the ship's rail at the named port of shipment. (Ship).

CFR Cost And Freight (named port of destination). The delivery of goods to the named port of destination (discharge) at the seller's expense. Buyer is responsible for the cargo insurance and other costs and risks. The

risk is transferred like FOB when the goods have effectively passed the ship's rail at the named port of shipment. *(The term **CFR** was formerly written as **C&F**. Many importers and exporters worldwide still use the term **C&F**.)* (Ship).

CIF Cost Insurance and Freight (named port of destination). The cargo insurance and delivery of goods to the named port of destination (discharge) at the seller's expense. Buyer is responsible for the import customs clearance and other costs and risks. The risk is transferred like FOB when the goods have effectively passed the ship's rail at the named port of shipment. The seller must provide a policy of marine insurance in accordance with minimum cover of Institute Cargo Clauses or any similar set of clauses, covering from transfer of risk until unloading at the port of destination. (Ship).

CPT Carriage Paid To… (named point of destination). The delivery of goods to the named place of destination (discharge) at seller's expense. Buyer assumes the cargo insurance, import customs clearance, payment of customs duties and taxes, and other costs and risks. The risk is transferred when the seller has delivered the goods into the custody of the first carrier. (Any means of transport).

CIP Carriage and Insurance Paid to… (named point of destination). The delivery of goods and the cargo insurance to the named place of destination (discharge) at seller's expense. Buyer assumes the import customs clearance, payment of customs duties and taxes, and other costs and risks. The risk is transferred like CPT when the seller has delivered the goods into the custody of the first carrier. The seller must provide a policy of marine insurance in accordance with minimum cover of Institute Cargo Clauses or any similar set of clauses, covering from transfer of risk until the named point of destination. (Any means of transport).

DAF Delivered At Frontier (named point). The delivery of goods to the specified point at the frontier at seller's expense. Buyer is responsible for the import customs clearance, payment of customs duties and taxes, and other costs and risks. The risk is transferred when the seller places the goods at the disposal of the buyer at the named place of delivery at the frontier (duty unpaid). (Lorry/railway).

DES Delivered Ex Ship (named port of destination). The delivery of goods on board the vessel at the named port of destination (discharge), at seller's expense. Buyer assumes the unloading fee, import customs clearance, payment of customs duties and taxes, cargo insurance, and other costs

and risks. The risk is transferred when the seller places the goods effectively at the disposal of the buyer on board the vessel at the named port of unloading. (Ship).

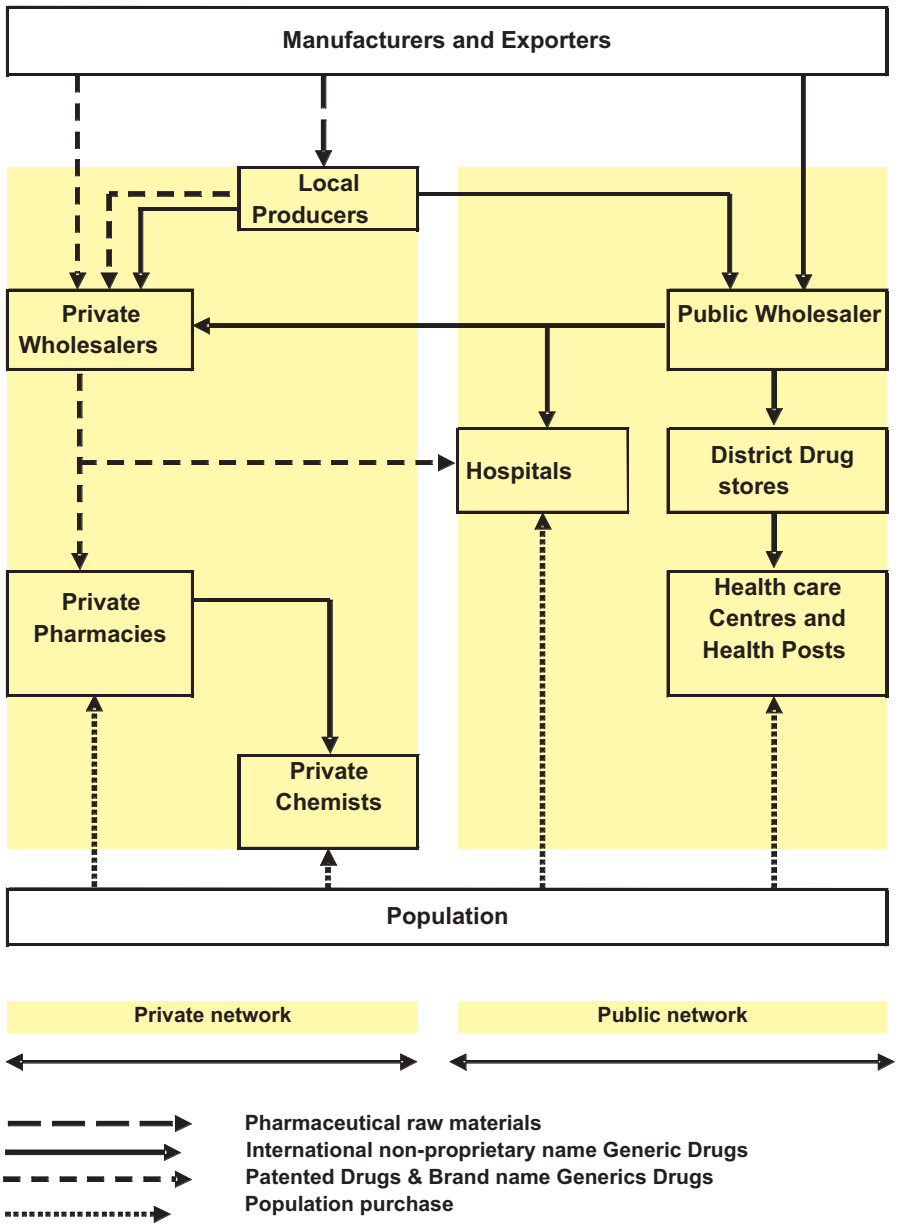
DEQ Delivered Ex Quay (named port of destination). The delivery of goods to the quay (the port) at destination at seller's expense. Seller is responsible for the import customs clearance and payment of customs duties and taxes at the buyer's end. Buyer assumes the cargo insurance and other costs and risks. The risk is transferred when the goods are placed to the disposal of the buyer on the quay at the port of destination (duty unpaid). (Ship).

DDU Delivered Duty Unpaid (named point). The delivery of goods and the cargo insurance to the final point at destination, which is often the project site or buyer's premises, at seller's expense. Buyer assumes the import customs clearance and payment of customs duties and taxes. The seller may opt not to insure the goods at his/her own risks. The risk is transferred when the seller places the goods at the disposal of the buyer at the named place of destination (duty unpaid). (Any means of transport).

DDP Delivered Duty Unpaid (named point). The seller is responsible for most of the expenses, which include the cargo insurance, import customs clearance, and payment of customs duties and taxes at the buyer's end, and the delivery of goods to the final point at destination, which is often the project site or buyer's premises. The seller may opt not to insure the goods at his/her own risks. The risk is transferred when the seller places the goods at the disposal of the buyer at the named place of destination (duty paid). (Any means of transport).

Annex 15

DRUG DISTRIBUTION SYSTEM FLOW CHART



Annex 16

SENSITIVITY ANALYSIS

Rationale

The sensitivity analysis examines the impact on net income and drug selling prices of changes in two factors: raw material prices which affect costs; and market share which affects sales. The effect of changes in drug selling prices were not included in the sensitivity analysis, because the market for drugs to treat HIV/AIDS, TB, and malaria is price competitive for the reasons mentioned earlier, and because gross margins are already quite high on the ethical drugs for hypertension, gastrointestinal ailments, and diabetes – increasing the already high profits on these drugs could require a considerable investment in advertising and promotion.

The sensitivity analysis is applied to the greenfield cases in order to provide a more coherent picture of what could occur when parameters are changed. Applying it to the extension cases would require making additional assumptions about what existing investors might choose to do and how cost savings would be spread among a product line that included those added in the extension case as well as those that are already manufactured in the existing plant.

Methodology

- The raw material price of API is an external factor that is beyond the direct control of the enterprise. For drugs such as antiretroviral drugs or ACTs, there are relatively few suppliers of API. Although benchmark prices are available, actual prices paid depend on negotiations between a drug manufacturer and its suppliers. The imaginary enterprise is thus vulnerable to fluctuations in these prices. A decrease in the price of API can lead directly to an increase in net income, which in turn can be used to benefit the shareholders, while a decrease could affect financial viability.

- Market share is a factor which is under the partial control of the enterprise: increased promotion of products sold in private market or increased lobbying with institutions and governments could have an effect on increasing market share. However, unlike changes in the price of API, corresponding increases or decreases in the need for working capital must be considered when re-allocating net income, i.e. an increase in net income resulting from increased sales will also mean that the need for working capital will increase in order to purchase additional raw material, etc.

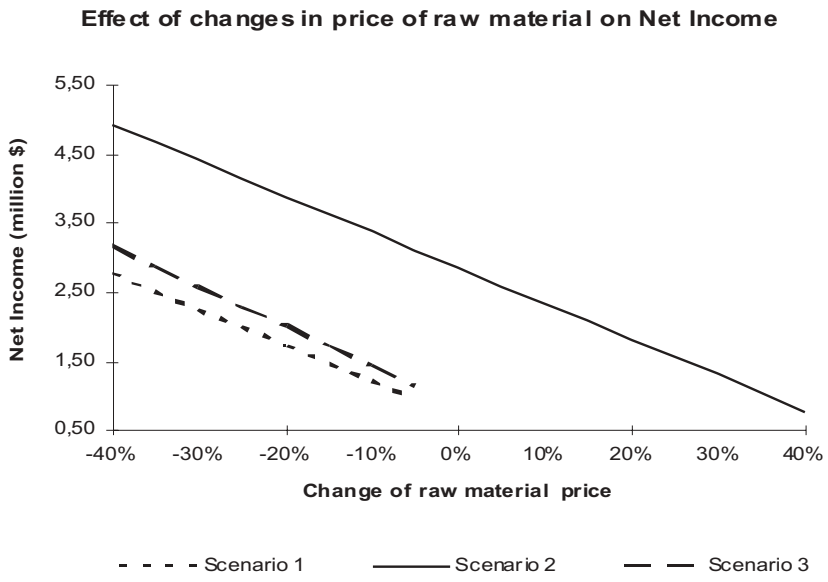
- Changes in the prices of other inputs, such as electricity, water, etc. were also not included because these changes would be too small to have a significant effect on profitability.

- The analysis of the effect on selling price considers that available cash that could be used to reduce drug prices[103] is equal to annual free cash flow as of year 3 less bank loan repayments. This amount is applied to a reduction in the selling prices of all the drugs produced.

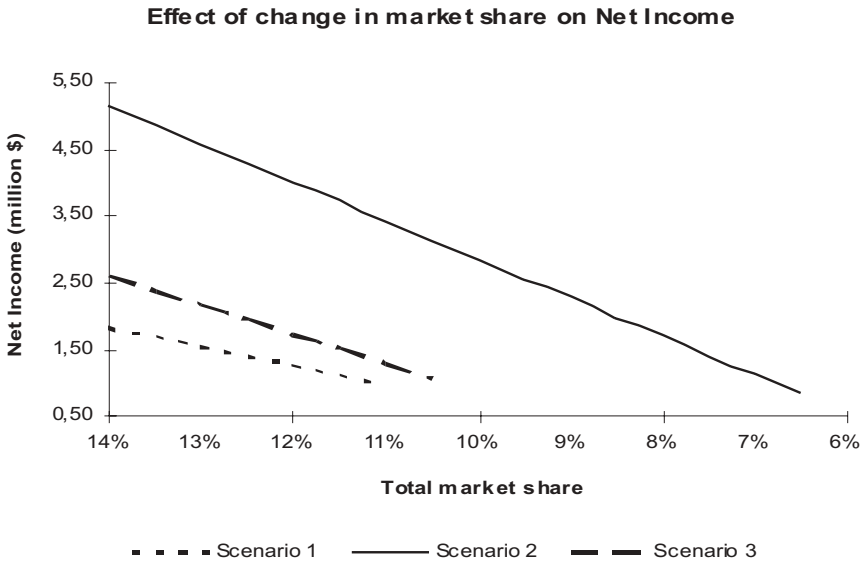
The analysis of the effect on net income concerns the effect on profitability of changes in raw material prices and market share. A minimum threshold for net income is applied in order to see whether it was possible to guarantee the repayment of a startup grant and capital (calculated per year, based on a 5 year repayment period).

Results

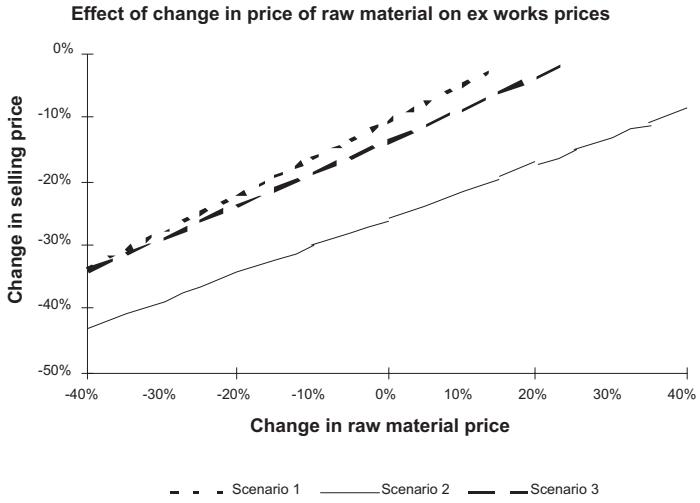
Change in price of RM	Scenario 1	Scenario 2	Scenario 3
-40%	2,76	4,94	3,15
-35%	2,50	4,68	2,87
-30%	2,24	4,42	2,58
-25%	1,98	4,16	2,29
-20%	1,72	3,90	2,00
-15%	1,46	3,64	1,71
-10%	1,20	3,38	1,42
-5%	0,94	3,12	1,14
0%		2,86	
5%		2,60	
10%		2,34	
15%		2,08	
20%		1,81	
25%		1,55	
30%		1,29	
35%		1,03	
40%		0,77	
Ratio Max/Min	2,9	6,4	2,8



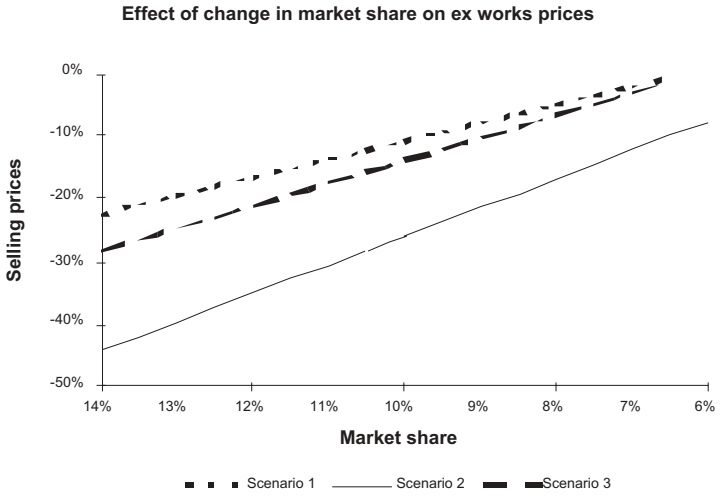
Market share	Scenario 1	Scenario 2	Scenario 3
14,0%	1,82	5,16	2,60
13,5%	1,68	4,87	2,38
13,0%	1,53	4,58	2,16
12,5%	1,39	4,30	1,94
12,0%	1,25	4,01	1,72
11,5%	1,11	3,72	1,50
11,0%	0,96	3,43	1,28
10,5%		3,14	1,07
10,0%		2,86	
9,5%		2,57	
9,0%		2,28	
8,5%		1,99	
8,0%		1,71	
7,5%		1,42	
6,5%		1,13	
6,5% 6,0%		0,84	
Ratio Max/Min	1,9	6,1	2,4



Change in price of RM	Scenario 1	Scenario 2	Scenario 3
-40%	-34%	-43%	-34%
-35%	-31%	-41%	-32%
-30%	-28%	-39%	-29%
-25%	-25%	-37%	-27%
-20%	-22%	-34%	-24%
-15%	-19%	-32%	-22%
-10%	-17%	-30%	-19%
-5%	-14%	-28%	-16%
0%	-11%	-26%	-14%
5%	-8%	-24%	-11%
10%	-5%	-22%	-9%
15%	-2%	-19%	-6%
20%		-17%	-4%
25%		-15%	-1%
30%		-13%	
35%		-11%	
40%		-9%	
Ratio Min/Max	14,9	4,9	25,0



Market share	Scenario 1	Scenario 2	Scenario 3
14,0%	-22%	-44%	-28%
13,5%	-21%	-42%	-27%
13,0%	-20%	-40%	-25%
12,5%	-18%	-37%	-23%
12,0%	-17%	-35%	-21%
11,5%	-15%	-33%	-19%
11,0%	-14%	-30%	-18%
10,5%	-12%	-28%	-16%
10,0%	-11%	-26%	-14%
9,5%	-9%	-24%	-12%
9,0%	-8%	-21%	-10%
8,5%	-6%	-19%	-9%
8,0%	-5%	-17%	-7%
7,5%	-4%	-14%	-5%
6,5%	-2%	-12%	-3%
6,5%	-1%	-10%	-1%
6,0%		-8%	
Ratio Max/Min	33,1	5,8	22,2



Annex 17

API purchase prices used in simulation

International Non-Proprietary Name	FOB unit price per kg. (us$)	Country of origin
Acetylsalicylic acid	2	China
Amlodipine besylate	80.2	India
Amodiaquine HCl	22.3	India
	21.4	India
Median price	21.85	
Artesunate HCl	572	Spain
Ascorbic Acid	9.7	India
	8.5	China
	8	China
	5.3	China
	12.5	China
	10	China
Median price	9.1	
Cafeine anhydrous	7	China
	6	India
	5.6	India
	5.4	China
	5.5	China
Median price	5.6	
Captopril	70.6	China
	70	Malaysia
	66	India
	59.4	India
	50	China
	45	China
	40	China
	140	India
Median price	62.7	
Ciprofloxacin HCl	24.2	India
	21.5	China
	18.5	China
	18.15	India
Median price	21.5	
Codeine phosphate	700	USA
	530	*
	1100	India
	1098	China
Median price	899	

International Non-Proprietary Name	FOB unit price per kg. (us$)	Country of origin
Didanosine	950	India
	600	Brazil
Median price	775	
Doxycycline HCl	45.5	China
	43.6	China
	43.3	India
Median price	43.6	
Ethambutol HCL	28	India
	27	India
	26	India
	26	India
	25	India
	22	India
	18.5	India
Median price	26	
Glibenclamide	60	India
	52	India
	48	India
	45	India
	37.4	India
Median price	48	
Gliclazide	90	India
	72.4	China
	65	China
	115.5	India
Median price	81.2	
Hydrochlorothiazide	8.8	China
	8.3	India
	7.8	India
	7.6	China
Median price	8.05	
Isoniazid	9	India
	8.5	India
	8.4	China
	8.3	India
	8.1	China
	7.9	India
	7.7	India
	7.5	India
Median price	8.2	

International Non-Proprietary (us$)	FOB unit price per kg. Name	Country of origin (us$)
Lamivudine	500	India
	427	Brazil
Median price	463.5	
Metformin	5.2	China
	5.1	India
	5	USA
	5	India
	4.3	India
	3.4	India
	3.2	India
	3.2	India
	2.2	India
Median price	4.3	
Nevirapine	700	Brazil
Omeprazole	64.9	India
Pyrazinamide	29	India
	24.2	India
	22	India
	20	India
	18	India
	17.8	India
	17	India
Median price	20	
Ranitidine	21.7	China
	16.8	India
	10.8	India
Median price	16.8	
Rifampicin	67.7	India
	44.9	India
	41.5	China
	39.5	China
Median price	43.2	
Stavudine	800	Brazil
Zidovudine	700	Brazil
	617.5	Brazil
	600	Brazil
	480	India
Median price	608.75	

"Source : International Trade Center in collaboration with the World Health Organization, Essential Drugs and Medicines Policy. April 2004. ""Pharmaceutical Starting Materials Essential Drugs Report (monthly)."" UNCTAD/WTO. "

Notes and references

1 The concept of a going concern means that the company “will continue to operate indefinitely, and will not go out of business and liquidate its assets. For this to happen, the company must be able to generate and/or raise enough resources to stay operational.” It covers both for-profit and non-profit entities. Definition found at: www.investorwords.com (Accessed 5/26/2004)

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http://www.cofacerating.com/en/index.html
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